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The Pittsburgh Common Cold Studies: Psychosocial Predictors of Susceptibility to Respiratory Infectious Illness

Sheldon Cohen

This article provides a selected overview of 20 years of research on the role of psychosocial factors in susceptibility to upper respiratory infections. We present evidence from our laboratory that psychological stress is associated with increased risk for developing respiratory illness for persons intentionally exposed to a common cold virus, that the longer the duration of the stressor the greater the risk, and that stress association with susceptibility may be mediated by stress-induced disruption of the regulation of proinflammatory cytokines. We further provide evidence that social relationships (social integration and social support) are also associated with risk for respiratory illness: Social integration is associated with reduced risk irrespective of stress level and social support protects persons from the pathogenic influences of stress. Finally, we report recent evidence that lower levels of early childhood socioeconomic status (SES) are associated with greater risk of viral-induced illness during adulthood, independent of adult SES.

Key words: psychoneuroimmunology, socioeconomic status, stress buffering, social integration, social rank, social support, infectious illness susceptibility, respiratory infections, common cold, influenza, cytokine regulation, cortisol regulation

Over the last 20 years, our laboratory has been interested in the extent to which social and psychological factors may influence susceptibility to infectious illness. In particular, we have employed a unique prospective design in which healthy participants are evaluated on psychosocial factors and then intentionally exposed to a virus that causes a mild cold. After exposure to the virus, participants are carefully monitored (in quarantine) for the development of a clinical illness as defined by the presence of both biologically verified infection and symptom expression. Approximately one-third of the participants we expose to a virus develop a clinical cold. The question we pose is whether we can predict from baseline psychosocial measures who will become ill.

The primary focus of this article is our work on psychological stress, social network composition, and childhood socioeconomic status (SES) as predictors of susceptibility to colds and flu. A summary of the studies we discuss is provided in Table 1. Other factors we have studied include sociability (Cohen, Doyle, Turner, Alper, & Skoner, 2003a), social rank (Cohen, 1999; Cohen, Line et al., 1997), and both positive and negative emotional styles (Cohen, Doyle, Turner, Alper, & Skoner, 2003b; Feldman, Cohen, Doyle, Skoner, & Gwaltney, 1999).

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Table 1. *Designs, Viruses Used, Psychological Predictor Variables Included, and Sample Sizes for Studies Discussed in This Article*

Code	Format	Virus	Psych Var	*N*
VCS 1	Viral-Challenge	RV, RSV, CV	Stress	420
VCS2	Viral-Challenge	RV	Stress, soc network	276
VCS3	Viral-Challenge	Influenza A	Stress	55
VCS4	Viral-Challenge	RV	Stress	334
EPIS	Epidemiological	None	Ill child	50
ANEXS	Animal Exper.	None	Stress, affiliation	43

Note. CV = corona virus; RSV = respiratory synctial virus; RV = rhinovirus; Psych Var = psychological variable; soc network = social network.

Psychological Stress and Susceptibility to Colds

Invasion of the body by a disease-causing agent is not sufficient cause for disease. Disease occurs when the immune system is compromised or unable to recognize the foreign material. When we began our work in the mid-1980s, evidence was accumulating that suggested that psychological stress could alter immune response in humans (e.g., review by Herbert & Cohen, 1993); however, it was still unclear whether stress effects on immunity were of the quality or quantity necessary to influence the body's ability to fight infectious disease (Cohen & Williamson, 1991; Laudenslager, 1987; O'Leary, 1990). Our work on stress and colds addressed two primary issues in this regard: (a) Does psychological stress increase susceptibility to infectious illness? and (b) How could stress "get under the skin" to influence our host resistance? We begin by describing a series of studies designed to answer these questions.

