

Types of Stressors That Increase Susceptibility to the Common Cold in Healthy Adults

Sheldon Cohen
Carnegie Mellon University

Ellen Frank
University of Pittsburgh School of Medicine

William J. Doyle and David P. Skoner
University of Pittsburgh School of Medicine and
Children's Hospital of Pittsburgh

Bruce S. Rabin
University of Pittsburgh School of Medicine

Jack M. Gwaltney, Jr.
University of Virginia Health Sciences Center

Two-hundred seventy-six volunteers completed a life stressor interview and psychological questionnaires and provided blood and urine samples. They were then inoculated with common cold viruses and monitored for the onset of disease. Although severe acute stressful life events (less than 1 month long) were not associated with developing colds, severe chronic stressors (1 month or longer) were associated with a substantial increase in risk of disease. This relation was attributable primarily to under- or unemployment and to enduring interpersonal difficulties with family or friends. The association between chronic stressors and susceptibility to colds could not be fully explained by differences among stressed and nonstressed persons in social network characteristics, personality, health practices, or prechallenge endocrine or immune measures.

Key words: stress, colds, infection, immunity, endocrine

On exposure to an infectious agent, only a proportion of people develop illness. The possibility that psychological stress contributes to this variability in response has received considerable attention (e.g., S. Cohen, Tyrrell, & Smith, 1991; Glaser et al., 1987; Stone et al., 1993; Turner Cobb & Steptoe, 1996). Probably because of their very high incidence, upper respiratory infections (URIs) have served as the primary model in the study of stress and susceptibility to infectious disease. Although there is a large literature on the relation between stress and self-reported episodes of colds and influenza (review in S. Cohen & Williamson, 1991), the most convincing work in this area provides biological verification of illness. This work includes three prospective epidemiological studies that found that family conflict and

disorder predicted serologically verified URIs (Clover, Abell, Becker, Crawford, & Ramsey, 1989; Graham, Douglas, & Ryan, 1986; Meyer & Haggerty, 1962). It also includes virus-challenge studies in which volunteers who completed stressful life event or emotional distress scales were subsequently exposed to a cold or influenza virus. The development of upper respiratory illness was verified by viral shedding and increases in virus-specific antibody titers. Although early work with this paradigm provided mixed support for a relation between stress and susceptibility to URIs (Totman, Kiff, Reed, & Craig, 1980, and Broadbent, Broadbent, Phillpotts, & Wallace, 1984, found effects; Greene, Betts, Ochitill, Iker, & Douglas, 1978, and Locke & Heisel, 1977, did not), studies using large samples and more

Sheldon Cohen, Department of Psychology, Carnegie Mellon University; Ellen Frank, Department of Psychiatry, University of Pittsburgh School of Medicine; William J. Doyle, Department of Otolaryngology, University of Pittsburgh School of Medicine, and Department of Otolaryngology, Children's Hospital of Pittsburgh; David P. Skoner, Department of Pediatrics, University of Pittsburgh School of Medicine, and Division of Allergy, Immunology, and Rheumatology, Children's Hospital of Pittsburgh; Bruce S. Rabin, Department of Pathology, University of Pittsburgh School of Medicine; Jack M. Gwaltney, Jr., Department of Internal Medicine, University of Virginia Health Sciences Center.

This work was supported by National Institute of Mental Health Grant MH50429, Research Scientist Development and Senior Scientist Awards from the National Institute of Mental Health (MH00721), National Institutes of Health Grant NCRG/GCRC 5M01 RR00056 to the University of Pittsburgh Medical Center

General Clinical Research Center, and National Institute of Mental Health Grant MH30915 to the Mental Health Research Center for Affective Disorder. Supplemental support was also provided by the Fetzer Institute and the John D. and Catherine T. MacArthur Foundation.

We are indebted to Janet Schlarb, James Seroky, Pat Fall, Susan Strelinski, Darleen Noah, Barbara Anderson, the staff of the General Clinical Research Center, the LEDS interviewers from the Depression and Manic-Depression Prevention Program, Theresa Whiteside and Robert McDonald and their laboratory staffs, and the volunteers for their contributions to the research. We also thank Stephen Lepore for his comments on an earlier draft of this article.

Correspondence concerning this article should be addressed to Sheldon Cohen, Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213. Electronic mail may be sent to scohen@cmu.edu.

sophisticated methodologies provide strong evidence for a dose-response relation between psychological stress and risk of developing a cold (S. Cohen et al., 1991; Stone et al., 1993). There is, however, some variability in how different stress measures are associated with colds. Emotional distress is associated with a greater risk of infection (S. Cohen, Tyrrell, & Smith, 1993), whereas stressful life events are associated with the risk of infected participants developing illness (S. Cohen, Tyrrell, & Smith, 1993; Stone et al., 1993).

Although existing evidence has increasingly supported a link between life stressors and susceptibility to URIs, we know little about the specific types of stressors that place people at increased risk. For example, are acute stressful events as important as ongoing chronic stressors? Are educational or reproductive events as important as losing a job or an interpersonal conflict? Moreover, up until now, we have been unable to establish the behavioral or biological pathways that link psychological stress to greater risk. Although earlier research has examined the potential role of health practices such as smoking, alcohol consumption, and exercise (S. Cohen et al., 1991; Turner Cobb & Steptoe, 1996) and of limited (quantitative) measures of immune status such as numbers of various types of white blood cells (S. Cohen et al., 1991), no evidence for mediation has been found.

This study uses the virus-challenge paradigm in an attempt to learn about the nature (duration and domain) of life stressors that compromise host resistance to URIs and to identify the behavioral and biological pathways that link stressors to disease susceptibility. We assessed acute and chronic stressors with an intensive interview technique *before* experimentally exposing healthy participants to one of two common cold viruses. We then carefully monitored participants for the development of infection and clinical illness. By intentionally exposing people to an upper respiratory virus, we were able to control for the possible effects of life stressors on exposure to infectious agents (as opposed to their effects on host resistance). We also evaluated behavioral, endocrinological, and immunological pathways through which stressors might influence susceptibility to infectious disease. Behavioral pathways we examined included smoking, drinking alcohol, diet, exercise, and sleep habits. Endocrine pathways included basal (prechallenge) urinary levels of epinephrine, norepinephrine, and cortisol. Finally, immune pathways included quantitations of white blood cell populations and natural killer (NK) cell activity. Control variables included demographic factors as well as prechallenge levels of virus-specific antibody, body mass, season, social network ties, and personality characteristics.

