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Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry

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Abstract

The present report meta-analyzes more than 300 empirical articles describing a relationship between psychological stress and parameters of the immune system in human participants. Acute stressors (lasting minutes) were associated with potentially adaptive upregulation of some parameters of natural immunity and downregulation of some functions of specific immunity. Brief naturalistic stressors (such as exams) tended to suppress cellular immunity while preserving humoral immunity. Chronic stressors were associated with suppression of both cellular and humoral measures. Effects of event sequences varied according to the kind of event (trauma vs. loss). Subjective reports of stress generally did not associate with immune change. In some cases, physical vulnerability as a function of age or disease also increased vulnerability to immune change during stressors.

Since the dawn of time, organisms have been subject to evolutionary pressure from the environment. The ability to respond to environmental threats or stressors such as predation or natural disaster enhanced survival and therefore reproductive capacity, and physiological responses that supported such responses could be selected for. In mammals, these responses include changes that increase the delivery of oxygen and glucose to the heart and the large skeletal muscles. The result is physiological support for adaptive behaviors such as “fight or flight.” Immune responses to stressful situations may be part of these adaptive responses because, in addition to the risk inherent in the situation (e.g., a predator), fighting and fleeing carries the risk of injury and subsequent entry of infectious agents into the bloodstream or skin. Any wound in the skin is likely to contain pathogens that could multiply and cause infection (Williams & Leaper, 1998). Stress-induced changes in the immune system that could accelerate wound repair and help prevent infections from taking hold would therefore be adaptive and selected along with other physiological changes that increased evolutionary fitness.

Modern humans rarely encounter many of the stimuli that commonly evoked fight-or-flight responses for their ancestors, such as predation or inclement weather without protection. However, human physiological response continues to reflect the demands of earlier environments. Threats that do not require a physical response (e.g., academic exams) may therefore have physical consequences, including changes in the immune system. Indeed, over the past 30 years, more than 300 studies have been done on stress and immunity in humans, and together they have shown that psychological challenges are capable of modifying various features of the immune response. In this article we attempt to consolidate empirical knowledge about psychological stress and the human immune system through meta-analysis. Both the construct of stress and the human immune system are complex, and both could consume book-

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length reviews. Our review, therefore, focuses on those aspects that are most often represented in the stress and immunity literature and therefore directly relevant to the meta-analysis.

Conceptualizing Stress

Despite nearly a century of research on various aspects of stress, investigators still find it difficult to achieve consensus on a satisfactory definition of this concept. Most of the studies contributing to this review simply define *stress* as circumstances that most people would find stressful, that is, stressors. We adopted Elliot and Eisdorfer's (1982) taxonomy to characterize these stressors. This taxonomy has the advantage of distinguishing among stressors on two important dimensions: duration and course (e.g., discrete vs. continuous). The taxonomy includes five categories of stressors. *Acute time-limited stressors* involve laboratory challenges such as public speaking or mental arithmetic. *Brief naturalistic stressors*, such as academic examinations, involve a person confronting a real-life short-term challenge. In *stressful event sequences*, a focal event, such as the loss of a spouse or a major natural disaster, gives rise to a series of related challenges. Although affected individuals usually do not know exactly when these challenges will subside, they have a clear sense that at some point in the future they will. *Chronic stressors*, unlike the other demands we have described, usually pervade a person's life, forcing him or her to restructure his or her identity or social roles. Another feature of chronic stressors is their stability—the person either does not know whether or when the challenge will end or can be certain that it will never end. Examples of chronic stressors include suffering a traumatic injury that leads to physical disability, providing care for a spouse with severe dementia, or being a refugee forced out of one's native country by war. *Distant stressors* are traumatic experiences that occurred in the distant past yet have the potential to continue modifying immune system function because of their long-lasting cognitive and emotional sequelae (Baum, Cohen, & Hall, 1993). Examples of distant stressors include having been sexually assaulted as a child, having witnessed the death of a fellow soldier during combat, and having been a prisoner of war.

In addition to the presence of difficult circumstances, investigators also use life-event interviews and life-event checklists to capture the total number of different stressors encountered over a specified time frame. Depending on the instrument, the focus of these assessments can be either major life events (e.g., getting divorced, going bankrupt) or minor daily hassles (e.g., getting a speeding ticket, having to clean up a mess in the house). With the more sophisticated instruments, judges then code stressor severity according to how the average person in similar biographical circumstances would respond (e.g., S. Cohen et al., 1998; Evans et al., 1995).

A smaller number of studies enrolled large populations of adults who were not experiencing any specific difficulty and examined whether their immune responses varied according to their reports of perceived stress, intrusive thoughts, or both. Other studies have examined stressed populations, in which a larger range of subjective responses may be detected. This work grows out of the view that people's biological responses to stressful circumstances are heavily dependent on their appraisals of the situation and cognitive and emotional responses to it (Baum et al., 1993; Frankenhauser, 1975; Tomaka, Blascovich, Kibler, & Ernst, 1997).

Overview of the Immune System

As many behavioral scientists are unfamiliar with the details of the immune system, we provide a brief overview. For a more complete treatment, the reader is directed to the sources for the information presented here (Benjamini, Coico, & Sunshine, 2000; Janeway & Travers, 1997; Rabin, 1999). Critical characteristics of various immune components and assays are also listed in Table 1.

Components of the Immune System

There are several useful ways of dividing elements of the immune response. For the purposes of understanding the relationship of psychosocial stressors to the immune system, it is useful to distinguish between *natural* and *specific* immunity. Natural immunity is an immune response that is characteristic not only of mammals but also lower order organisms such as sponges. Cells involved in natural immunity do not provide defense against any particular pathogen; rather, they are all-purpose cells that can attack a number of different pathogens[1] and do so in a relatively short time frame (minutes to hours) when challenged. The largest group of cells involved in natural immunity is the granulocytes. These cells include the *neutrophil* and the *macrophage*, phagocytic cells that, as their name implies, eat their targets. The generalized response mounted by these cells is *inflammation*, in which neutrophils and macrophages congregate at the site of injury or infection, release toxic substances such as oxygen radicals that damage invaders, and phagocytose both invaders and damaged tissue. Macrophages in particular also release communication molecules, or *cytokines*, that have broad effects on the organism, including fever and inflammation, and also promote wound healing. These proinflammatory cytokines include interleukin(IL)-1, IL-6, and tumor necrosis factor alpha (TNFα). Other granulocytes include the mast cell and the eosinophil, which are involved in parasitic defense and allergy.

Another cell involved in natural immunity is the natural killer cell. Natural killer cells recognize the lack of a self-tissue molecule on the surface of cells (characteristic of many kinds of virally infected and some cancerous cells) and lyse those cells by releasing toxic substances on them. Natural killer cells are thought to be important in limiting the early phases of viral infections, before specific immunity becomes effective, and in attacking self-cells that have become malignant.

Finally, complement is a family of proteins involved in natural immunity. Complement protein bound to microorganisms can up-regulate phagocytosis and inflammation. Complement can also aid in antibody-mediated immunity (discussed below as part of the specific immune response).

Specific immunity is characterized by greater specificity and less speed than the natural immune response. Lymphocytes have receptor sites on their cell surfaces. The receptor on each cell fits with one and only one small molecular shape, or antigen, on a given invader and therefore responds to one and only one kind of invader. When activated, these antigen-specific cells divide to create a population of cells with the same antigen specificity in a process called *clonal proliferation*, or the *proliferative response*. Although this process is efficient in terms of the number of cells that have to be supported on a day-to-day basis, it creates a delay of up to several days before a full defense is mounted, and the body must rely on natural immunity to contain the infection during this time.

There are three types of lymphocytes that mediate specific immunity: T-helper cells, T-cytotoxic cells, and B cells. The main function of T-helper cells is to produce cytokines that direct and amplify the rest of the immune response. T-cytotoxic cells recognize antigen expressed by cells that are infected with viruses or otherwise compromised (e.g., cancer cells) and lyse those cells. B cells produce soluble proteins called *antibody* that can perform a number of functions, including neutralizing bacterial toxins, binding to free virus to prevent its entry into cells, and opsonization, in which a coating of antibody increases the effectiveness of natural

[1]The term *pathogen* is used here to refer to microorganisms that can cause disease. This term is most appropriate in the evolutionary context we proposed in the article's introduction because it focuses on susceptibility to infection. However, the reader should be aware that pathogens are only a subset of *antigens*, that is, all substances that evoke an immune response. Other antigenic substances include, for example, transformed self-cells (i.e., cancer cells), transplanted tissue, and allergens (i.e., antigens that evoke an allergic response).

immunity. There are five kinds of antibody: Immunoglobulin (Ig) A is found in secretions, IgE binds to mast cells and is involved in allergy, IgM is a large molecule that clears antigen from the bloodstream, IgG is a smaller antibody that diffuses into tissue and crosses the placenta, and IgD is of unknown significance but may be produced by immature B cells.

An important immunological development is the recognition that specific immunity in humans is composed of cellular and humoral responses. Cellular immune responses are mounted against intracellular pathogens like viruses and are coordinated by a subset of T-helper lymphocytes called *Th1* cells. In the Th1 response, the T-helper cell produces cytokines, including IL-2 and interferon gamma (IFNγ). These cytokines selectively activate T-cytotoxic cells as well as natural killer cells. Humoral immune responses are mounted against extracellular pathogens such as parasites and bacteria; they are coordinated by a subset of T-helper lymphocytes called *Th2* cells. In the Th2 response, the T-helper cell produces different cytokines, including IL-4 and IL-10, which selectively activate B cells and mast cells to combat extracellular pathogens.

Immune Assays

Immune assays can quantify cells, proteins, or functions. The most basic parameter is a simple count of the number of cells of different subtypes (e.g., neutrophils, macrophages), typically from peripheral blood. It is important to have an adequate number of different types of immune cells in the correct proportions. However, the normal range for these enumerative parameters is quite large, so that "correct" numbers and proportions can cover a wide range, and small changes are unlikely to have any clinical significance in healthy humans.