Stress Predicts Susceptibility to the Common Cold

In our first viral-challenge study (VCS1), we administered three questionnaires to assess psychological stress at baseline: a stressful life events scale, perceived stress scale, and negative affect scale. Participants were then exposed to one of five viruses that cause a common cold and monitored closely for infection and illness. We standardized the stress scores within each of the three scales and added them together to create a stress index. We found that the higher the score on the stress index, the greater was the probability of developing a clinical cold following viral exposure (Cohen, Tyrrell, & Smith, 1991, 1993). As apparent from Figure 1 (collapses across viruses), this was a graded relation with every increase in stress associated with an increase in risk. Moreover, the association occurred for all of the five viruses tested (three rhinovirus types, respiratory syncytial virus, and a corona virus). This association occurred independent of immunity to the virus at baseline as assessed by the amount of specific antibody to the challenge virus. It was also independent of age, sex, education, allergic status, body mass index, and season of the year. Finally, we examined whether we could explain the association between stress and colds by stress-related health behaviors (smoking, alcohol consumption, sleep quality, exercise, diet) or nonspecific quantitative measures of immune function (white blood cell counts and total immunoglobulin levels). None of the hypothesized mediators we assessed were able to explain the relation.

The Type of Stressor Matters

The second study (VCS2) focused on identifying the *types* of stressful life events that were associated with increased susceptibility to infectious illness (Cohen et al., 1998). Using an intensive stress interview technique, we demonstrated that there were two types of stressful life events strongly associated with greater susceptibility: enduring (1-month or longer) interpersonal problems with family and friends and enduring problems related to work (under- or unemployment). Moreover, across all types of events, the longer the stressful life event lasted, the greater was the risk for developing a clinical illness (Figure 2). These effects held across two rhinoviruses

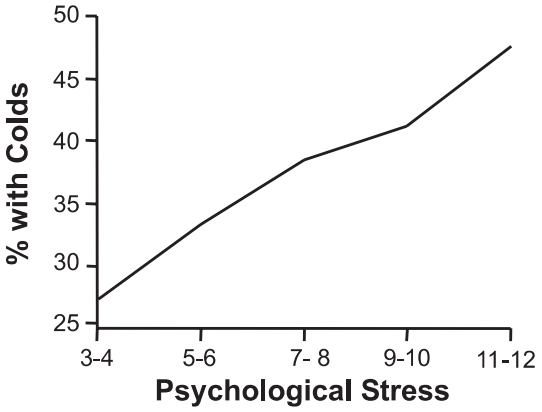

Figure 1. Increases in psychological stress are associated with increases in risk for developing a cold after exposure to a cold virus.
Note. The data are from "Psychological Stress and Susceptibility to the Common Cold," by S. Cohen, D. A. Tyrrell, & A. P. Smith, 1991, *New England Journal of Medicine, 325,* p. 609.

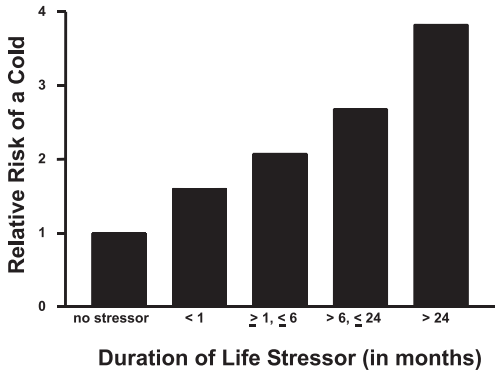

Figure 2. Increases in the duration of stressful events are associated with increased risk for developing a cold after exposure to a cold virus.

Note. Figure reprinted from "Types of Stressors that Increase Susceptibility to the Common Cold in Adults," by S. Cohen et al., 1998, *Health Psychology, 17,* p. 219. Copyright ©1998 by the American Psychological Association. Reproduced with permission.

we administered (RV39 & Hanks) and were equal for persons with and without prior immunity (specific antibody) to the challenge virus.