Method

Participants

The participants were 125 men and 151 women who responded to newspaper advertisements and were judged to be in good health after a medical examination. Ages ranged from 18 to 55 years; 19.5% had a high school education or less, 58% had some college, and 22.5% had completed a bachelor's degree; 81.2% were White, 15.2% African American, 2.2% Asian, and 1.4% Hispanic. Volun-

teers were studied in six groups (four in the spring and two in the fall); $n_s = 40-60$). Volunteers were paid \$800 for their participation.

Experimental Plan

All volunteers came to the hospital for medical eligibility screenings. Participants were required to be free of disease based on examination and laboratory testing (see S. Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). They also could not be pregnant or currently lactating or on a regular medication regimen. Social networks, health practices (except diet), age, education, race, gender, body weight, and height were also assessed at the screening and used as baseline data for those who were deemed eligible.

Eligible volunteers returned to the hospital both 4 and 5 weeks after screening to have blood drawn for assessment of NK cell activity (based on both blood draws) and antibody to the challenge virus (based on second blood draw). A personality questionnaire was administered twice, once at each blood draw. Participants also returned to the hospital during the 4th or 5th week after screening for the life stressor interview.

After completing life stressor, social network, personality, health practice, immune, and prechallenge antibody measures, participants entered quarantine. During the first 24 hr of quarantine (before viral exposure), they received a nasal examination (including a nasal wash culture for rhinovirus) and were excluded if there was any indication of recent or current URI or illness. An update life stressor interview was administered at this time to identify events occurring between the initial interview and quarantine. Baseline respiratory symptoms, nasal mucociliary clearance, and nasal mucus production were assessed at this time. Urine samples for endocrine assessment and information on dietary intake were also collected.

At the end of the first 24 hr of quarantine, participants 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, they were housed individually but were allowed to interact with each other at a distance of 3 feet or more. Nasal secretion samples for virus culture were collected on each of the 5 days. Participants were also tested each day for respiratory symptoms, nasal mucociliary clearance, and nasal mucus production with the same procedures as used at baseline. Approximately 28 days after challenge, another blood sample was collected for serological testing. All investigators were unaware of participants' status on psychosocial, endocrine, health practice, immune, and prechallenge antibody measures.

Standard Control Variables

We used eight control variables that might provide alternative explanations for the relation between life stressors and colds. These included prechallenge antibody to the virus to which they were exposed, age, body mass index (weight in kilograms divided by height in meters squared), season (fall or spring), race (White or not), gender, education (high school graduate or less, some college, and bachelor's degree or greater), and virus type (RV39 or Hanks).

Life Stressor Assessment

Life stressors were assessed by a standardized semistructured interview, the Bedford College Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1989; Harris, 1991). The LEDS provides a number of significant advantages over the checklist approach to the assessment of life events, including strict criteria

for what constitutes a stressful life event; classification of each event on the basis of severity of threat, emotional significance, and domain of life experience in which it occurred (e.g., work, relationship); identification of the temporal course (onset and offset) of each event; and information on the extent to which persons of various levels of intimacy with the respondent are involved in the event. The LEDS has been found to have acceptable levels of reliability and validity (Brown & Harris, 1989; Wethington, Brown, & Kessler, 1995).

The LEDS diverges from other life stressor measures in providing consensually defined contextual ratings of threat. For example, although loss of employment receives a uniform score within many checklist approaches, the LEDS differentiates leaving an unsatisfying job because of lack of financial need from being fired after 20 years of dedicated and fulfilling service. Raters who are unaware of the individual's subjective response to an event are provided with extensive information regarding each event and the context in which it occurred, and then rely on thorough "dictionaries" of precedent examples to rate several scales, including long-term threat, timing of the event (onset and offset), and extent to which the event is focused on the participant or on others. The dictionary ratings are based on the likely response of an average person to an event occurring in the context of the participant's particular set of biographical circumstances.

The two primary scores provided by the LEDS indicate whether a severe acute event and whether a severe chronic difficulty was experienced during the last year. Acute events have durations of less than 1 month, and indeed most last only minutes or hours (e.g., a severe reprimand at work or a fight with a spouse). Difficulties typically last a month or more and involve the disruption of everyday routines (e.g., ongoing marital problems or unemployment). We use the LEDS terminology in referring to "acute stressful life events" but, to maintain consistency with common terminology in the field, refer to "chronic difficulties" as "chronic stressors."

Although the duration of an acute event is short, the impact may last months or years, and it is the long-term threat of the event that is thought to determine its implications for health. For this reason, we focused on those events that are rated as having marked or moderate long-term threat. After LEDS practice, we also included only those events in which the participant alone or together with a significant other is the major focus (e.g., excludes events focused on pets and possessions and events with sole focus on another person). We calculated two versions of acute events: one based on events that occurred during the previous year and the other limited to events that occurred during the previous 6 months.

We similarly focused on chronic stressors that are rated as having a high moderate or marked long-term threat. They also must not have ended more than 6 months before assessment (beginning of quarantine in our study). In calculating chronic stressors, we also excluded physical illness stressors in the volunteer to avoid confounding a chronic health condition with susceptibility. In our analyses, we compared three duration criteria for chronic stressors: 1, 3, and 6 months. The interview also classifies each chronic stressor into 1 of 10 domains: work, marital-partner relationship, other relationships, money-possessions, housing, crime-legal, education, reproduction, bereavement, and miscellaneous. Because of insufficient numbers of chronic stressors in some domains in our sample, we collapsed these into three categories: work, marital-partner or other relationships, and other stressors.

LEDS interviews were conducted by trained interviewers between 1 and 14 days before virus challenge with a short update interview on the first day of quarantine, just before challenge. Interviews were rated by a consensus group consisting of no fewer than four persons. Interviewing and rating were conducted in an

independent laboratory with all staff unaware of other measures in the study.

Pathways Linking Life Stressors to Susceptibility

Health practices and markers of endocrine and immune function were assessed before virus challenge as possible factors linking life stressors to susceptibility. Smokers were defined as those smoking cigarettes, cigars, or a pipe on a daily basis (S. Cohen, Tyrrell, Russell, Jarvis, & Smith, 1993). In calculating the average number of alcoholic drinks consumed per day, a bottle or can of beer, glass of wine, and shot of whiskey were each treated as a single drink (S. Cohen, Tyrrell, Russell, et al., 1993). Exercise was assessed by a question asking the number of times per week that the participant engaged in an activity long enough to work up a sweat, get the heart thumping, or get out of breath (Paffenbarger, Blair, Lee, & Hyde, 1993). Quality of sleep was measured by scales assessing subjective sleep quality, sleep latency, disturbance, and efficiency (percentage of time in bed sleeping; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Dietary intake of vitamin C and zinc was also assessed by standard questionnaire (Block, Hartman, & Naughton, 1990). Analyses including diet variables are limited to 228 participants who completed the questionnaire according to standard criteria (Block, Thompson, Hartman, Larkin, & Guire, 1992).