Protein production—either of antibody or cytokines—can be measured in vitro by stimulating cells and measuring protein in the supernatant or in vivo by measuring protein in peripheral blood. For both antibody and cytokine, higher protein production may represent a more robust immune response that can confer protection against disease. Two exceptions are levels of proinflammatory cytokines (IL-1, IL-6, and TNFα) and antibody against latent virus. Proinflammatory cytokines are increased with systemic inflammation, a risk factor for poorer health resulting from cardiac disease, diabetes mellitus, or osteoporosis (Ershler & Keller, 2000; Luster, 1998; Papanicoloaou, Wilder, Manolagas, & Chrousos, 1998). Antibody production against latent virus occurs when viral replication triggers the immune system to produce antibodies in an effort to contain the infection. Most people become infected with latent viruses such as Epstein-Barr virus during adolescence and remain asymptomatically infected for the rest of their lives. Various processes can activate these latent viruses, however, so that they begin actively replicating. These processes may include a breakdown in cellular immune response (Jenkins & Baum, 1995). Higher antibody against latent viruses, therefore, may indicate poorer immune control over the virus.

Functional assays, which are performed in vitro, measure the ability of cells to perform specific activities. In each case, higher values may represent more effective immune function. Neutrophils' function can be quantified by their ability to migrate in a laboratory assay and their ability to release oxygen radicals. The natural killer cytotoxicity assay measures the ability of natural killer cells to lyse a sensitive target cell line. Lymphocyte proliferation can be stimulated with mitogens that bypass antigen specificity to activate cells or by stimulating the T cell receptor.

Pathways Between Stress and the Immune System

How could stress "get inside the body" to affect the immune response? First, sympathetic fibers descend from the brain into both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid tissues (Felten & Felten, 1994). These fibers can release a wide variety of substances that influence immune responses by binding to receptors on white blood

cells (Ader, Cohen, & Felten, 1995; Felten & Felten, 1994; Kemeny, Solomon, Morley, & Herbert, 1992; Rabin, 1999). Though all lymphocytes have adrenergic receptors, differential density and sensitivity of adrenergic receptors on lymphocytes may affect responsiveness to stress among cell subsets. For example, natural killer cells have both high-density and high-affinity β_2-adrenergic receptors, B cells have high density but lower affinity, and T cells have the lowest density (Anstead, Hunt, Carlson, & Burki, 1998; Landmann, 1992; Maisel, Fowler, Rearden, Motulsky, & Michel, 1989). Second, the hypothalamic–pituitary–adrenal axis, the sympathetic–adrenal–medullary axis, and the hypothalamic–pituitary–ovarian axis secrete the adrenal hormones epinephrine, norepinephrine, and cortisol; the pituitary hormones prolactin and growth hormone; and the brain peptides melatonin, β-endorphin, and enkephalin. These substances bind to specific receptors on white blood cells and have diverse regulatory effects on their distribution and function (Ader, Felten, & Cohen, 2001). Third, people's efforts to manage the demands of stressful experience sometimes lead them to engage in behaviors—such as alcohol use or changes in sleeping patterns—that also could modify immune system processes (Kiecolt-Glaser & Glaser, 1988). Thus, behavior represents a potentially important pathway linking stress with the immune system.

Maier and Watkins (1998) proposed an even closer relationship between stress and immune function: that the immunological changes associated with stress were adapted from the immunological changes in response to infection. Immunological activation in mammals results in a syndrome called *sickness behavior*, which consists of behavioral changes such as reduction in activity, social interaction, and sexual activity, as well as increased responsiveness to pain, anorexia, and depressed mood. This syndrome is probably adaptive in that it results in energy conservation at a time when such energy is best directed toward fighting infection. Maier and Watkins drew parallels between the behavioral, neuroendo-crine, and thermoregulatory responses to sickness and stress. The common thread between the two is the energy mobilization and redirection that is necessary to fight attackers both within and without.

Models of Stress, the Immune System, and Health

Conceptualizations of the nature of the relationship between stress and the immune system have changed over time. Selye's (1975) finding of thymic involution led to an initial model in which stress is broadly immunosuppressive. Early human studies supported this model, reporting that chronic forms of stress were accompanied by reduced natural killer cell cytotoxicity, suppressed lymphocyte proliferative responses, and blunted humoral responses to immunization (see S. Cohen, Miller, & Rabin, 2001; Herbert & Cohen, 1993;Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996, for reviews). Diminished immune responses of this nature were assumed to be responsible for the heightened incidence of infectious and neoplastic diseases found among chronically stressed individuals (Andersen, Kiecolt-Glaser, & Glaser, 1994; S. Cohen & Williamson, 1991).

Although the global immunosuppression model enjoyed long popularity and continues to be influential, the broad decreases in immune function it predicts would not have been evolutionarily adaptive in life-threatening circumstances. Dhabhar and McEwen (1997, 2001) proposed that acute fight-or-flight stressors should instead cause redistribution of immune cells into the compartments in which they can act the most quickly and efficiently against invaders. In a series of experiments with mice, they found that during acute stress, T cells selectively redistributed into the skin, where they contributed to enhancement of the immune response. In contrast, during chronic stress, T cells were shunted away from the skin, and the immune response to skin test challenge was diminished (Dhabhar & McEwen, 1997). On the basis of these findings they proposed a biphasic model in which acute stress enhances, and chronic stress suppresses, the immune response.

A modification of this model posits that short-term changes in all components of the immune system (natural and specific) are unlikely to occur because they would expend too much energy to be adaptive in life-threatening circumstances. Instead, stress should shift the balance of the immune response toward activating natural processes and diminishing specific processes. The premise underlying this model is that natural immune responses are better suited to managing the potential complications of life-threatening situations than specific immune responses because they can unfold much more rapidly, are subject to fewer inhibitory constraints, and require less energy to be diverted from other bodily systems that support the fight-or-flight response (Dopp, Miller, Myers, & Fahey, 2000; Sapolsky, 1998).

Even with this modification of the biphasic model, neither it nor the global immunosuppression model sufficiently explains findings that link chronic stress with both disease outcomes associated with inadequate immunity (infectious and neoplastic disease) and disease outcomes associated with excessive immune activity (allergic and autoimmune disease). To resolve this paradox, some researchers have chosen to focus on how chronic stress might shift the balance of the immune response. The most well-known of these models hypothesizes that chronic stress elicits simultaneous enhancement and suppression of the immune response by altering patterns of cytokine secretion (Marshall et al., 1998). Th1 cytokines, which activate cellular immunity to provide defense against many kinds of infection and some kinds of neoplastic disease, are suppressed. This suppression has permissive effects on production of Th2 cytokines, which activate humoral immunity and exacerbate allergy and many kinds of autoimmune disease. This shift can occur via the effects of stress hormones such as cortisol (Chiappelli, Manfrini, Franceschi, Cossarizza, & Black, 1994). Th1-to-Th2 shift changes the balance of the immune response without necessarily changing the overall level of activation or function within the system. Because a diminished Th1-mediated cellular immune response could increase vulnerability to infectious and neoplastic disease, and an enhanced Th-2 mediated humoral immune response could increase vulnerability to autoimmune and allergic diseases, this cytokine shift model also is able to reconcile patterns of stress-related immune change with patterns of stress-related disease outcomes (Marshall et al., 1998).

Who Is Vulnerable to Stress-Induced Immune Changes?

If the stress response in the immune system evolved, a healthy organism should not be adversely affected by activation of this response because such an effect would likely have been selected against. Although there is direct evidence that stress-related immunosuppression can increase vulnerability to disease in animals (e.g., Ben Eliyahu, Shakhar, Page, Stefanski, & Shakhar, 2000; Quan et al., 2001; Shavit et al., 1985; Sheridan et al., 1998), there is little or no evidence linking stress-related immune change in healthy humans to disease vulnerability. Even large stress-induced immune changes can have small clinical consequences because of the redundancy of the immune system's components or because they do not persist for a sufficient duration to enhance disease susceptibility. In short, the immune system is remarkably flexible and capable of substantial change without compromising an otherwise healthy host.

However, the flexibility of the immune system can be compromised by age and disease. As humans age, the immune system becomes senescent (Boucher et al., 1998; Wikby, Johansson, Ferguson, & Olsson, 1994). As a consequence, older adults are less able to respond to vaccines and mount cellular immune responses, which in turn may contribute to early mortality (Ferguson, Wikby, Maxson, Olsson, & Johansson, 1995; Wayne, Rhyne, Garry, & Goodwin, 1990). The decreased ability of the immune system to respond to stimulation is one indicator of its loss of flexibility.

Loss of self-regulation is also characteristic of disease states. In autoimmune disease, for example, the immune system treats self-tissue as an invader, attacking it and causing pathology

such as multiple sclerosis, rheumatoid arthritis, Crohn's disease, and lupus. Immune reactions can also be exaggerated and pathological, as in asthma, and suggest loss of self-regulation. Finally, infection with HIV progressively incapacitates T-helper cells, leading to loss of the regulation usually provided by these cells. Although each of these diseases has distinct clinical consequences, the change in the immune system from flexible and balanced to inflexible and unbalanced suggests increased vulnerability to stress-related immune dysregulation; furthermore, dysregulation in the presence of disease may have clinical consequences (e.g., Bower, Kemeny, Taylor, & Fahey, 1998).

The Present Analysis

We performed a meta-analysis of published results linking stress and the immune system. We feel that this area is in particular need of a quantitative review because of the methodological nature of most studies in this area. For practical and economic reasons, many psychoneuroimmunology studies have a relatively small sample size, creating the possibility of Type II error. Furthermore, many studies examine a broad range of immunological parameters, creating the possibility of Type I error. A quantitative review, of which meta-analysis is the best example, can better distinguish reliable effects from those arising from both Type I and Type II error than can a qualitative review.