Finally, we examined the possibility that health behaviors, endocrine response (24-hour urine epinephrine, norepinephrine, and cortisol), or markers of immune status (natural killer cell cytotoxicity and white blood cell counts assessed at baseline) might constitute the pathways through which psychosocial factors influence susceptibility. Interestingly, we found that many of the proposed mediators were associated with susceptibility to clinical illness as predicted. Nonsmoking, regular exercise, and greater sleep efficiency (percent of time in bed sleeping) were all associated with *less* susceptibility to developing a cold (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Cohen, Tyrrell, Russell, Jarvis, & Smith, 1993), and higher 24-hour urinary epinephrine and norepinephrine were both associated with *greater* susceptibility (Cohen, Doyle, et al., 1997). However, these effects appeared to be relatively independent of the associations between psychological stress and susceptibility, and hence our data did not support these factors as contributors to the pathways linking psychosocial factors and disease resistance. Neither the immune measures nor the 24-hr urine cortisols were associated with susceptibility to clinical illness. In short, although we replicated and extended the association between psychological stress and disease resistance we found in the original study, we were still unable to identify any mediating pathways.

Stress Association with Colds is Mediated by Cytokine Regulation

Up until this point, the major outcome in our studies had been whether persons exposed to a virus develop a clinical illness (both infection and symptoms). More recently, we became interested in the possibility that stress influences resistance to respiratory infectious illness through its influence on proinflammatory cytokines. Proinflammatory cytokines are produced in response to infection and are thought to trigger the symptoms that are associated with upper respiratory viral infections. To address the role of cytokines, we altered our challenge model to focus on illness expression among infected persons. We selected only persons without previous exposure to the virus (no antibody to the challenge virus at study onset) and we chose to use an influenza A virus that results in infection in 98% or more of participants without previous exposure. We then examined the extent to which psychological stress predicted illness expression among the infected participants.

Our hypothesis was that stress may interfere with the body's ability to turn off cytokine production. Appropriate regulation would allow the production of enough cytokine to help rid the body of the virus but not so much that it produced a massive symptomatic response. If stress short-circuited the body's ability to turn off cytokine release, then it could trigger a severe symptomatic response. In a study of an influenza virus, we assessed the potential role of infection-induced local (in nasal secretions) release of the proinflammatory cytokine interleukin-6 (IL-6) as a mediator of the association between stress and illness expression (VCS3; Cohen, Doyle, & Skoner, 1999). After completing a measure of psychological stress (Perceived Stress Scale, PSS), 55 participants were experimentally infected with an influenza A virus. They were then monitored in quarantine for 8 days (baseline and 7 days after inoculation) for upper respiratory symptoms, mucus production, and levels of IL-6 in their nasal secretions. Analyses controlled (covaried) for age, gender, ethnicity, body mass, and season. The results for mucus weights and IL-6 are presented in Figures 3 and 4. Higher psychological stress assessed prior to the viral challenge was associated with greater symptom scores, greater mucus weights, and higher IL-6 lavage concentrations in response to infection. (Stress was not associated with basal levels of cytokines.) The IL-6 response was temporally related to both markers of illness expression, and mediation analyses indicated that these data were consistent with IL-6 acting as a major pathway through which stress was associated with increased symptoms of illness (Cohen et al., 1999). However, this is a correlational analysis, and this pattern of data is also consistent with rises in IL-6 occurring in response to tissue damage associated with illness symptoms.

Chronic Stress Influences Cortisol Regulation

How could stress interfere with the body's ability to turn off the proinflammatory cytokine response? A

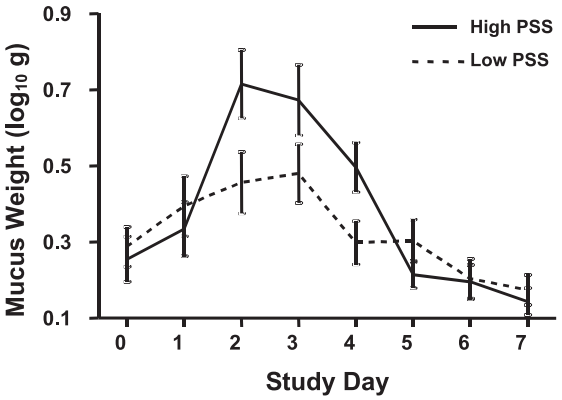

Figure 3. Increases in perceived stress (low = below median and high = above median) are associated with greater production of mucus (mucus weights) among participants infected with an influenza A virus. Viral inoculation occurred at the end of day 0. SEs are indicated.