Epinephrine, norepinephrine, and cortisol were assessed as biological markers of stress at the time of viral exposure (Baum & Grunberg, 1995). These hormones were measured in 24-hr urine samples collected the day before virus challenge. High-performance liquid chromatography with electrochemical detection was used for measurement of the urinary catecholamines. Urinary cortisol assays were performed by a double-antibody competitive radioimmunoassay.

NK cell activity is thought to play an important role in limiting viral infection (Whiteside, Bryant, Day, & Herberman, 1990). NK cell activity was measured in the two blood samples drawn before virus challenge. We conducted a whole blood NK cell assay (Fletcher, Baron, Ashman, Fischl, & Klimas, 1987). The results of the two blood draws ($r = .50, p < .001$) were averaged to estimate cytotoxicity. We also assessed total number of white blood cells as well as total number of monocytes, neutrophils, eosinophils, and lymphocytes by a complete blood count with differential. Numbers of T (CD3+), B (CD19+), T helper (CD4+), cytotoxic/suppressor T (CD8+), and NK (CD16+CD56+) cells were determined with flow cytometry with appropriate monoclonal antibodies. Again, the cell counts were based on the average of the two blood samples. Correlations between cell counts from the two blood draws ranged from .62 to .82 ($p < .001$ for all correlations).

Alternative Explanations

We present data on personality characteristics and social network ties to assess whether associations between stress and the incidence of colds might be attributable to other individual or social factors.

Personality. The Big Five personality factors are thought to represent the basic structure of personality. The factors are commonly described as extraversion, agreeableness, conscientiousness, emotional stability, and openness. We used a modified version of Goldberg's (1992) adjective scale measure of the Big Five. Our version includes 50 adjectives, 10 for each factor. The scale was administered twice (at each blood draw), and we averaged the two scores. Correlations between the same subscales at the two administrations were .86 for extraversion, .84 for agreeableness, .87 for conscientiousness, .79 for emotional stability, and .81 for

openness. Average of Cronbach's α for the two assessments ranged from .79 to .86.

Social network ties. We also examined the potential overlap between measures of stress and social networks. The Social Network Index assesses participation in 12 types of social relationships (S. Cohen et al., 1997). These include relationships with a spouse, parents, parents-in-law, children, other close family members, close neighbors, friends, coworkers, schoolmates, fellow volunteers, members of groups without religious affiliations (e.g., social, recreational, professional), and members of religious groups. One point was assigned for each type of relationship (possible score of 12) for which respondents indicate that they speak (in person or on the telephone) to someone in that relationship at least once every 2 weeks.

Infection and Illness

Infectious diseases result from the growth and action of microorganisms or parasites in the body (see S. Cohen & Williamson, 1991). Infection is the multiplication of an invading microorganism. Clinical disease occurs when infection is followed by the development of symptoms characteristic of the disease.

We used two common procedures for detecting infection by a specific virus. In the viral isolation procedure, nasal secretions were inoculated into cell cultures. If the virus is present in nasal secretions, it grows in the cell cultures and can be detected. Alternatively, one can indirectly assess the presence of a replicating virus by looking at changes in serum antibody levels to that virus. An invading microorganism (i.e., infection) triggers the immune system to produce antibody. 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.

Nasal washes were performed daily during quarantine to provide samples of nasal secretions for virus culture (Gwaltney, Colonno, Hamparian, & Turner, 1989). Neutralizing antibodies to the challenge virus were tested in pre- and 28-day postchallenge serum samples (Gwaltney et al., 1989). Serum antibody titers are reported as reciprocals of the initial dilution of serum.

On each day of quarantine, we collected two objective signs of disease—mucus weights and mucociliary clearance function—and one subjective measure—self-reported symptoms. Mucus weights were determined by collecting used tissues in sealed plastic bags (Doyle, McBride, Swarts, Hayden, & Gwaltney, 1988). The bags were weighed, and the weight of the tissues and bags was subtracted. To adjust for baseline, mucus weight on the day before challenge (mode = 0) was subtracted from each daily mucus weight after virus challenge. The adjusted postchallenge weights were summed 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 nasopharynx. Clearance function was assessed as the time required for a dye administered into the nose to reach the nasopharynx (Doyle et al., 1988). Each daily time was adjusted (by subtracting) for baseline, and the adjusted average time in minutes was calculated across the postchallenge days of the trial.

On each day of quarantine, participants rated the severity of eight symptoms (congestion, runny nose, sneezing, cough, sore throat, malaise, headache, and chills) during the previous 24-hr period (Farr et al., 1990). Ratings ranged from 0 (*none*) to 4 (*very severe*) for each symptom. The symptom scores were summed within each day. The baseline (24 hr before challenge) score (mode = 0) was subtracted from each daily score. Finally, adjusted daily symptoms were summed across the 5 postchallenge days to

create a total symptom score. Participants were also asked each day whether they had a cold.

Volunteers were considered to have a cold if they were both infected and met illness criteria. They were classified as infected if the challenge virus was isolated on any of the 5 postchallenge study days or there was a fourfold or greater rise in virus-specific serum neutralizing antibody titer. The illness criterion was based on selected objective indicators of illness: a total adjusted mucus weight of at least 10 g or an adjusted average mucociliary nasal clearance time of at least 7 mins. By basing the definition of a cold entirely on objective indicators, we are able to exclude interpretations of our data based on psychological influences on symptom reporting.

There is substantial evidence for the validity of the objective criterion. Those participants with colds by this criterion had higher mean total adjusted symptom scores ($M = 19.28$, $SD = 14.7$) than those without ($M = 5.67$, $SD = 8.1$), $t(274) = -9.88$, $p < .001$. The percentage of those developing colds decreased with increasing prechallenge antibody titers (63% for < 2 ; 40% for 2, 4; 15% for 8, 16; 9% for 32, 64; $p < .001$). There was also reasonable concordance between the objective criterion and traditional criteria based on self-reported symptoms (80% agreement for RV39 and 74% for Hanks). Finally, only 3.6% of those meeting either clearance time or mucus weight criteria were not infected based on viral culture or antibody response.