We combined studies in such a way as to test the models of stress and immune change reviewed above. First, we examined each stressor type separately, yielding separate effects for stressors of different duration and trajectory. Second, we examined both healthy and medical populations, allowing comparison of the effects of stress on resilient and vulnerable populations; along the same lines, we also examined the effects of age. Finally, we examined all immune parameters separately so that patterns of response (e.g., global immunosuppression vs. cytokine shift) would be clearer.

Method

Article Identification

Articles for the meta-analysis were identified through computerized literature searches and searches of reference lists. MEDLINE and PsycINFO were searched for the years 1960 –2001. Following the example of Herbert and Cohen (1993), we used the terms *stress*, *hassles*, and *life events* in combination with the term *immune* to search both databases. The reference lists of 11 review articles on stress and the immune system (Benschop, Geenen, et al., 1998; Biondi, 2001; Cacioppo, 1994; S. Cohen & Herbert, 1996; S. Cohen et al., 2001; Herbert & Cohen, 1993; Kiecolt-Glaser, Cacioppo, Malarkey, & Glaser, 1992; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Maier, Watkins, & Fleshner, 1994; O'Leary, 1990; Zorrilla et al., 2001) were then searched to identify additional articles.

We selected only articles that met a number of inclusion criteria. The first criterion was that the work had to include a measure of stress. This criterion could be met if a sample experiencing a stressor was compared with an unstressed control group, if a sample experiencing a stressor was compared with itself at a baseline that could reasonably be considered low stress, or if differing degrees of stress in a sample were assessed with an explicit measure of stress. This criterion was not met if, for example, anxiety—an affective state—was used as a proxy for stress, or it seemed likely that a "baseline" assessment occurred during periods of significant stress. The second criterion was that the stressor had to be psychosocial. Stressors that included a significant physical element such as pain, cold, or physical exhaustion were eliminated (e.g., Antarctic isolation, space flight, military training). The third criterion was that the work had to include a measure of the immune system. This criterion was met by any enumerative or functional in vitro or in vivo immune assay. However, clinical disease outcomes such as HIV

progression or rhinovirus infection did not meet this criterion. Finally, we eliminated articles from which a meaningful effect size could not be abstracted. For example, when between- and within-subjects observations were treated as independent, the reported effect was likely to be inflated. In a few cases, effects of stress and clinical status were confounded—that is, a stressed clinical group was compared with an unstressed healthy group—and hence these studies were excluded from the meta-analysis.

Stressor Classification

We coded stressors in the articles into five classes: acute time-limited, brief naturalistic, event sequence, chronic, and distant. The most difficult distinctions among event sequence, chronic, and distant stressors were based on temporal and qualitative considerations. Event sequences included discrete stressors occurring 1 year or less before immune assessment and could be of any severity. These were most often normative stressors such as bereavement. Chronic stressors were ongoing stressors such as caregiving and disability. Distant stressors were severe, traumatic events that could meet the stressor criterion for posttraumatic stress disorder (American Psychiatric Association, 1994), such as combat exposure or abuse, and had happened more than 1 year before immune assessment. Most stressors in this category occurred 5 to 10 years before immune assessment. Disagreements in stressor classification were resolved by consensus. Subgroups for moderator analyses were similarly decided.

The Meta-Analysis

Overview of procedures—Meta-analysis is a tool for synthesizing research findings. It proceeds in two phases. In the first, effect sizes are computed for each study. An effect size represents the magnitude of the relationship between two variables, independent of sample size. In this context it can be viewed as a measure of how much two groups, one experiencing a stressor and the other not, differ on a specific immune outcome. In the second phase, effect sizes from individual studies are combined to arrive at an aggregate effect size for each immune outcome of interest.

We used Pearson's *r* as the effect size metric in this meta-analysis. Effect sizes for individual studies were computed using descriptive statistics presented in the original published reports. When these statistics were not available, we requested them from authors. This strategy was successful in most circumstances. To compute Pearson's *r* from descriptive statistics in between-subjects designs, we subtracted the control group mean from the stressed group mean and divided this value by the pooled sample standard deviation. The value that emerged from this computation, known as Cohen's *d*, was then converted into a Pearson's *r* by taking the square root of the quantity $d^2/(d^2 + 4)$. (See Rosenthal, 1994.) To compute Pearson's *r* from descriptive statistics in within-subjects designs, we subtracted the group mean at baseline from the group mean during stress and divided this quantity by the sample standard deviation at baseline. This *d* value was converted into a Pearson's *r* by taking the square root of the quantity $d^2/(d^2 + 4)$. In cases in which descriptive statistics were not available, Pearson's *r* was computed from inferential statistics using standard formulae (Rosenthal, 1994). These formulae had to be modified slightly for studies that used within-subjects designs because effect sizes are systematically overestimated when they are calculated from repeated measures test statistics (Dunlap, Cortina, Vaslow, & Burke, 1996). In these situations we derived effect size estimates using the formula $d = t_c[2\ (1 - r)]^{1/2}$, where t_c corresponds to the value of the *t* statistic for correlated measures, and *r* corresponds to the value of the correlation between outcome measures at pretest and posttest (Dunlap et al., 1996). Because very few studies reported the value of *r*, we used a value of .60 to compute effect sizes in this meta-analysis. This represents the average correlation between pre-stress and poststress measures of immune function in a series of studies performed in our laboratories. To ensure that the meta-analytic findings were robust to variations in *r*, we conducted follow-up analyses using *r* values ranging from .45 to .

75. Very similar findings emerged from these analyses, suggesting that the values we present below are reliable estimates of effect size. If anything, they are probably conservative estimates, because the pre–post correlation between immune measures often is substantially lower than .60.

The effect size estimates from individual studies were subsequently aggregated using random-effects models with the software program Comprehensive Meta-Analysis (Borenstein & Rothstein, 1999). The random-effects model views each study in a meta-analysis as a random observation drawn from a universe of potential investigations. As such, it assumes that the magnitude of the relationship between stress and the immune system differs across studies as a result of random variance associated with sampling error and differences across individuals in the processes of interest. Because of these assumptions, random-effects models not only permit one to draw inferences about studies that have been done but also to generalize to studies that might be done in the future (Raudenbush, 1994; Shadish & Haddock, 1994). It also bears noting that in the population of studies on stress and immunity there is likely to be a fair amount of nonrandom variance, as researchers who examine ostensibly similar phenomena may still differ in terms of the samples they recruit, the operational definition of stress they use, and the laboratory methods they utilize to assess a specific immune process.

Separate random-effects models were computed for each immune outcome included in the meta-analysis. Prior to computing the random-effects model, *r* values derived from each study were *z*-transformed by the software program, as recommended by Shadish and Haddock (1994), to stabilize variance. The *z* values were later back-transformed into *r* values to facilitate interpretation of the meta-analytic findings. In the end, each random-effects model yielded an aggregate weighted effect size *r*, which can be interpreted the same way as a correlation coefficient, ranging in value from −1.00 to 1.00. Each *r* statistic was weighted before aggregation by multiplying its value by the inverse of its variance; this procedure enabled larger studies to contribute to effect size estimates to a greater extent than smaller ones. Weighting effect sizes is important because larger studies provide more accurate estimates of true population parameters (Shadish & Haddock, 1994). After each aggregate effect size had been derived, we computed 95% confidence intervals around it, assessed whether it was statistically significant, and computed a heterogeneity coefficient to determine whether the studies contributing to it had yielded consistent findings. Following convention, aggregate effect sizes were considered statistically different from zero when (a) their corresponding *z* value was greater than 1.96 and (b) the 95% confidence intervals around them did not include the value zero (Rosenthal, 1991; Shadish & Haddock, 1994).

To determine whether the studies contributing to each aggregate effect size shared a common population value, we computed the heterogeneity statistic *Q* (Shadish & Haddock, 1994). This statistic is chi-square distributed with $k - 1$ degrees of freedom, where *k* represents the number of independent effect sizes included. When a statistically significant heterogeneity test emerged, we searched for moderators (characteristics of the participants, stressful experience, or measurement strategy) that could explain the variability across studies. The first step in this process involved estimating correlations between participant characteristics (e.g., mean age, percentage female) and immune effects to examine whether the strength of effects varied according to demographics. When it was possible to do so, we then stratified the studies according to characteristics of the stressful experience (e.g., duration, quality) or the measurement strategy (e.g., interview, checklist), and computed separate random-effects analyses for each subgroup.

Handling missing data—Occasionally authors of studies failed to report the descriptive or inferential statistics needed to compute an effect size. In some of these cases, the authors noted that there was a significant difference between a stressed and control group. When this

occurred, we computed effect sizes assuming that *p* values were equivalent to .05. This represents a conservative approach because the actual *p* values were probably smaller. In other cases, the authors noted that a stressed and control group did not differ with respect to an immune outcome, but failed to provide any further statistical information. When this occurred, we computed effect sizes assuming that there was no difference at all between the groups (*r* = .00). Because there is seldom no difference at all between two groups, this also represents a conservative strategy. Imputation was used in less than 7% of cases.