Note. Figure reprinted from "Psychological Stress, Cytokine Production, and Severity of Upper Respiratory Illness," by S. Cohen, W. J. Doyle, & D. P. Skoner, 1999, *Psychosomatic Medicine, 61,* p. 177. Copyright © 1999 by the American Psychosomatic Society. Reproduced with permission.

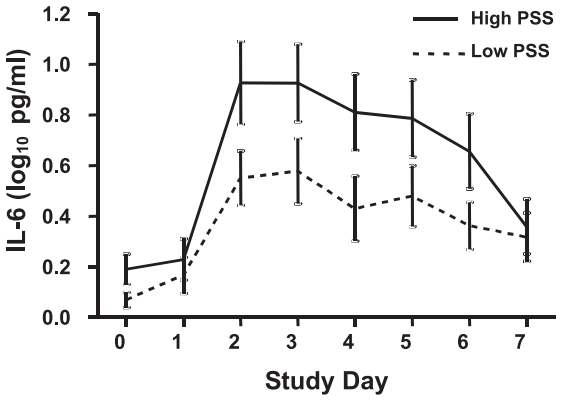

Figure 4. Increases in perceived stress (low = below median and high = above median) are associated with greater production of IL–6 in nasal secretions among participants infected with an influenza A virus. Viral inoculation occurred at the end of day 0. SEs are indicated.

Note. Figure reprinted from "Psychological Stress, Cytokine Production, and Severity of Upper Respiratory Illness," by S. Cohen, W. J. Doyle, & D. P. Skoner, 1999, *Psychosomatic Medicine, 61,* p. 178. Copyright © 1999 by the American Psychosomatic Society. Reproduced with permission.

likely culprit is the hormone cortisol. Cortisol release is triggered by psychological stress. Moreover, one of the functions of cortisol is to regulate (turn off) cytokine production. This picture is complicated, however, under chronic stressful conditions, because a feedback system often turns off the release of cortisol when there is too much in circulation. Moreover, receptors for cortisol on immune cells downregulate (turn in and become less sticky) when flooded with cortisol. In short, chronic stress may impair the immune system's capacity to respond to hormonal signals that terminate inflammation (Avitsur, Stark, & Sheridan, 2001; Stark et al., 2001).

To investigate this hypothesis, we studied a group of 50 healthy adults—25 parents of a young child with cancer and 25 matched control parents of healthy children (EPIS; Miller, Cohen, & Ritchey, 2002). We chose parents of cancer patients because they were experiencing a chronic and extremely stressful life event. When compared to control parents, parents of cancer patients reported more psychological distress and had *lower* cortisol levels (most notable during the morning hours). We also treated a blood sample from each participant with dexamethasone (dex)—a synthetic glucocorticoid (cortisol-like substance)—and then stimulated the cells to produce cytokine. When we added the dex to the blood samples from control sample, as expected, their cells produced less IL-6 than cells that were not treated with dex. The dex was turning off the cells' production of cytokine. When we added dex to the blood samples from the parents of cancer patients, the dex was significantly less effective in turning off cytokine production. These findings suggest that prolonged stress alters the course of inflammatory disease by decreasing cortisol's effectiveness in regulating proinflammatory cytokine response. This is consistent with our finding in VCS3 that stress was associated with increased production of IL-6 (suggesting decreased effectiveness of cortisol) and increased illness expression.

In sum, our work on stress and upper respiratory symptoms has led us to a somewhat unexpected conclusion. Stress effects may not be due to stress-elicited *suppression* of immune function. Instead, chronic stress may influence resistance to respiratory viruses by interfering with the immune system's ability to respond to hormonal signals that turn off the release of proinflammatory cytokines. Consequently, persons under stress produce too much cytokine (the immune system overresponds) that in turn triggers and prolongs the symptoms of upper respiratory infections.