Statistical Analyses

We used stepwise logistic regression to predict the binary outcome incidence of a cold (Hosmer & Lemeshow, 1989) and multiple linear regression to predict continuous outcomes (J. Cohen & Cohen, 1975). To provide an estimate of relative risk, we present odds ratios (ORs) and 95% confidence intervals (CIs) based on a comparison of persons with and without acute events and with and without chronic stressors. These ORs provide an estimate of how much more likely it is that an outcome (e.g., colds) would occur in those with versus those without events or those with versus those without chronic stressors. We sequentially added variables to the first step of regression analyses to determine whether the association between acute stressful events or chronic stressors (entered in second step) and susceptibility to colds is substantially reduced after controlling for the contribution of other variables.

Results

Rates of Infections and Colds

Participants can be infected (replicate virus) without developing a cold. Ninety-nine percent who entered the trial without antibody (titer of ≤ 2) to the virus to which they were exposed were infected, whereas 69% of those with antibody (titer of ≥ 4) were infected. This resulted in a total infection rate of 84%. Fifty-eight percent of those without antibody developed colds, whereas only 19% of those with antibody developed colds. This resulted in a total of 40% of participants with colds.

Standard Controls and Susceptibility

As we have reported elsewhere (S. Cohen et al., 1997), when the eight standard controls were entered into the regression simultaneously to test the independent contribution of each control variable, incidence of colds decreased

with increased antibody titers ($p < .001$) and increased with age ($p < .03$) and exposure to RV39 as opposed to Hanks ($p < .03$). Unexpectedly, the most colds occurred among those with high school diplomas or less education followed by college graduates; the fewest colds occurred among those with some college education ($p < .04$).

Acute Stressful Life Events, Chronic Stressors, and Susceptibility

A total of 179 participants had at least one event occurring within 1 year of study onset, and 119 had at least one event occurring within 6 months. Neither acute events during the 12 months (43% colds for those with events vs. 33% for those without; adjusted OR = 1.4; CI = .76, 2.55) or 6 months (40% colds for those with events vs. 39% for those without; adjusted OR = 1.0; CI = .54, 1.74) preceding quarantine were associated with the likelihood of developing a cold.

A total of 75 participants had a chronic stressor lasting 1 month or longer, 70 had a chronic stressor lasting 3 months or longer, and 58 had a chronic stressor lasting 6 months or longer. Table 1 presents rates of colds for those with and without chronic stressors stratified by virus type and by prechallenge antibody status. As apparent from Table 1, those with chronic stressors were at higher risk for colds than those without irrespective of the duration criterion applied (1-month adjusted OR = 2.2, CI = 1.08, 4.34; 3-month adjusted OR = 2.9, CI = 1.39, 5.88; 6-month adjusted OR = 2.3, CI = 1.10, 4.94). Moreover, there were no interactions between any of the standard control variables and chronic stressors in predicting colds. Hence, the relations were similar for the two virus types, for different levels of serological status, age, gender, race, education, and body mass and across the two seasons. Of special note for interpretation of our data is the similar association between chronic stressors and rates of colds across virus types and across prechallenge seropositive and seronegative results (observed [unadjusted] rates are presented in Table 1).

In an additional analysis, we compared the risk of developing colds among persons with stressors of different

durations. Each participant was assigned to a group based on his or her longest stressor (including acute and chronic stressors as determined by the LEDSS). The groups were as follows: no acute or chronic stressor ($n = 83$), a stressor lasting less than 1 month ($n = 118$), a stressor lasting at least 1 month but not exceeding 6 months ($n = 17$), a stressor lasting more than 6 months but not exceeding 2 years ($n = 32$), and a stressor lasting more than 2 years ($n = 26$). As depicted in Figure 1, there was a linear increase in the relative risk for colds with increased duration of the stressor. However, when broken into these small groups, only the last OR (more than 2 years) was reliably greater than 1.0.

To assess the independent association of chronic stressors and acute events and the possibility that chronic stressors and acute events might interact, we fit a regression equation in which the standard controls were entered in the first step, whether or not the participant (a) had a chronic stressor lasting at least 3 months and (b) had an acute event during the last 12 months in the second step, and the interaction of chronic stressors and acute events in the last. Again, the occurrence of a chronic stressor (OR = 2.8, CI = 1.32, 5.74) was associated with developing a cold, but the occurrence of an event was not (OR = 1.2, CI = .62, 2.21). There was a marginal interaction ($\beta = 1.4, p < .13$) suggesting that having a chronic stressor without an event (69% colds) was associated with greater risk for colds than a chronic stressor accompanied by an event (49%), an event alone (40%), or neither a chronic stressor nor an event (27%). Identical analyses using the 1- and 6-month duration criteria for chronic stressors yielded similar results (interaction with 1 month, $\beta = 1.5, p < .09$; with 6 month, $\beta = 1.7, p < .08$).

We were also interested in examining whether the type (domain) of the chronic stressor mattered in predicting susceptibility. Chronic stressors were categorized into three domains: interpersonal, work, and other. Seventeen people had more than one stressor lasting 1 month or longer. For the purpose of these analyses, those with a work or interpersonal stressor were assigned to those categories irrespective of whether or not they had another type of chronic stressor (six

Table 1
Percentages (and Numbers) of Persons With Colds for Chronic Stressors Lasting at Least 1 Month, 3 Months, and 6 Months, Stratified by Prechallenge Antibody Titer and Virus

Prechallenge antibody titer and virus type	≥ 1 month		≥ 3 months		≥ 6 months	
	No chronic stressor	Chronic stressor	No chronic stressor	Chronic stressor	No chronic stressor	Chronic stressor
≤ 2						
RV39	60.4 (32/53)	72.2 (13/18)	58.2 (32/55)	81.3 (13/16)	59.6 (34/57)	78.6 (11/14)
Hanks	46.4 (26/56)	76.5 (13/17)	46.4 (26/56)	76.5 (13/17)	48.3 (29/60)	76.9 (10/13)
Both viruses	53.2 (58/109)	74.3 (26/35)	52.3 (58/111)	78.8 (26/33)	53.8 (63/117)	77.8 (21/27)
≥ 4						
RV39	20.4 (10/49)	33.3 (9/27)	19.2 (10/52)	37.5 (9/24)	21.4 (12/56)	35.0 (7/20)
Hanks	9.3 (4/43)	15.4 (2/13)	9.3 (4/43)	15.4 (2/13)	8.9 (4/45)	18.2 (2/11)
Both viruses	15.2 (14/92)	27.5 (11/40)	14.7 (14/95)	29.7 (11/37)	15.8 (16/101)	29.0 (9/31)
Total	35.8 (72/201)	49.3 (37/75)	35.0 (72/206)	52.9 (37/70)	36.2 (79/218)	51.7 (30/58)

Note. The first number in each set of parentheses is the number of people with colds, and the second number is the number of participants.