Handling dependent data—The validity of a meta-analysis rests on the assumption that each value contributing an aggregate effect size is statistically independent of the others (Rosenthal, 1991). We devised a number of strategies to avoid violating this independence assumption. First, in studies that assessed stimulated-lymphocyte proliferation at multiple mitogen dosages, we computed the average effect size across mitogen dosages, and we used this value to derive aggregate indices. We used an analogous strategy for studies that assessed natural killer cell cytotoxicity at multiple effector:target cell ratios. Second, in studies that utilized designs in which multiple laboratory stressors were compared with a control condition, the average effect size across stressor conditions was computed and later used to derive aggregate indices. Because this averaging procedure in most cases yielded an effect size that was smaller than that of the most potent stressor, we also computed meta-analyses using the larger of the effect sizes from each study rather than the average. Doing so did not alter any of the substantive findings we report. Third, in studies in which immune outcomes were assessed on multiple occasions during a stressful experience, the average effect size across occasions was used to derive aggregate indices. Note that we did not conduct meta-analyses of recovery effects, that is, immune values after a stressor had ended. Although such an analysis would answer interesting questions about the stress-recovery process, there were not enough studies that included similar immune outcomes assessed at similar time points after stress to permit a complete analysis. Fourth, because some data were published in more than one outlet, we contacted authors of multiple publications to determine sample independence or dependence.

Results

Preliminary Findings

The meta-analysis is based on effect sizes derived from 293 independent studies. These studies were reported in 319 separate articles in peer-reviewed scientific journals (see Table 2). A total of 18,941 individuals participated in these studies. Their mean age was 34.8 years (*SD* = 15.9). Although the studies collectively included a broad range of age groups (range = 5–78 years), most focused heavily on younger adults. More than half of the studies (51.3%) had a mean age under 30.0 years, and more than four fifths (84.8%) had a mean age under 55.0 years. Slightly more than two thirds of the studies (68.5%) included women; in the average study almost half (42.8%) of the participants were female. The vast majority of studies (84.8%) focused on medically healthy adults.[2] Of those that included medical populations, most focused on HIV/AIDS (*k* = 18; 38.3%), arthritis (*k* = 6; 12.8%), cancer (*k* = 5; 10.6%), or asthma (*k* = 4; 8.5%).

With respect to the kinds of stressors examined by studies in the meta-analysis, the most commonly utilized models were acute laboratory challenges (*k* = 85; 29.0%) and brief naturalistic stressors (*k* = 63; 21.5%). Stressful event sequences (*k* = 30; 10.2%), chronic

[2]The proportion of student samples varied across stressor categories. Nearly all of the studies of brief naturalistic stressors used student samples (*k* = 60; 95.2%) because these stressors were predominantly examinations. Student samples were also used in a large minority of acute time-limited stressor studies (*k* = 31; 40.5%) but constituted a small minority of samples used in studies of life-event checklists (*k* = 8; 14.0%) and studies of event sequences (*k* = 2; 6.6%), and student samples were not used in studies of chronic stressors or stress appraisals and intrusions. These are rough estimates, as some studies did not specify whether young adult samples were drawn from a student population.

stressors (k = 23; 7.8%), and distant traumatic experiences (k = 9; 3.1%) were explored less frequently. More than a quarter of the studies in the meta-analysis modeled the stress process by administering nonspecific life-event checklists (k = 53; 18.1%) and/or global perceived stress measures (k = 21; 7.1%) to participants. A small minority of studies examined whether reports of perceived stress or intrusive memories were associated with the extent of immune dysregulation within populations who had suffered a specific traumatic experience (k = 9; 3.1%).

The studies in the meta-analysis examined 292 distinct immune system outcomes. A minority of these outcomes were assessed in three or more studies (k = 87; 30.0%), and as such, they are the focus of the meta-analyses we present in the rest of this article (see Table 1). The most commonly assessed enumerative outcomes were counts of T-helper lymphocytes (k = 90; 30.7%), T-cytotoxic lymphocytes (k = 81; 27.6%), natural killer cells (k = 67; 22.9%), and total lymphocytes (k = 52; 17.7%). The most commonly assessed functional outcomes were natural killer cell cytotoxicity (k = 94; 32.1%) and lymphocyte proliferation stimulated by the mitogens phytohemagglutinin (PHA; k = 65; 22.2%), concanavalin A (ConA; k = 39; 13.3%), and pokeweed mitogen (PWM; k = 26; 8.9%).

Interpreting the Meta-Analytic Findings

Table 1 lists the immune parameters analyzed with the arm of the immune system to which they belong (natural or specific) and, briefly, their function. Where relevant, cell surface markers used to identify classes of immunocytes in flow cytometry are given. For example, the cell surface marker CD19 is used to identify B lymphocytes. Recall that different models of stress and the immune system posit differential effects of stress on subsets of the immune system—for example, natural versus specific immunity or cellular (Th1) versus humoral (Th2) immunity. Table 1 acts as a guide for interpreting the pattern of results in light of these models.

In the following sections we describe the meta-analytic results for each stressor category. A useful rule of thumb for judging effect sizes is to consider values of .10, .30, and .50 as corresponding to small, medium, and large effects, respectively (J. Cohen & Cohen, 1983); more generally, the aggregate effect size r can be interpreted in the same fashion as a correlation, with values ranging from −1.00 to 1.00. Positive values indicate that the presence of a stressor increases a particular immune parameter relative to some baseline (or control) condition. We should caution the reader that in some analyses, our statistics are derived from as few as three independent studies. Although meta-analyses of small numbers of studies do not pose any major statistical problems, it is important to remember that they have limited power to detect statistically significant effect sizes. What a meta-analysis can accurately provide in these instances, however, is an estimate of how much and what direction a given stressor's presence influences a specific immune outcome (i.e., an effect size estimate).

Meta-Analytic Results for the Effects of Stressors

Acute time-limited stressors—Acute time-limited stressors included primarily experimental manipulations of stressful experiences, such as public speaking and mental arithmetic, that lasted between 5 and 100 min. Reliable effects on the immune system included increases in immune parameters, especially natural immunity. The most robust effect of this kind of experience was a marked increase in the number of natural killer cells (r =.43) and large granular lymphocytes (r =.53) in peripheral blood (see Table 3). This effect is consistent with the view that acute stressors cause immune cells to redistribute into the compartments in which they will be most effective (Dhabhar & McEwen, 1997). However, other types of lymphocytes did not show robust redistribution effects: B cells and T-helper cells showed very little change (rs = −.07 and .01, respectively), and this change was not statistically significant across studies. T-cytotoxic lymphocytes did tend to increase reliably in peripheral blood,

though to a lesser degree than their natural immunity counterparts (r =.20); this increase drove a reliable decline in the T-helper:T-cytotoxic ratio (r = −.23). However, natural killer cells as well as T-cytotoxic cells can express CD8, the marker most often used to define the latter population. Because some studies did not use the T cell receptor (CD3) to differentiate between CD3–CD8+ natural killer cells and CD3+CD8+ T-cytotoxic cells, it is possible that the effect for "T-cytotoxic cells" is actually being driven by natural killer cells (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996).

The results for cell percentages roughly parallel those for number. However, the percentage data are harder to interpret because any given parameter is linearly dependent on the other parameters: For example, the enumerative data suggest that the decrease in percentage T-helper cells (r = −.24) is probably an artifact of the increases in percentage natural killer cells (r = .24) and percentage T-cytotoxic cells (r = .09).

Another effect that may be considered a redistribution effect is the significant increase in secretory IgA in saliva (r = .22). The time frame of these acute stressors is too short for the synthesis of a significant amount of new antibody; therefore, this increase is probably due to release of already-synthesized antibody from plasma cells and increased translocation of antibody across the epithelium and into saliva (Bosch, Ring, de Geus, Veerman, & Amerongen, 2002). This effect therefore represents relocation, albeit of an immune protein rather than an immune cell.

There were also a number of functional effects. First, natural killer cell cytotoxicity significantly increased with acute stressors (r = .30), but only when the concomitant increase in proportion of natural killer cells in the effector mix was not removed statistically. When examined on a per-cell basis, cytotoxicity did not significantly increase (r = .12). One could, therefore, consider the increase in cytotoxicity a methodological artifact of the definition of *effector* in effector:target ratios. However, to the degree that one is interested in the general cytotoxic potential of the contents of peripheral blood rather than that of a specific natural killer cell, the uncorrected value is more illustrative. Second, mitogen-stimulated proliferative responses decreased significantly. Again, this could be a methodological artifact of the mix of cells in the assay. However, the proportion of total T and B cells, which are responsible for the proliferative response to PWM and ConA, did not decrease as reliably or as much as did the proliferative response (rs = −.05 to −.11 vs. −.10 to −.17), suggesting that acute stressors do decrease this function of specific immunity. Finally, the production of two cytokines, IL-6 and IFNγ, was increased significantly following acute stress (rs = .28 and .21, respectively).

The data for acute stressors, therefore, support an upregulation of natural immunity, as reflected by increased number of natural killer cells in peripheral blood, and potential downregulation of specific immunity, as reflected by decreased proliferative responses. Other indicators of upregulated natural immunity include increased neutrophil numbers in peripheral blood (r = .30), increased production of a proinflammatory cytokine (IL-6), and increased production of a cytokine that potently stimulates macrophages and natural killer cells as well as T cells (IFNγ). The only exception to this pattern was the increased secretion of IgA antibody, which is a product of the specific immune response. An interesting question for future research is whether this effect is part of a larger nonspecific protein release in the oral cavity in response to acute stress (cf. Bosch et al., 2002).

It bears noting that a number of the findings presented in Table 3 are accompanied by significant heterogeneity statistics. To identify moderating variables that might explain some of this heterogeneity, we examined whether effect sizes varied according to demographic characteristics of the sample (mean age and percentage female) or features of the acute challenge (its duration and nature). Neither of the demographic characteristics showed a

consistent relationship with immune outcomes. Although these findings suggest that acute time-limited stressors elicit a similar pattern of immune response for men and women across the life span, this conclusion needs to be viewed somewhat cautiously given the narrow range of ages found in these studies. We also did not find a consistent pattern of relationships between features of the acute challenge and immune outcomes. Acute stressors elicited similar patterns of immune change across a wide spectrum of durations ranging from 5 though 100 min and irrespective of whether they involved social (e.g., public speaking), cognitive (e.g., mental arithmetic), or experiential (e.g., parachute jumping) forms of stressful experience.