Social Environments and Susceptibility to Colds

In VCS2, we found that enduring interpersonal problems with family and friends were associated with greater susceptibility to disease. Interpersonal conflict was presumed to be detrimental to health because it is a potent source of psychological stress (Cohen, 2004; Rook, 1984). However, there is also substantial evidence that our social networks can be beneficial to our health. We have distinguished between two types of models that describe how social relationships might benefit health outcomes: the stress-buffering model and the main effect model (Cohen, 1988, 2004; Cohen

& Wills, 1985). The stress-buffering model suggests that the benefits of social relationships derive from their role in protecting people from the pathogenic influences of stress. The main effect model predicts that the social environment's influence on health is independent of current stress level.

We have also emphasized the need to distinguish between different conceptions of social networks and supports (Cohen, 1988, 2004; Cohen & Wills, 1985). The relevant literature consists primarily of studies using limited numbers of structural measures of social groups such as network size and social integration and those using functional measures of social support such as availability or receipt of emotional, informational, and tangible support. Correlations between and within structural and functional groupings of measures tend to be small to moderate (Cohen, 1991). The two measures with the most consistent relations with health are *social integration* (having a diverse social network; e.g., being married, belonging to church and social groups, having close family and friends) and *social support* (the availability of social resources to help one cope in stressful situations). Social integration has consistently been associated with more positive health outcomes irrespective of whether persons are facing adversity or not, whereas measures of social support tend to be beneficial only in the presence of stress (Cohen, 2004; Cohen & Wills, 1985). In the following, we discuss some of our research on the role of social integration and social support in susceptibility to colds as well as in changes in physiological mechanisms that play a role in host resistance.

Social Integration is Associated with Greater Resistance to Disease

There is substantial evidence that those who are socially integrated, that is, those having multiple social roles (e.g., marriage, work, neighbors, friends, social groups, religious groups) are healthier and live longer than those who are not (Berkman, 1995; Cohen, 2004; Cohen, Gottlieb, & Underwood, 2000; Helgeson, Cohen, & Fritz, 1998; Seeman, 1996). Unfortunately, the mechanisms linking diverse networks to a broad range of diseases have not been identified. Infectious agents have recently been implicated in the development of a range of diseases not traditionally thought to have infectious etiologies such as coronary artery disease (Gupta & Camm, 1998), asthma (Kraft, Cassell, Pak, & Martin, 2002), and some cancers (Butel, 2000). We hypothesized that persons who had multiple social roles might be less susceptible to infectious disease and that this increase in host resistance might help explain associations between social integration and total morbidity and mortality. In VCS2, we assessed the role of social integration in susceptibility (Cohen, Doyle, et al., 1997). We used a scale we developed, the Social Network Index (Cohen, 1991), at baseline to assess social integration—the number of social roles (domains) in which a person has social contacts. As described earlier, participants were subsequently exposed to one of two rhinovirus types.

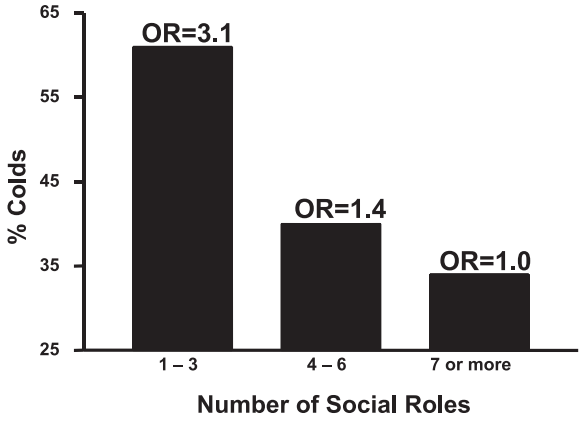

Figure 5. Greater numbers of social roles are associated with a lower risk for developing a cold among persons exposed to a cold virus.
Note. Data from "Social Ties and Susceptibility to the Common Cold," by S. Cohen, W. J. Doyle et al., 1997, *Journal of the American Medical Association, 277,* p. 1943.