Figure 1. 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.

overlaps with work and six with interpersonal stressors). However, the 5 persons with both work and interpersonal stressors were excluded. (Three of these 5 persons developed colds.) We then fit logistic regression equations, including standard control variables, in which each of the three domains (work, interpersonal, other) was contrasted with the group of participants not experiencing a chronic stressor (OR = 1). Three separate equations were fit: 1-, 3-, and 6-month criteria for a chronic stressor. As apparent from Figure 2, having either a work or interpersonal chronic

stressor was associated with greater risk for colds in comparison with those with no chronic stressor. The effect of a chronic work stressor is attenuated (and drops below statistical significance) when a 6-month criterion is applied. Having other types of chronic stressors was not associated with greater risk for colds.

We considered the possibility that chronic stressors at work were in fact interpersonal stressors as well. To pursue this issue, we had each of the 30 (1-month criterion) chronic stressors coded by two coders for interpersonal content (criteria from Johnson, Monroe, Simons, & Thase, 1994). Only 2 of the 30 were found to be interpersonal conflicts at work. However, 27 were attributable to unemployment or underemployment.

Finally, we considered the possibility that those with a work or an interpersonal stressor had more chronic stressors than those with another type of stressor. The differences between groups did not approach significance (1.2 chronic stressors for work, 1.3 for relationships, and 1.1 for other). Nor was there an association between number of chronic stressors (for those with at least one stressor) and colds.

Pathways Linking Chronic Stressors to Colds

Because the association between chronic stressors and incidence of colds was greatest using a 3-month criterion, we used 3-month or longer stressors in testing potential pathways.

Pathogenic mechanisms. Amount of viral replication (over the 5 days after exposure) was assessed as a possible mechanism responsible for greater incidence of colds among persons with chronic stressors. Greater replication was associated with a greater likelihood of developing a cold (adjusted $\beta = 1.04 \pm .18$, $p < .001$ for all participants;

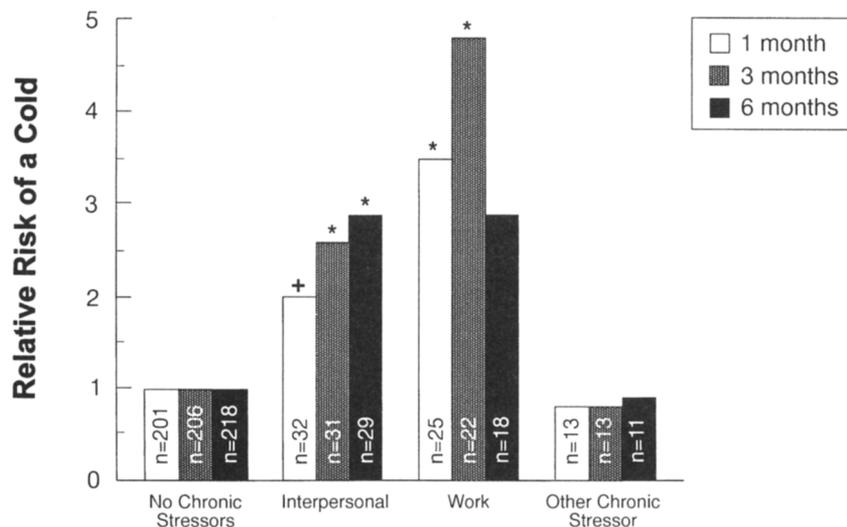


Figure 2. Relative risk (odds ratios adjusted for standard controls) of developing a cold contrasting persons with interpersonal, work, and other chronic stressors with those with no chronic stressors. The odds ratios are derived from separate analyses using the "at least 1 month," "at least 3 months," and "at least 6 months" criteria for chronic stressors. Sample sizes are indicated inside each bar. * $p < .05$; + $p < .15$.

$\beta = .93 \pm .19$, $p < .001$ for infected participants only). Although higher mean replication was found in persons with chronic stressors, this relation was only marginal: mean for chronic stressors, $1.76 \log_{10}$ titer, and mean for no stressors, $1.62 \log_{10}$ titer; $F(1, 263) = 2.02$, $p < .16$, for all participants; mean for chronic stressors, $2.17 \log_{10}$ titer, and mean for no stressors, $1.89 \log_{10}$ titer; $F(1, 220) = 2.82$, $p < .10$, for infected participants only. When we added total viral replication as an additional control variable, it had little effect on the relation between chronic stressors and colds (Table 2).

Health practices. As we have reported earlier (S. Cohen et al., 1997), smokers (adjusted for standard controls OR = 3.0, CI = 1.48, 6.06), persons exercising two or fewer times a week (adjusted OR = 1.8, CI = 1.01, 3.24), those with sleep efficiency of .80 or less (adjusted OR = 2.6, CI = 1.16, 5.78), those drinking one or fewer drinks per day (adjusted OR = 2.0, CI = 1.02, 3.84), and those who ingest 85 mg or less of vitamin C a day (adjusted OR = 2.0, CI = 1.04, 3.82) were all at greater risk for developing colds. There were no associations between zinc ingestion and colds or between the other sleep measures and colds. Table 3 presents the relation between each of these health practices and having a chronic stressor lasting 3 months or longer. Those with chronic stressors were more likely to be smokers. There were also marginal associations between having a stressor and less exercise and poorer sleep efficiency.

To determine whether health practices might operate as pathways through which chronic stressors were related to colds, smoking status, exercise frequency, sleep efficiency, vitamin C, and alcohol consumption were entered along with the standard controls in the first step of the regression equation. Simultaneous addition of all of these health practices to the regression equation slightly reduced the association between chronic stressors and susceptibility to colds (OR = 2.1, CI = 0.92, 4.84, $n = 226$ compared with OR = 2.7, CI = 1.23, 5.86 with the same reduced sample standard controls only). Similar results were obtained when diet was dropped from this analysis and the entire sample of

274 (with complete data on all variables in equation) was used (see Table 2).