Brief naturalistic stressors—Table 4 presents the meta-analysis of brief naturalistic stressors for medically healthy adults. The vast majority of these stressors ($k = 60$; 95.2%) involved students facing academic examinations. In contrast to the acute time-limited stressors, examination stress did not markedly affect the number or percentage of cells in peripheral blood. Instead, the largest effects were on functional parameters, particularly changes in cytokine production that indicate a shift away from cellular immunity (Th1) and toward humoral immunity (Th2). Brief stressors reliably changed the profile of cytokine production via a decrease in a Th1-type cytokine, IFNγ ($r = -.30$), which stimulates natural and cellular immune functions, and increases in the Th2-type cytokines IL-6 ($r = .26$), which stimulates natural and humoral immune functions, and IL-10 ($r = .41$), which inhibits Th1 cytokine production. Note that IFNγ and IL-6 share the property of stimulating natural immunity but differentially stimulate cytotoxic versus inflammatory effector mechanisms. Their dissociation after brief naturalistic stress indicates differential effects between Th1 and Th2 responses rather than natural and specific responses.

The functional assay data are consistent with this suggestion of suppression of cellular immunity via decreased Th1 cytokine production: The T cell proliferative response significantly decreased with brief stressors ($r = -.19$ to $-.32$), as did natural killer cell cytotoxicity ($r = -.11$). Increased antibody production to latent virus, particularly Epstein-Barr virus ($r = .20$), is also consistent with suppression of cellular immunity, enhancement of humoral immunity, or both.

There was also evidence that age contributed to vulnerability to stress-related immune change during brief naturalistic stressors, even within a limited range of relatively young ages. When we examined whether effect sizes varied according to demographic characteristics of the sample, sex ratio did not show a consistent pattern of relations with immune processes. However, the mean age of the sample was strongly related to study effect size. To the extent that a study enrolled participants of older ages, it was likely to observe more pronounced decreases in natural killer cell cytotoxicity ($r = -.58$, $p = .04$; $k = 14$), T lymphocyte proliferation to the mitogens PHA ($r = -.58$, $p = .04$; $k = 13$) and ConA ($r = -.31$, $p = .38$; $k = 9$), and production of the cytokine IFNγ ($r = -.63$, $p = .09$; $k = 8$) in response to brief naturalistic stress. The strength of these findings is particularly surprising given the narrow range of ages found in studies of brief natural stress; the mean participant age in this literature ranged from 15.7 to 35.0 years.

We also calculated effect sizes for three studies examining the effects of examination stress on individuals with asthma (see Table 5). These three studies, all emanating from a team of investigators at the University of Wisconsin—Madison, found that stress reliably increased superoxide release ($r = .20$ to $.37$) and decreased natural killer cell cytotoxicity ($r = -.33$). Because natural killer cells are stimulated by Th1 cytokines, this change is consistent with a Th1-to-Th2 shift. However, stress also reliably increased T cell proliferation to PHA ($r = .32$), which is not consistent with such a shift. The generally larger effect sizes are consistent with the idea that individuals with immunologically mediated disease are more susceptible to stress-related immune dysregulation, but the reversed sign for T cell proliferation also indicates that

that pattern of dysregulation may also be more disorganized. That is, the organized pattern of suppression of Th1 but not Th2 immune responses in healthy individuals undergoing brief stressors may reflect regulation in the healthy immune system. In contrast, the lack of regulation in a diseased immune system may lead to more chaotic changes during stressors.

Stressful event sequences—The meta-analysis of stressful event sequences is presented in Table 6. With the exception of significant increases in the number of circulating natural killer cells and the number of antibodies to the latent Epstein-Barr virus, the findings indicate that stressful event sequences are not associated with reliable immune changes. For many immune outcomes, however, significant heterogeneity statistics are evident. Studies of healthy adults generally fell into two categories that yielded disparate patterns of immune findings. The largest group of studies focused on the death of a spouse as a stressor and, as such, used samples consisting primarily of older women. Collectively, these studies found that losing a spouse was associated with a reliable decline in natural killer cell cytotoxicity ($r = -.23$, $p = .01$; $k = 6$) but not with alterations in stimulated-lymphocyte proliferation by the mitogens ConA ($r = -.04$, $p = .45$; $k = 4$), PHA ($r = -.01$, $p = .93$; $k = 7$), or PWM ($r = -.08$, $p = .76$; $k = 3$) or with changes in the number of T-helper lymphocytes ($r = .07$, $p = .52$; $k = 6$) or T-cytotoxic lymphocytes ($r = -.13$, $p = .45$; $k = 5$) in peripheral blood. The next largest group of studies in this area examined immune responses to disasters, which may have different neuroendocrine consequences than loss; whereas loss is generally associated with increases in cortisol, trauma may be associated with decreases in cortisol (Yehuda, 2001;Yehuda, McFarlane, & Shalev, 1998). Natural disaster samples tended to focus on middle-aged adults of both sexes who were direct victims of the disaster, rescue workers at the scene, or personnel at nearby medical centers. There were medium-size effects suggesting increases in natural killer cell cytotoxicity ($r = .25$, $p = .53$; $k = 4$) and stimulated-lymphocyte proliferation by the mitogen PHA ($r = .26$, $p = .33$; $k = 2$), as well as decreases in the number of T-helper lymphocytes ($r = -.20$, $p = .43$; $k = 2$) and T-cytotoxic lymphocytes ($r = -.23$, $p = .55$; $k = 2$) in the circulation. However, none of them was statistically significant because of the small number of studies involved, and therefore these effects should be considered suggestive but not reliable.

An additional group of studies in this area examined immune responses to a positive initial biopsy for breast cancer in primarily middle-aged female participants before and after the procedure. The three studies of this nature did not yield a consistent pattern of relations with any of the immune outcomes.

In summary, stressful event sequences did not elicit a robust pattern of immune changes when considered as a whole. When these sequences are broken down into categories reflecting the stressor's nature, the meta-analysis yields evidence of declines in natural immune response following the loss of a spouse, nonsignificant increases in natural and specific immune responses following exposure to natural disaster, and no immune alterations with breast biopsy. Unfortunately, we cannot determine whether these disparate patterns of immune response are attributable to features of the stressors, demographic or medical characteristics of the participants, or some interaction between these factors.

Chronic stressors—Chronic stressors included dementia caregiving, living with a handicap, and unemployment. Like other nonacute stressors, they did not have any systematic relationship with enumerative measures of the immune system. They did, however, have negative effects on almost all functional measures of the immune system (see Table 7). Both natural and specific immunity were negatively affected, as were Th1 (e.g., T cell proliferative responses) and Th2 (e.g., antibody to influenza vaccine) parameters. The only nonsignificant change was for antibody to latent virus; this effect size was substantial ($r = .44$), but there was also substantial heterogeneity. Further analyses showed that demographics did not moderate

this effect: Immune responses to chronic stressors were equally strong across the age spectrum as well as across sex.

Distant stressors—Distant stressors were traumatic events such as combat exposure or abuse occurring years prior to immune assessment. The meta-analytic results for distant stressors appear in Table 8. The only immune outcome that has been examined regularly in this literature is natural killer cell cytotoxicity, and it is not reliably altered in persons who report a distant traumatic experience.

Meta-Analytic Results for the Effects of Checklists and Ratings

Nonspecific life events—Most of the studies in this area examined whether immune responses varied as a function of the number of life events a person endorsed on a standard checklist, a person's rating of the impact of those events, or both. As Table 9 illustrates, this methodology yielded little in the way of significant outcomes in healthy participants. To determine whether vulnerability to life events might vary across the life span, we divided studies into two categories on the basis of a natural break in the age distribution. These analyses provided evidence that older adults are especially vulnerable to life-event–induced immune change. In studies that used samples of adults who had a mean age above 55, life events were associated with reliable declines in lymphocyte-proliferative responses to PHA ($r = -.40$, $p = .05$; $k = 2$) and natural killer cell cytotoxicity ($r = -.59$, $p = .001$; $k = 2$). These effects were much weaker in studies with a mean age below 55: Life events were not associated with proliferative responses to PHA ($r = -.22$, $p = .24$; $k = 2$), and showed a reliable but modest relationship with natural killer cell cytotoxicity ($r = -.10$, $p = .03$; $k = 8$). The differences in effect size between older and younger adults were statistically significant for natural killer cell cytotoxicity ($p < .001$) but not PHA-induced proliferation ($p < .15$). None of the other moderators we examined—sex ratio, kind of life event assessed (daily hassle vs. major event), or the method used to do so (checklist vs. interview)—was related to immune outcomes.

Table 10 presents the relationship between life events and immune parameters in participants with HIV/AIDS. The presence of life events was associated with a significant reduction in the number of natural killer cells and a marginal reduction in the number of T-cytotoxic lymphocytes. It is unrelated to the number of T-helper lymphocytes, the percentage of T-cytotoxic lymphocytes, and the T-helper:T-cytotoxic ratio, all of which are recognized indicators of disease progression for patients with HIV/AIDS.

We have already proposed that immunological disease diminishes the resilience and self-regulation of the immune system, making it more vulnerable to stress-related disruption, and this may be the case in HIV-infected versus healthy populations. However, studies of HIV-infected populations also utilized more refined measures of life events (interviews that factor in biographical context) than did studies of healthy populations (typically, checklist measures). Unfortunately, we cannot differentiate between these explanations on the basis of the available data.

Global stress appraisals and intrusive thoughts—The meta-analysis of stress appraisals and intrusive thoughts is displayed in Table 11. These studies generally enrolled large populations of adults who were not experiencing any specific form of stress and examined whether their immune responses varied according to stress appraisals and/or intrusive thoughts. This methodology was unsuccessful at documenting immune changes related to stress. Because of the small number of studies in this category, moderator analyses could not be performed.