The results are depicted in Figure 5. Greater numbers of social roles were associated with less susceptibility to clinical illness. This association occurred irrespective of the challenge virus. It was also independent of the stress associations reported previously. There were also no stress-by-social integration interactions and hence no evidence for a stress-buffering effect of social network diversity (not even a supportive pattern). Moreover, mere numbers of people in the social network (independent of roles) were *not* associated with disease susceptibility. The association between social networks and colds was unaffected by the addition of controls (covariates) for age, sex, season, body mass index, education, race, and immunity to the virus at baseline as assessed by specific antibody to the challenge virus.

Social Support Buffers the Effects of Stress on Disease

The previously described work focused on social integration, which is expected to have a direct effect (irrespective of stress level) on immunity and health. As noted earlier, we hypothesize that social support influences health through a different pathway (i.e., by protecting people from the potentially detrimental influences of stress; Cohen, 1988, 2004; Cohen & Wills, 1985). We were interested in experimentally manipulating chronic stress and obtaining objective measures of social interaction. To accomplish these goals, we conducted the next study with nonhuman primates. This

study addressed the question of whether close relationships buffer the effects of chronic stress on cellular immune response (ANEXS; Cohen, Kaplan, Cunnick, Manuck, & Rabin, 1992). There, 43 male cynomolgus monkeys were randomly assigned to stable or unstable social conditions for 26 months. Animals in the stable social condition remained in a cage with the same four animals over the course of the entire study. Those in the unstable condition were rotated every month so that at least three animals with whom they had not been housed in the previous month were substituted for animals previously in the cage. The proportion of time spent in affiliative behaviors was assessed by observations made twice weekly. T-cell immune response (mitogen stimulated proliferation) was assessed weekly for 3 weeks immediately following the 26 months of manipulation. Although immune response was relatively suppressed among animals in the unstable social condition, this suppression occurred primarily among animals with low levels of affiliation (stress by affiliation interaction; Figure 6). A similar stress-buffering analysis was applied in our study of parents of cancer patients (EPIS; Miller et al., 2002). In that case, we found that parents of children with cancer who reported the availability of material aid were protected from stress-associated effects (showed little glucocorticoid resistance; Figure 7). Both studies are consistent with the hypothesis that social support operates as a stress-buffer, protecting people (and monkeys) from the potential pathogenic influences of stress.

Childhood SES and Susceptibility to the Common Cold

SES during childhood as measured by living conditions, family income, and parental education and employment has been repeatedly associated with adult health status (Aber, Bennett, Conley, & Li, 1997; Gissler, Rahkonen, Jarvelin, & Hemminki, 1998; Nelson, 1992; Roberts & Power, 1996). Lower childhood SES has been reported to be a risk factor for mortality (Davey-Smith, Hart, Blane, Gillis, & Hawthorne, 1997; Davey-Smith, McCarron, Okasha, & McEwen, 2001; Nystrom, 1994; Vagero & Leon, 1994) primarily resulting from cardiovascular disease (Davey-Smith, Hart, Blane, & Hole, 1998; Frankel, Davey-Smith, & Gunnell, 1999; Heslop, Davey-Smith, Macleod, & Hart, 2001) but also from respiratory disease, stroke, and stomach and lung cancer (Davey-Smith et al., 1998). There is also evidence relating lower childhood SES to increased risk for adult cardiovascular disease (Poulton, Caspi, Milne, Thomson, Taylor, Sears, et al., 2002; Wannamethee, Whincup, Shaper, & Walker, 1996), chronic bronchitis (Marmot, Shipley, Brunner, & Hemingway, 2001), and periodontal disease (Poulton et al., 2002).