Hormones and immune markers. We have reported elsewhere (S. Cohen et al., 1997) that persons with levels of norepinephrine above the median level ($29.6 \mu\text{g}/\text{total volume}$) were at greater risk for developing colds than those with levels below the median (OR = 1.9, CI = 1.04, 3.50). A similar but weaker relation was found for epinephrine (median = $3.78 \mu\text{g}/\text{total volume}$; OR = 1.8, CI = 0.94, 3.58). Cortisol levels, NK cell cytotoxicity, and the blood cell counts were not associated with colds.

None of the endocrine measures were associated with experiencing a chronic stressor (see Table 3). Among those with chronic stressors, helper T cells ($750 \pm 232/\text{mm}^3$) were higher than in those without ($638 \pm 227/\text{mm}^3$), $F(1, 262) = 5.38$, $p < .03$. There was also a marginal association between having a stressor and greater numbers of neutrophils (with chronic stressor $4,160 \pm 1,374/\text{mm}^3$; without stressor $3,714 \pm 1,345/\text{mm}^3$), $F(1, 263) = 2.39$, $p < .13$.

We entered as controls any endocrine or immune measure we found to be even marginally associated with either chronic stressors or with colds. Hence, epinephrine, norepinephrine, number of helper T cells, and number of neutrophils were entered along with the standard controls in the first step of the regression equation. Simultaneous addition of all of these hormone and immune measures to the regression equation did not substantially alter the association between chronic stressors and susceptibility to colds (see Table 2). Hence, none of these variables were primary contributors to the association between chronic stressors and colds in this study.

Alternative Explanations

Personality. We have reported that only extraversion was associated with susceptibility; those with low scores ("introverts," below median of 28.5) were at greater risk for colds (adjusted OR = 2.7, CI = 1.45, 4.92) in this sample (S. Cohen et al., 1997). Extraversion scores were not associated with having a chronic stressor (28.2 for those with stressor vs. 26.8 for those without), adjusted for standard controls, $F(1, 263) = 1.86$, $p < .18$. Moreover, adding extraversion to the regression equation, including standard controls and chronic stressors lasting 3 months or longer, did not substantially reduce the relation between chronic stressors and incidence of colds (see Table 2). The interaction between chronic stressors and extraversion did not reach significance, suggesting that the stressor effect is relatively similar across introverts and extraverts.

Social network ties. We have reported elsewhere that greater social network diversity was associated with less susceptibility in this sample (adjusted OR = 4.2 [1.34, 13.29] comparing those with one to three roles with those with six or more; S. Cohen et al., 1997). Social network diversity was marginally associated with having a chronic stressor (5.5 ± 1.9 roles for those with stressors and 5.8 ± 1.7 roles for those without), adjusted for standard controls, $F(1, 263) = 2.91$, $p < .09$. However, adding network diversity to the regression equation only slightly reduced the relation

Table 2
Odds of Developing a Cold for Persons With Chronic Stressors (3-Month Criterion) in Comparison to Those Without Chronic Stressors When Different Explanatory Variables Are Controlled For

Explanatory variables in equation	Odds ratio (95% CI)
Eight standard control variables (SC)	2.9 (1.39–5.88)
Testing pathways	
SC and total viral replication	2.5 (1.16–5.56)
SC and health practices	2.2 (1.02–4.61)
SC and endocrine and immune markers	2.7 (1.26–5.70)
Testing alternative explanations	
SC and personality (extraversion/introversion)	2.7 (1.30–5.60)
SC and social network diversity	2.6 (1.27–5.48)

Note. The explanatory variables are added to the first step of the equation, and chronic stressors are entered into the second step. CI = confidence interval.

Table 3
Percentage of Persons With Health Practice and Endocrine Risk Factors for Colds Stratified by Experience of a Chronic Stressor Lasting 3 Months or Longer

Variable	Chronic stressor	No chronic stressor	Odds ratio	CI
Health practices				
Smokers	51.4	28.6	2.95	1.49–5.85
Exercising ≤ 2 times/week	62.9	49.0	1.57	0.86–2.86
With sleep efficiency $\leq .80$	27.1	16.5	1.87	0.91–3.85
Drinking ≤ 1 drink/day	71.4	69.1	0.94	0.48–1.84
Ingesting ≤ 85 mg vitamin C per day	39.0	37.9	1.01	0.52–1.94
Endocrine measures				
≥ 3.78 $\mu\text{g}/24$ hr ^a of epinephrine	47.8	51.0	0.90	0.46–1.77
≥ 29.7 $\mu\text{g}/24$ hr ^a of norepinephrine	58.0	47.6	1.05	0.57–1.95
≥ 33 $\mu\text{g}/24$ hr ^a of cortisol	52.2	50.5	1.25	0.67–2.34

Note. Odds ratios adjusted for standard control variables are reported along with 95% confidence intervals (CI). The odds ratios indicate the likelihood that the specific risk factor would be present among those with chronic stressors as opposed to those without. Analysis of vitamin C was done on a subsample of 228 participants who completed the diet questionnaires accurately.

^aMedian value.

between chronic stressors and incidence of colds (see Table 2). There was also no interaction between chronic stressors and network diversity, suggesting that the chronic stressor effect was similar across levels of social network diversity.

Discussion

This study provides additional supporting evidence for the role of psychological stress in susceptibility to upper respiratory infectious disease (see, e.g., virus-challenge studies by S. Cohen et al., 1991; Stone et al., 1993; epidemiologic studies by Graham, Douglas, & Ryan, 1986; Meyer & Haggerty, 1962). It also furthers our understanding of the types of stressors that alter host resistance. Although acute (lasting less than 1 month) stressful events did not alter susceptibility to colds, enduring chronic stressors (lasting 1 month or longer) were associated with greater susceptibility to rhinovirus-induced colds. Moreover, there was some indication that the longer the duration of the stressor, the greater was the risk for colds. These relations were unaffected by controls for prechallenge virus-specific antibody, age, education, race, gender, body mass, season, and virus type. They also occurred equally across demographic characteristics and variations in body mass, season, virus type, and prechallenge serostatus. Persons experiencing chronic stressors associated with marked or severe long-term threats were between two and three times more likely to develop colds than those without such an experience. This result supports the generally held (but seldom tested) hypothesis that chronic stressors are a more important determinant of disease risk than are acute stressful events (e.g., Lepore, Miles, & Levy, 1997). This may be viewed as inconsistent with some of the self-reported illness epidemiology studies that suggest that acute dips in positive daily events in the days just before the onset of an illness are markers of risk (Evans & Edgerton, 1991; Evans, Pitts, & Smith, 1988; Stone, Bruce, & Neale, 1984). This discrepancy may be attributable to limitations of the epidemiological studies, including the possibility of premorbid influences of infec-

tion on daily events, and to influences of daily events on self-report of illness. Alternatively, the difference may be attributable to the kinds of events being studied: the acute events that constitute marked or severe long-term threats as assessed by the LEDS in contrast to the minor day-to-day events and associated acute affective changes assessed in the epidemiological studies.