The meta-analysis results shown in Table 12 address a similar question with regard to persons who are in the midst of a specific event sequence or a chronic stressor. To the extent that they appraise their lives as stressful or report the occurrence of intrusive thoughts, these individuals

exhibit a significant reduction in natural killer cell cytotoxicity. Although this effect does not extend to the number of T-helper and T-cytotoxic lymphocytes in the circulation, it suggests that a person's subjective representation of a stressor may be a determinant of its impact on the immune response.

Evidence Regarding Type I Error and Publication Bias

The large number of effect sizes generated by the meta-analysis raises the possibility of Type I error. One strategy for evaluating this concern involves dividing the number of significant findings in a meta-analysis by the total number of analyses conducted. When we performed this calculation, a value of 25.6% emerged, suggesting that more than one fourth of the analyses yielded reliable findings. This exceeds the 5% value at which investigators typically become concerned about Type I error rates and gives us confidence that the meta-analytic findings presented here are robust.

A second concern arises from the publication bias toward positive findings, which could skew meta-analytic results toward larger effect sizes. Fortunately, recent advances in meta-analysis enable one to evaluate the extent of this publication bias by using graphical techniques. A funnel plot can be drawn in which effect sizes are plotted against sample sizes for any group of studies. Because most studies in any given area have small sample sizes and therefore tend to yield more variable findings, the plot should end up looking like a funnel, with a narrow top and a wide bottom. If there is a bias against negative findings in an area, the plot is shifted toward positive values or a chunk of it will be missing entirely.

We drew funnel plots for all of the immune outcomes in the meta-analysis for which there were a sufficient number of observations. Although not all of them yielded perfect funnels, there was no systematic evidence of publication bias. Space limitations prevent us from including all plots; however, Figure 1 displays three plots that are prototypical of those we drew. As is evident from the data in the figure, psychoneuroimmunology researchers seem to be reporting positive and negative findings—and not hiding unfavorable outcomes when they do emerge. Thus, we do not have any major concerns about publication bias leading this meta-analysis to dramatically overestimate effect sizes.

Discussion

The immune system, once thought to be autonomous, is now known to respond to signals from many other systems in the body, particularly the nervous system and the endocrine system. As a consequence, environmental events to which the nervous system and endocrine system respond can also elicit responses from the immune system. The results of meta-analysis of the hundreds of research reports generated by this hypothesis indicate that stressful events reliably associate with changes in the immune system and that characteristics of those events are important in determining the kind of change that occurs.

Models of Stress and the Immune System

Selye's (1975) seminal findings suggested that stress globally suppressed the immune system and provided the first model for how stress and immunity are related. This model has recently been challenged by views that relations between stress and the immune system should be adaptive, at least within the context of fight-or-flight stressors, and an even newer focus on the balance between cellular and humoral immunity. The present meta-analytic results support three of these models. Depending on the time frame, stressors triggered adaptive upregulation of natural immunity and suppression of specific immunity (acute time-limited), cytokine shift (brief naturalistic), or global immunosuppression (chronic).

When stressors were acute and time-limited—that is, they generally followed the temporal parameters of fight-or-flight stressors—there was evidence for adaptive redistribution of cells and preparation of the natural immune system for possible infection, injury, or both. In evolution, stressor-related changes in the immune system that prepared the organisms for infections resulting from bites, puncture wounds, scrapes, or other challenges to the integrity of the skin and blood could be selected for. This process would be most adaptive when it was also efficient and did not divert excess energy from fight-or-flight behavior. Indeed, changes in the immune system following acute stress conformed to this pattern of efficiency and energy conservation. Acute stress upregu-lated parameters of natural immunity, the branch of the immune system in which most changes occurred, which requires only minimal time and energy investment to act against invaders and is also subject to the fewest inhibitory constraints on acting quickly (Dopp et al., 2000; Sapolsky, 1998). In contrast, energy may actually be directed away from the specific immune response, as indexed by the decrease in the proliferative response. The specific immune response in general and proliferation in particular demand time and energy; therefore, this decrease might indicate a redirection away from this function. Similar redirection occurs during fight-or-flight stressors with regard to other nonessential, future-oriented processes such as digestion and reproduction. As stressors became more chronic, the potential adaptiveness of the immune changes decreased. The effect of brief stressors such as examinations was to change the potency of different arms of specific immunity —specifically, to switch away from cellular (Th1) immunity and toward humoral (Th2) immunity.

The stressful event sequences tended to fall into two substantive groups: bereavement and trauma. Bereavement was associated with decreased natural killer cell cytotoxicity. Trauma was associated with nonsignificantly increased cytotoxicity and increased proliferation but decreased numbers of T cells in peripheral blood. The different results for loss and trauma mirror neuroendocrine effects of these two types of adverse events. Loss—maternal separation in nonhuman animals and bereavement in humans—is commonly associated with increased cortisol production (Irwin, Daniels, Risch, Bloom, & Weiner, 1988; Laudenslager, 1988; McCleery, Bhagwagar, Smith, Goodwin, & Cowen, 2000). In contrast, trauma and posttraumatic stress disorder are commonly associated with decreased cortisol production (see Yehuda, 2001; Yehuda et al., 1998, for reviews). To the degree that cortisol suppresses immune function such as natural killer cell cytotoxicity, these results have the potential to explain the different effects of loss and trauma event sequences.

The most chronic stressors were associated with the most global immunosuppression, as they were associated with reliable decreases in almost all functional immune measures examined. Increasing stressor duration, therefore, resulted in a shift from potentially adaptive changes to potentially detrimental changes, initially in cellular immunity and then in immune function more broadly. It is important to recognize that although the effects of chronic stressors may be due to their duration, the most chronic stressors were associated with changes in identity or social roles (e.g., acquiring the role of caregiver or refugee or losing the role of employee). These chronic stressors may also be more persistent, that is, constantly rather than intermittently present. Finally, chronic stressors may be less controllable and afford less hope for control in the future. These qualities could contribute to the severity of the stressor in terms of both its psychological and physiological impact.

Increasing stressor chronicity also impacted the type of parameter in which changes were seen. Compared with the natural immune system, the specific immune system is time and energy intensive and as such is expected to be invoked only when circumstances (either a stressor or an infection; cf. Maier & Watkins, 1998) persist for a longer period of time. Affected immune domains—natural versus specific—were consistent with the duration of the stressors—acute versus chronic. Furthermore, changing immune responses via redistribution of cells can happen

much faster than changes via the function of cells. The time frames of the stressor and the immune domain were also consistent; acute stress affected primarily enumerative measures, whereas stressors of longer duration affected primarily functional measures.

The results of these analyses suggest that the dichotomization of the immune system into natural and specific categories and, within specific immunity, into cellular and humoral measures, is a useful starting point with regard to understanding the effects of stressors. Categorizing an immune response is a difficult process, as each immune response is highly redundant and includes natural, specific, cellular, and humoral immune responses acting together. Given this redundancy, the differential results within these theoretical divisions were remarkably, albeit not totally, consistent. As further immunological research defines these divisions more subtly, the results with regard to stressors may become even clearer. However, the present results suggest that the categories used here are meaningful.

The results of this meta-analysis reflect the theoretical and empirical progress of this literature over the past 4 decades. Increased differentiation in the quality of stressors and the immunological parameters investigated have allowed complex models to be tested. In contrast, previous meta-analyses were bound by a small number of more homogenous studies. Herbert and Cohen (1993) reported on 36 studies published between 1977 and 1991, finding broadly immunosuppressive effects of stress. Zorrilla et al. (2001) reported on 82 studies published between 1980 and 1996, finding potentially adaptive effects of acute stressors in addition to evidence for immunosuppression with longer stressors. It is important to note that meta-analytic findings are bound by the models tested in the literature. As more complex models are tested, more complex relationships emerge in meta-analysis. We next consider some such areas of complexity that should be considered in future psychoneuroimmunology research.

Individual Differences and Immune Change Under Stress

The meta-analytic results indicate that organismic variables such as age and disease status moderate vulnerability to stress-related decreases in functional immune measures. Both aging and HIV are associated with immune senescence and loss of responsiveness (Effros et al., 1994; Effros & Pawelec, 1997), and both are also associated with disruption of neuroendocrine inputs to the immune system (Kumar et al., 2002; Madden, Thyagarajan, & Felten, 1998). The loss of self-regulation in disease and aging likely makes affected people more susceptible to negative immunological effects of stress. Finally, the meta-analysis did not reveal effects of sex on immune responses to stressors. However, these comparisons simply correlated the sex ratio of the studies with effect sizes. Grouping data by sex would afford a more powerful comparison, but few studies organized their data that way. Gender may moderate the effects of stress on immunity by virtue of the effects of sex hormones on immunity; generally, men are considered to be more biologically vulnerable (Maes, 1999), and they may be more psychosocially vulnerable (e.g.,Scanlan, Vitaliano, Ochs, Savage, & Borson, 1998).

It seems likely to us that individual differences in subjective experience also make a substantive contribution to explaining this phenomenon. Studies have convincingly demonstrated that people's cardiovascular and neuroendocrine responses to stressful experience are dependent on their appraisals of the situation and the presence of intrusive thoughts about it (Baum et al., 1993; Frankenhauser, 1975; Tomaka et al., 1997). Although the same logic should apply to people's immune responses to stressful experience, few of the studies in this area have included measures of subjective experience, and those reports were limited by methodological issues such as aggregation across heterogeneous stressors. As a consequence, measures of subjective experience were not significantly associated with immune parameters in healthy research participants, with the exception of a modest ($r = -.10$) relationship between intrusive thoughts and natural killer cell cytotoxicity. Psychological variables such as personality and emotion can give rise to individual differences in psychological and concomitant immunological

responses to stress. Optimism and coping, for example, moderated immunological responses to stressors in several studies (e.g., Barger et al., 2000; Bosch et al., 2001; Cruess et al., 2000; Segerstrom, 2001; Stowell, Kiecolt-Glaser, & Glaser, 2001).