As mentioned earlier, infectious agents have recently been implicated in the development of a range of diseases not traditionally thought to have infectious etiologies. Hence, an association between childhood SES and adult host resistance would suggest a hypothetical pathway through which childhood experiences might influence a broad range of health outcomes. To pursue this possibility, we conducted a preliminary study using the viral-challenge paradigm to determine if childhood SES is associated with adult susceptibility to infectious illness, and, if so, whether the effect is limited to a critical period of low SES exposure, can be undone by changes in childhood SES, and is explained by adult SES.

In VCS4, prior to being exposed to the virus, we had volunteers report their own and their parents' level of education and the ages during their childhood when their parents owned their homes (Cohen, Doyle, Turner, Alper, & Skoner, 2004). Volunteers' current

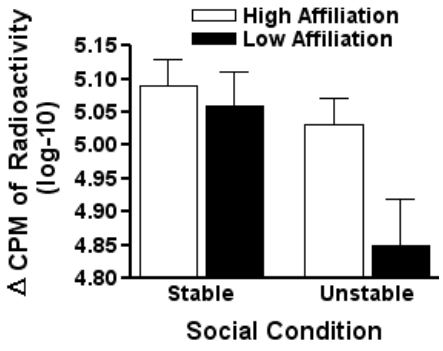

Figure 6. Chronic stress (unstable social environment) interacts with affiliation in predicting cellular immune response in cynomolgus macaques.

Note. Data from "Chronic Social Stress, Affiliation and Cellular Immune Response in Nonhuman Primates," by S. Cohen et al., 1992, *Psychological Science, 3,* p. 303.

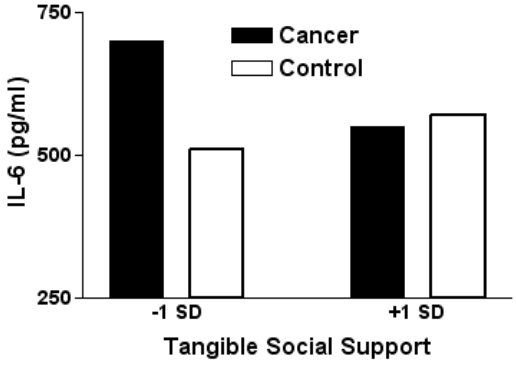

Figure 7. Stress (child with cancer of matched control) and instrumental social support interact in predicting the ability of dexamethasone to suppress IL–6 production.

Note. Data from "Chronic Psychological Stress and the Regulation of Pro-Inflammatory Cytokines: A Glucocorticoid Resistance Model," by G. E. Miller et al., 2002, *Health Psychology, 21,* p. 537.