Chronic stressors based on interpersonal conflicts (relative risk as high as 2.9) and problems concerning work (relative risk as high as 4.8; mostly attributable to under- and unemployment) were primarily responsible for the associations found in this study. Because many types of chronic stressors had low (or no) frequencies in our sample, this result should not be interpreted as meaning that these are the only types of enduring stressors that place people at risk. Instead, it indicates that these stressors, when they occur, are potent. These results are, however, consistent with other evidence that both interpersonal conflicts (Bolger, DeLongis, Kessler, & Schilling, 1989; Brown & Harris, 1989; Kiecolt-Glaser et al., 1993) and unemployment (Kasl, 1978) are detrimental to health.

Although the association (Chronic Stressors \times Acute Events interaction) was marginal, the finding that having a concurrent event was protective for persons with chronic stressors is provocative. It is consistent with some evidence from the mental health literature (McGonagle & Kessler, 1990), and suggests the possibility that events distract from chronic stressors rather than accumulate to create greater impact.

Altered host susceptibility for those experiencing a chronic stressor could be a manifestation of a more virulent course of infection as indicated by greater viral replication. Although those with chronic stressors shed marginally greater amounts of virus than those without, amount of viral shedding accounted for only a small proportion of the relation between chronic stressors and the development of colds. These results suggest that chronic stressors may be associated with more than one disease process (i.e., extent of viral

replication and a process or processes that modulate the production of cold signs and symptoms).

Although chronic stressors were associated with several behavioral risk factors for colds, including being a smoker, exercising fewer than two times a week, and poor sleep quality, together these accounted for only a small part of the relation between experiencing a chronic stressor and developing a cold. These results are consistent with our failure in an earlier virus-challenge study to explain the relation between psychological stress and colds by differences in health practices (S. Cohen et al., 1991) as well as a similar failure in an epidemiological study of psychological stress and self-reported URI (Turner Cobb & Steptoe, 1996). In the context of finding associations between smoking, alcohol consumption, sleep quality, diet, and exercise and colds, the failure of these health practices to explain the relation between stress and colds increases our confidence that this relation is not primarily mediated by health practices.

We were surprised that chronic stressors were not associated with elevated epinephrine, norepinephrine, or cortisol, hormones whose elevation is generally associated with chronic psychological stress (Baum & Grunberg, 1995). Elevated levels of epinephrine and norepinephrine were associated with greater risk for colds. These hormones are sensitive to relatively low levels of psychological stress as well as to the severe threats that are represented by chronic stressors (difficulties) in the LEDS (Baum & Grunberg, 1995). Hence, it is possible that any association with chronic stressors might be obscured by other less severe stressful experiences that are not picked up by the LEDS. For example, it might be variations in the acute elevation of epinephrine and norepinephrine in response to anxiety about the virus challenge or quarantine period that is responsible for the variation in catecholamines that is associated with susceptibility to colds.

We can only speculate on what mechanisms might mediate the association of chronic stressors and colds. Our data suggest eliminating a number of possibilities. At least for those who were seronegative before viral inoculation, the relation was attributable to increased colds among infected persons (99% were infected) and not increased incidence of infection. This result is consistent with those of earlier studies of stressful life events (S. Cohen et al., 1991; Stone et al., 1993). The similarity of the association across serostatus also suggests that the mechanism is not primarily mediated by a memory antibody response. In addition, we found little evidence here for the role of either numbers of circulating white blood cell populations or NK cell activity. It is possible, however, that other characteristics of immune status operate as pathways. For example, behavioral effects on cytokine release in the nasal passage may effect the triggering of symptoms (Akira & Kishimoto, 1992). It is also possible that these associations are mediated not by the immune system but rather by effects of chronic stressors on the nasal mucosa with resultant changes in airflow, ciliary movement, and local membrane defense that might increase susceptibility (Swartz, 1991).

References

- Akira, S., & Kishimoto, T. (1992). IL-6 and NF-IL6 in acute phase response and infection. *Immunological Reviews*, *127*, 25–50.
- Baum, A., & Grunberg, N. (1995). Measurement of stress hormones. In S. Cohen, R. C. Kessler, & L. Underwood Gordon (Eds.), *Measuring stress* (pp. 175–192). New York: Oxford University Press.
- Block, G., Hartman, A. M., & Naughton, D. (1990). A reduced dietary questionnaire: Development and validation. *Epidemiology*, *1*, 58–64.
- Block, G., Thompson, F. E., Hartman, A. M., Larkin, F. A., & Guire, K. E. (1992). Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period. *Journal of the American Dietetic Association*, *92*, 686–693.
- Bolger, N., DeLongis, A., Kessler, R. C., & Schilling, E. A. (1989). Effects of daily stress on negative mood. *Journal of Personality and Social Psychology*, *57*, 808–817.
- Broadbent, D. E., Broadbent, M. H. P., Phillpotts, R. J., & Wallace, J. (1984). Some further studies on the prediction of experimental colds in volunteers by psychological factors. *Journal of Psychosomatic Research*, *28*, 511–523.
- Brown, G. W., & Harris, T. O. (Eds.). (1989). *Life events and illness*. New York: Guilford Press.
- Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index. *Psychiatry Research*, *28*, 193–213.
- Clover, R. D., Abell, T., Becker, L. A., Crawford, S., & Ramsey, C. N. (1989). Family functioning and stress as predictors of influenza B infection. *The Journal of Family Practice*, *28*, 536–539.
- Cohen, J., & Cohen, P. (1975). *Applied multiple regression/correlation analysis for the behavioral sciences*. Hillsdale, NJ: Erlbaum.
- 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*, 1940–1944.
- Cohen, S., Tyrrell, D. A. J., Russell, M. A. H., Jarvis, M. J., & Smith, A. P. (1993). Smoking, alcohol consumption and susceptibility to the common cold. *American Journal of Public Health*, *83*, 1277–1283.
- Cohen, S., Tyrrell, D. A. J., & Smith, A. P. (1991). Psychological stress and susceptibility to the common cold. *New England Journal of Medicine*, *325*, 606–612.
- Cohen, S., Tyrrell, D. A. J., & Smith, A. P. (1993). Life events, perceived stress, negative affect and susceptibility to the common cold. *Journal of Personality and Social Psychology*, *64*, 131–140.
- Cohen, S., & Williamson, G. M. (1991). Stress and infectious disease in humans. *Psychological Bulletin*, *109*, 5–24.
- Doyle, W. J., McBride, T. P., Swartz, J. D., Hayden, F. G., & Gwaltney, J. M., Jr. (1988). The response of the nasal airway, middle ear and Eustachian tube to provocative rhinovirus challenge. *American Journal of Rhinology*, *2*, 149–154.
- Evans, P. D., & Edgerton, N. (1991). Life-events and mood as predictors of the common cold. *British Journal of Medical Psychology*, *64*, 35–44.
- Evans, P. D., Pitts, M. K., & Smith, K. (1988). Minor infection, minor life events and the four day desirability dip. *Journal of Psychosomatic Research*, *32*, 533–539.
- Farr, B. M., Gwaltney, J. M., Hendley, J. O., Hayden, F. G., Naclerio, R. M., McBride, T., Doyle, W. J., Sorrentino, J. V., & Proud, D. (1990). A randomized controlled trial of glucocorti-