Mechanisms of Stress Effects on the Immune System

Virtually nothing is known about the psychological pathways linking stressors with the immune system. Many theorists have argued that affect is a final common pathway for stressors (e.g., S. Cohen, Kessler, & Underwood, 1995; Miller & Cohen, 2001), yet studies have enjoyed limited success in attempting to explain people's immune responses to life experiences on the basis of their emotional states alone (Bower et al., 1998; Cole, Kemeny, Taylor, Visscher, & Fahey, 1996; Miller, Dopp, Myers, Stevens, & Fahey, 1999; Segerstrom, Taylor, Kemeny, & Fahey, 1998). Furthermore, many studies have focused on the immune effects of emotional valence (e.g., unhappy vs. happy; Futterman, Kemeny, Shapiro, & Fahey, 1994), but the immune system may be even more closely linked to emotional arousal (e.g., stimulated vs. still), especially during acute stressors (S. Cohen et al., 2000). Finally, it is possible that emotion will prove to be relatively unimportant and that other mental processes such as motivational states or cognitive appraisals will prove to be the critical psychological mechanisms linking stress and the immune system (cf. Maier, Waldstein, & Synowski, 2003).

In terms of biological mechanisms, the field is further along, but much remains to be learned. A series of studies in the mid-1990s was able to show via beta-adrenergic blockade that activation of the sympathetic nervous system was responsible for the immune system effects of acute stressors (Bachen et al., 1995; Benschop, Nieuwenhuis, et al., 1994). Apart from these findings, however, little is known about biological mechanisms, especially with regard to more enduring stressors that occur in the real world. Studies that have attempted to identify hormonal pathways linking stressors and the immune system have enjoyed limited success, perhaps because they have utilized snapshot assessments of hormones circulating in blood. Future studies can maximize their chances of identifying relevant mediators by utilizing more integrated measures of hormonal output, such as 24-hr urine collections or diurnal profiles generated through saliva collections spaced throughout the day (Baum & Grunberg, 1995; Stone et al., 2001).

Future studies could also benefit from a greater emphasis on behavior as a potential mechanism. This strategy has proven useful in studies of clinically depressed patients, in which decreased physical activity and psychomotor retardation (Cover & Irwin, 1994; Miller, Cohen, & Herbert, 1999), increased body mass (Miller, Stetler, Carney, Freedland, & Banks, 2002), disturbed sleep (Cover & Irwin, 1994; Irwin, Smith, & Gillin, 1992), and cigarette smoking (Jung & Irwin, 1999) have been shown to explain some of the immune dysregulation evident in this population. There is already preliminary evidence, for instance, that sleep loss might be responsible for some of the immune system changes that accompany stressors (Hall et al., 1998; Ironson et al., 1997).

Stress, the Immune System, and Disease

The most pressing question that future research needs to address is the extent to which stressor-induced changes in the immune system have meaningful implications for disease susceptibility in otherwise healthy humans. In the 30 years since work in the field of psychoneuroimmunology began, studies have convincingly established that stressful experiences alter features of the immune response as well as confer vulnerability to adverse medical outcomes that are either mediated by or resisted by the immune system. However, with the exception of recent work on upper respiratory infection (S. Cohen, Doyle, & Skoner, 1999), studies have not yet tied these disparate strands of work together nor determined whether immune system changes are the mechanism through which stressors increase susceptibility to

disease onset. In contrast, studies of vulnerable populations such as people with HIV have shown changes in immunity to predict disease progression (Bower et al., 1998).

To test an effect of this nature, researchers need to build clinical outcome assessments into study designs where appropriate. For example, chronic stressors reliably diminish the immune system's capacity to produce antibodies following routine influenza vaccinations (see Table 7). Yet as far as we are aware, none of these studies has tracked illness to explore whether stress-related disparities in vaccine response might be sufficient to heighten susceptibility to clinical infection with influenza. Cytokine expression represents a relatively new and promising example of an avenue for research linking stress, immune change, and disease. For example, chronic stress may elicit prolonged secretion of cortisol, to which white blood cells mount a counterregulatory response by downregulating their cortisol receptors. This downregulation, in turn, reduces the cells' capacity to respond to anti-inflammatory signals and allows cytokine-mediated inflammatory processes to flourish (Miller, Cohen, & Ritchey, 2002). Stress therefore might contribute to the course of diseases involving excessive nonspecific inflammation (e.g., multiple sclerosis, rheumatoid arthritis, coronary heart disease) and thereby increase risk for excess morbidity and mortality (Ershler & Keller, 2000;Papanicoloaou et al., 1998;Rozanski, Blumenthal, & Kaplan, 1999). Another example of the importance of cytokines to clinical pathology is in asthma and allergy, in which emerging evidence implicates excess Th2 cytokine secretion in the exacerbation of these diseases (Busse & Lemanske, 2001;Luster, 1998).

Conclusion

Sapolsky (1998) wrote,

> Stress-related disease emerges, predominantly, out of the fact that we so often activate a physiological system that has evolved for responding to acute physical emergencies, but we turn it on for months on end, worrying about mortgages, relationships, and promotions. (p. 7)

The results of this meta-analysis support this assertion in one sense: Stressors with the temporal parameters of the fight-or-flight situations faced by humans' evolutionary ancestors elicited potentially beneficial changes in the immune system. The more a stres-sor deviated from those parameters by becoming more chronic, however, the more components of the immune system were affected in a potentially detrimental way.

Further research is needed to support two other ideas elicited by this quote: the idea that subjective experience such as worry is more likely to result in stress-related immune change than objective experience and the idea that stress-related immune change results in stress-related disease. Though the results of the meta-analysis were not encouraging on the first point, many of these studies suffered from methodological limitations. We hope that these results will inform investigations that go beyond the relationship between a stressful event and an immune parameter to investigate the psychological phenomena that mediate that relationship. Finally, these results can also inform investigations into stress, immunity, and disease process. Whether the disease is characterized by natural or specific immunity, its cytokine profile, and its regulation by anti-inflammatory agents such as cortisol, may determine the disparate effects of different kinds of stressors.

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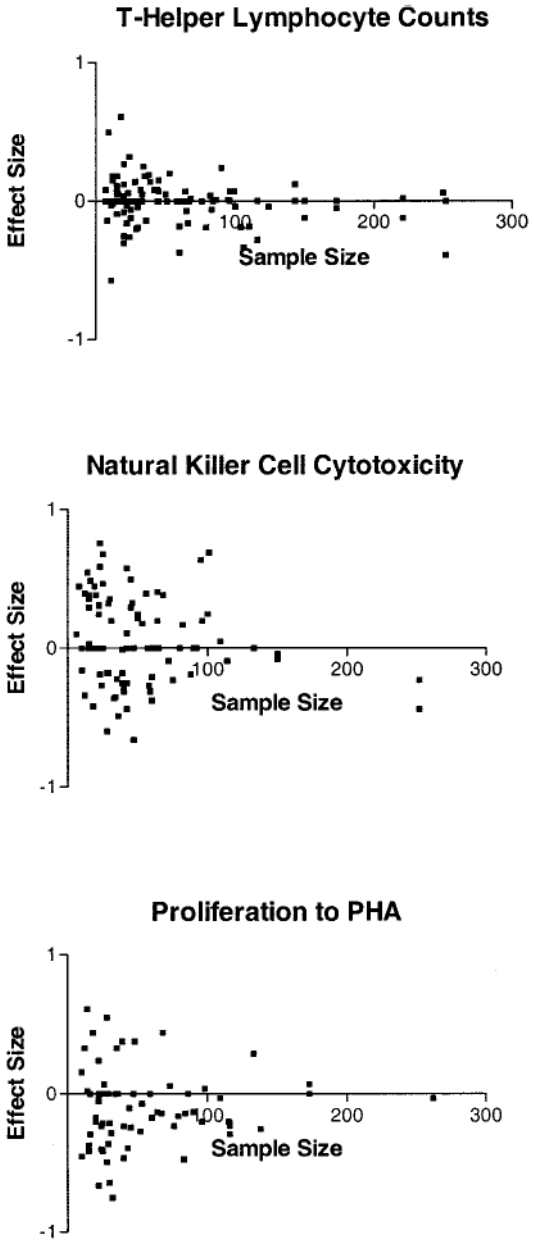

Figure 1.
Funnel plots depicting relationship between effect size and sample size. PHA = phytohemagglutinin.