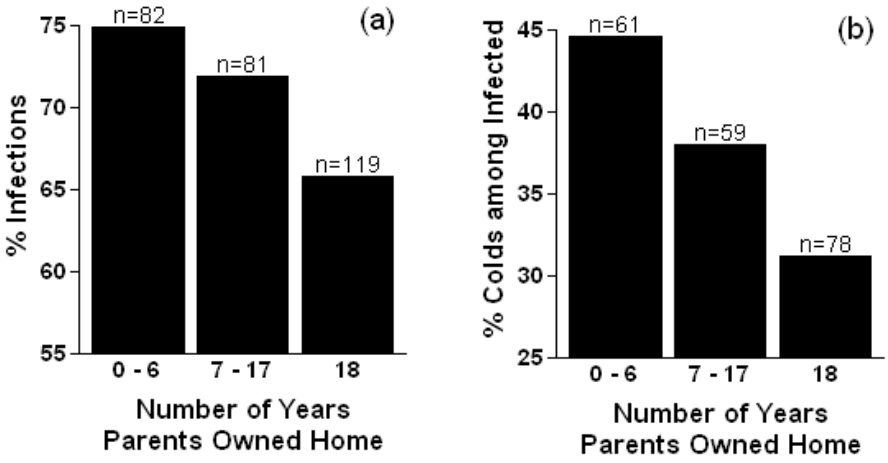

Figure 8. Adjusted (for standard controls) incidences of infection (a) and clinical illness among infected volunteers (b) decrease as a function of years of parental home ownership (tertiled).
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home ownership was recorded from real estate records. Subsequently, they were given nasal drops containing one of two rhinoviruses and monitored in quarantine for infection and signs and symptoms of a common cold. For both viruses, susceptibility to colds decreased with the number of childhood years during which their parents owned their home (odds ratios by tertiles adjusted for demographics, body mass, and season and prechallenge viral-specific immunity were 3.7 for fewest years, 2.6 the mid tertile of number of years, and 1 for the most years). This decreased risk was attributable to both lower risk for infection and lower risk for illness in infected participants (Figure 8). Moreover, those whose parents did not own their home during their early life but did during adolescence were at the same increased risk as those whose parents never owned their home. These associations were independent of parent education level and of adult education, home ownership, and personality characteristics. Finally, we assessed the role of home ownership at different ages by creating ownership variables based on 2-year intervals starting from 1–2. As apparent from Figure 9, the largest associations occurred early in life. The later the experience with parental home ownership, the less its association with disease risk. These data suggest that very early (or possibly even prenatal) experiences are responsible for the association of childhood SES and susceptibility to colds as adults.

In short, a marker of low income and wealth during early childhood was associated with decreased resistance to upper respiratory infections in adulthood. Higher risk was not ameliorated by higher SES during adolescence and is independent of adult SES. Our ongoing work is looking more closely at the nature of

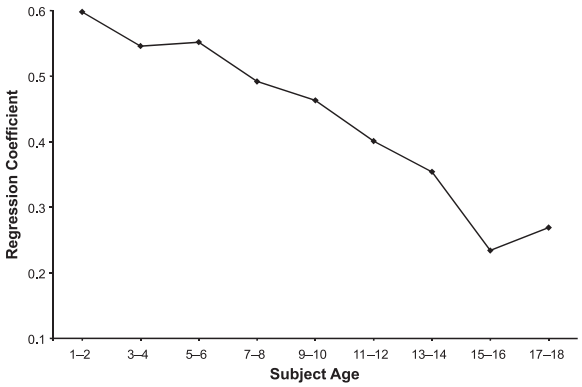

Figure 9. Adjusted effect size (regression coefficient) for the associations between parental home ownership and adult susceptibility to colds decrease with age of exposure.
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childhood environments that might influence adult health (social and physical environments, parental behaviors, etc.) and attempting to identify specific aspects of immunity and behavior that might mediate these associations. We are also exploring alternative explanations for the association such as parental age, family stability, and single parent households.

Summary

This article provided an overview of three of the areas of research we have pursued. In our early work, we found that psychological stress was associated with

greater susceptibility to colds and influenza, that this risk increased with the duration of major stressful events, and that the increased risk is probably attributable to stress-induced and endocrine mediated disruption of the regulation of proinflammatory cytokines. In our work on social environments, we found that social integration predicted susceptibility with persons with more diverse social networks less susceptible to disease. This association occurred independently of previous exposure to the challenge-viruses as indicated by baseline viral-specific antibody. Moreover, support and affiliative behaviors operated as stress-buffers, protecting (in this case) animals from stress-triggered immunosuppression and humans from stress-triggered insensitivity to hormonal control of cytokine production. Finally, we discussed our preliminary work on the potential role of childhood SES in adult susceptibility. We found not only that parental home ownership predicted susceptibility during childhood but that very early childhood exposure was the most critical. In fact, exposure during adolescence did not contribute much and (when SES in adolescence was greater than it was in childhood) did not buffer the effects of early exposure. The association between childhood SES and adult susceptibility was not mediated by current (adulthood) SES.

In sum, we have been fortunate to have the opportunity to work with a paradigm that allowed us to intentionally expose people to an infectious virus and objectively determine their host resistance to disease. This work has been exceptionally exciting in two ways. First, it has demonstrated that a wide range of different social and psychological factors are likely to influence our ability to fight off infectious illness. Second, it has allowed us to begin to understand the psychological and biological mechanisms that are responsible for these effects.

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