- coid prophylaxis against experimental rhinovirus infection. *Journal of Infectious Diseases*, 162, 1173-1177.
- Fletcher, M. A., Baron, G. C., Ashman, M. R., Fischl, M. A., & Klimas, N. G. (1987). Use of whole blood methods in assessment of immune parameters in immunodeficiency. *Diagnostic and Clinical Immunology*, 5, 68-91.
- Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C. E., Pinsky, D., Kotur, M., Post, A., Beck, M., & Kiecolt-Glaser, J. K. (1987). Stress-related immune suppression: Health implications. *Brain, Behavior, and Immunity*, 1, 7-20.
- Goldberg, L. R. (1992). The development of markers for the Big-Five factor structure. *Psychological Assessment*, 4, 26-42.
- Graham, N. M. H., Douglas, R. B., & Ryan, P. (1986). Stress and acute respiratory infection. *American Journal of Epidemiology*, 124, 389-401.
- Greene, W. A., Betts, R. F., Ochitill, H. N., Iker, H. P., & Douglas, R. G. (1978). Psychosocial factors and immunity: Preliminary report. *Psychosomatic Medicine*, 40, 87.
- Gwaltney, J. M., Jr., Colonno, R. J., Hamparian, V. V., & Turner, R. B. (1989). Rhinovirus. In N. J. Schmidt & R. W. Emmons (Eds.), *Diagnostic procedures for viral, rickettsial and chlamydial infections* (6th ed., pp. 579-614). Washington, DC: American Public Health Association.
- Harris, T. O. (1991). Life stress and illness: The question of specificity. *Annals of Behavioral Medicine*, 13, 211-219.
- Hosmer, D. W., Jr., & Lemeshow, S. (1989). *Applied logistic regression*. New York: Wiley.
- Johnson, S. L., Monroe, S., Simons, A., & Thase, M. E. (1994). Clinical characteristics associated with interpersonal depression: Symptoms, course and treatment response. *Journal of Affective Disorders*, 31, 97-109.
- Kasl, S. V. (1978). Epidemiological contributions to the study of work stress. In C. I. Cooper & R. Payne (Eds.), *Stress at work* (pp. 3-48). New York: Wiley.
- Kiecolt-Glaser, J. K., Malarkey, W. B., Chee, M., Newton, T., Cacioppo, J. T., Mao, H.-Y., & Glaser, R. (1993). Negative behavior during marital conflict is associated with immunological down-regulation. *Psychosomatic Medicine*, 55, 395-409.
- Lepore, S. J., Miles, H. J., & Levy, J. S. (1997). Relation of chronic and episodic stressors to psychological distress, reactivity, and health problems. *International Journal of Behavioral Medicine*, 4, 39-59.
- Locke, S. E., & Heisel, J. S. (1977). The influence of stress and emotions on the human immune response. *Biofeedback and Self-Regulation*, 2, 320.
- McGonagle, K. A., & Kessler, R. C. (1990). Chronic stress, acute stress, and depressive symptoms. *American Journal of Community Psychology*, 18, 681-706.
- Meyer, R. J., & Haggerty, R. J. (1962). Streptococcal infections in families. *Pediatrics*, 29, 539-549.
- Paffenbarger, R. S., Jr., Blair, S. N., Lee, I., & Hyde, R. T. (1993). Measurement of physical activity to assess health effects in free-living populations. *Medicine and Science in Sports and Exercise*, 25, 60-70.
- Stone, A. A., Bovbjerg, D. H., Neale, J. M., Napoli, A., Valdimarsdottir, H., & Gwaltney, J. M., Jr. (1993). Development of common cold symptoms following experimental rhinovirus infection is related to prior stressful life events. *Behavioral Medicine*, 8, 115-120.
- Stone, A. A., Bruce, R., & Neale, J. M. (1984). Changes in daily event frequency precede episodes of physical symptoms. *Journal of Human Stress*, 46, 892.
- Swartz, M. N. (1991). Editorial: Stress and the common cold. *New England Journal of Medicine*, 325, 654-655.
- Totman, R., Kiff, J., Reed, S. E., & Craig, J. W. (1980). Predicting experimental colds in volunteers from different measures of recent life stress. *Journal of Psychosomatic Research*, 24, 155-163.
- Turner Cobb, J. M., & Steptoe, A. (1996). Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. *Psychosomatic Medicine*, 58, 404-412.
- Wethington, E., Brown, G. W., & Kessler, R. C. (1995). Interview measurement of stressful life events. In S. Cohen, R. C. Kessler, & L. Underwood Gordon (Eds.), *Measuring stress* (pp. 59-79). New York: Oxford University Press.
- Whiteside, T. L., Bryant, J., Day, R., & Herberman, R. B. (1990). Natural killer cytotoxicity in the diagnosis of immune dysfunction: Criteria for a reproducible assay. *Journal of Clinical Laboratory Analysis*, 4, 102-114.