Table 1

Immune Parameters Reported and Critical Characteristics

Parameter	Arm of immune system	Function	Cell surface marker
Cell			
Leukocytes	Natural	All white cells	
Granulocytes	Natural	Inflammation	
Neutrophils	Natural	Inflammation, phagocytosis	
Eosinophils	Natural	Inflammation	
Monocytes/macrophages	Natural	Inflammation, phagocytosis	
Lymphocytes	Specific	All lymphocytes	CD2
T lymphocytes	Specific	Cellular immunity	CD3, CD45RA (naive)
T-helper lymphocytes	Specific	Cellular (Th1) or humoral (Th2) immunity	CD4
T-cytotoxic lymphocytes	Specific	Cellular (Th1) immunity	CD8
B lymphocytes	Specific	Humoral (Th2) immunity	CD19, CD20
Activated B lymphocytes	Specific	Humoral (Th2) immunity	CD23, CD30
Natural killer cells	Natural	Cellular (Th1) immunity	CD16, CD56, CD57
Immunoglobulin			
IgA, IgG, IgM	Specific	Humoral (Th2) immunity	
Anti-EBV IgG	Specific	Index of EBV replication/activation	
Anti-HSV IgG	Specific	Index of HSV replication/activation	
Anti-influenza IgG postimmunization	Specific	Humoral (Th2) immunity	
Cytokine			
Interleukin-1β	Natural	Inflammation, T cell activation	
Interleukin-2	Specific	T cell activation (Th1)	
Interleukin-4	Specific	B cell activation, antibody production (Th2)	
Interleukin-6	Natural	Inflammation	
Interleukin-10	Specific	Inhibits T cell activation (Th2)	
Interferon-γ	Natural and specific	Macrophage, natural killer cell, and T cell activation (Th1)	
Tumor necrosis factor-α	Natural	Inflammation	
Complement	Natural	Increases effectiveness of natural immunity	C3
Functional assay			
Neutrophil superoxide release	Natural	Inflammation	
Natural killer cell cytotoxicity	Natural	Cellular (Th1) immunity	
Proliferation to ConA	Specific	Cellular (Th1) immunity (T cell proliferation)	
Proliferation to PHA	Specific	Cellular (Th1) immunity (T cell proliferation)	
Proliferation to PWM	Specific	Cellular (Th1) and humoral (Th2) immunity (T and B cell proliferation)	

Note. Th1 = cells that direct a response to intracellular pathogens; Th2 = cells that direct a response to extracellular pathogens; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; EBV = Epstein-Barr virus; HSV = herpes simplex virus; ConA = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen.

Table 2

Studies Used in the Meta-Analysis by Type of Stressor

Acute time-limited	Brief naturalistic	Event sequence	Chronic	Distant	Life event	Stress appraisal
Ackerman et al., 1996, 1998	Baker et al., 1984, 1985	Antoni et al., 1990	Bauer et al., 2000	Boscarino & Chang, 1999	Abdeljaber et al., 1994	Andersen et al., 1998
Aloe et al., 1994	Bisselli et al., 1993	Aragona et al., 1996	Dekaris et al., 1993	Inoue-Sakurai et al., 2000	Benschop, Jabaaij, et al., 1998	de Gucht et al., 1999
Arber et al., 1992	Borella et al., 1999	Arnetz et al., 1991	Dimsdale et al., 1994	Laudenslager et al., 1998	Biondo et al., 1994	Halim et al., 2000
Bachen et al., 1992, 1995	Bosch et al., 1996	Bartrop et al., 1977	Drummond & Hewson-Bower 1997	Mosnaim et al., 1993	Birmaher et al., 1994	Hall et al., 1998
Barger et al., 2000	Boyce et al., 1993, 1995	Beem et al., 1999	Esterling et al., 1994, 1996	Spivak et al., 1997	Byrnes et al., 1998	Ironson et al., 1997
Beck et al., 2000	Davidson et al., 1999	Cruess et al., 2000	Gennaro, Fehder, Cnaan, et al., 1997	Watson et al., 1983	F. Cohen et al., 1999	Kawakami et al., 1997
Benschop, Brosschot, et al., 1994	Deinzer & Schüller, 1998	Delahanty et al., 1997	Gennaro, Fehder, Nuamah, et al., 1997	Wilson et al., 1999	Evans et al., 1995	Kawamura et al., 2001
Benschop et al., 1995	Deinzer et al., 2000	Dworsky et al., 1989	Glaser & Kiecolt-Glaser, 1997		Gomez et al., 1994	Kusaka et al., 1992
Benschop, Jacobs, et al., 1996	Dobbin et al., 1991	Goodkin et al., 1996	Glaser et al., 1998, 2000, 2001		González-Quijano et al., 1998	Lerman et al., 1999
Benschop, Nieuwenhuis, et al., 1994	Fittschen et al., 1990	Ironson et al., 1990, 1997	Irwin et al., 1991, 1997		Goodkin, Blaney, et al., 1992	Maes et al., 1999
Bongartz et al., 1987	Gilbert et al., 1996	Irwin et al., 1986, 1988	Kiecolt-Glaser et al., 1991, 1995, 1996		Goodkin, Fuchs, et al., 1992	Marsland et al., 2001
Bosch et al., 2001	Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985	Irwin, Daniels, Smith, et al., 1987	Kiecolt-Glaser, Glaser, et al., 1987		Graham et al., 1988	McClelland et al., 1982
Breznitz et al., 1998	Glaser, Kiecolt-Glaser, Stout, et al., 1985	Irwin, Daniels, & Weiner, 1987	Lauc et al., 1998		Howland et al., 2000	McDade, 2001
Bristow et al., 1997	Glaser et al., 1986, 1987, 1990, 1991, 1993, 1994, 1996, 1999	Kiecolt-Glaser, Fisher, et al., 1987	Lutgendorf et al., 1999		Irwin, Daniels, Bloom, et al., 1987	Nakamura et al., 1999
Brosschot et al., 1991, 1992, 1994	Gruzelier et al., 2001	Kiecolt-Glaser et al., 1988	McKinnon et al., 1989		Irwin et al., 1990	Nakata et al., 2000
Burleson et al., 1998	Guidi et al., 1999	Lane et al., 1983	Mills et al., 1997, 1999		Jabaaij et al., 1993, 1996	Scanlan et al., 1998
Cacioppo et al., 1995, 1998	Halvorsen & Vassend, 1987	Lutgendorf et al., 1997, 2001	Nakano et al., 1998		Kemeny et al., 1989	Schaubroeck et al., 2001
Caggiula et al., 1995	Jemmott & Magloire, 1988	McClelland et al., 1991	Pariante et al., 1997		Kessler et al., 1991	Söderfeldt et al., 2000
Caudell & Gallucci, 1995	Jemmott et al., 1983	Nagabhushan et al., 2001	Sabioncello et al., 2000		Kubitz et al., 1986	Song et al., 1999
Chi et al., 1993	Kamei et al., 1997, 1998	Pettingale et al., 1994	Scanlan et al., 1998		Leserman et al., 1997	Theorell et al., 1990
S. Cohen et al., 2000	Kang et al., 1996, 1997, 1998	Solomon et al., 1997	Schlesinger & Yodfat, 1988		Levy et al., 1989	Tjemsland et al., 1997
Cruse et al., 1993	Kiecolt-Glaser et al., 1986, 1993, 1994, 1997, 2001	Spratt & Denney, 1991	Stowell et al., 2001		Liang et al., 1997	Værnes et al., 1991
Delahanty et al., 1996, 1998, 2000	Kugler et al., 1996	Udelman, 1982	Vedhara et al., 1999		B. S. Linn et al., 1988	Vitaliano et al., 1998
Dopp et al., 2000	Lacey et al., 2000	Weiss et al., 1996	Vitaliano et al., 1998		M. W. Linn et al., 1983, 1984	Wilcox et al., 2000

Acute time-limited	Brief naturalistic	Event sequence	Chronic	Distant	Life event	Stress appraisal
Dugué et al., 1993 Endresen et al., 1991 Geenen et al., 1998 Gerits & DeBrabander, 1999 Gerritsen et al., 1996 Goebel & Mills, 2000 Goebel et al., 2000 Herbert et al., 1994 Jacobs et al., 2001 Jern et al., 1989 Johnson et al., 1996 Kamei et al., 1998 Kang & Fox, 2000 Landmann et al., 1984 Larson et al., 2001 Manuck et al., 1991 Marsland et al., 1995, 1997, 2001 Matthews et al., 1995 McDonald & Yagi, 1960 Miller, Dopp, et al., 1999 Mills & Dimsdale, 1996 Mills, Berry, et al., 1995 Mills et al., 1996, 1998 Mills, Haeri, & Dimsdale, 1995 Mills, Ziegler, et al., 1995 Moyna et al., 1999 Naliboff et al., 1991 Naliboff, Solomon, Gilmore, Benton, et al., 1995 Naliboff, Solomon, Gilmore, Fahey, et al., 1995 Neumann & Chi, 1999 Neumann et al., 1998, 2000 Ohira et al., 1999 Olff et al., 1995 Pawlak et al., 1999, 2000 Pehlivanođlu et al., 2001 Peters et al., 1999 Pike et al., 1997 Redwine et al., 2001 Ring et al., 2000 Rohleder et al., 2001 Sauer et al., 1995 Schedlowski, Jacobs, Alker, et al., 1993 Schedlowski, Jacobs, & Stratmann, et al., 1993 Schmid-Ott et al., 1998, 2001 Sgoutas-Emch et al., 1994 Sieber et al., 1992 Spangler, 1997 Stone et al., 1993 Tsopanakis & Tsopanakis, 1998 Uchino et al., 1995	Lowe et al., 2000 Maes et al., 1997, 1998, 1999 Marchesi et al., 1989 Marshall et al., 1998 Marucha et al., 1998 McClelland et al., 1985 Ockenfels et al., 1994 Paik et al., 2000 Segerstrom, 2001 Segerstrom et al., 1998 Song et al., 1999 Uchakin et al., 2001 Van Rood et al., 1995 Vassend & Halvorsen, 1987 Vedhara & Nott, 1996 Wadee et al., 2001 Whitehouse et al., 1996 Wolf et al., 1994 Workman & La Via, 1987	Zisook et al., 1994			Martin & Dobbin 1988 McClelland et al., 1980 McDade et al., 2000 McIntosh et al., 1993 McNaughton et al., 1990 Miletic et al., 1996 H. Moss et al., 1998 R. B. Moss et al., 1989 Mulder et al., 1995 Patterson et al., 1995 Perry et al., 1992 Petrey et al., 1991 Rabkin et al., 1991 Ravindran et al., 1996 Schlesinger & Yodfat, 1991 Shea et al., 1991 Thomason et al., 1996 Thornton et al., 2000 Vialettes et al., 1989 Zautra et al., 1989	

Acute time-limited	Brief naturalistic	Event sequence	Chronic	Distant	Life event	Stress appraisal
Van der Pompe et al., 1997, 1998						
Van der Voort et al., 2000						
Wang et al., 1998						
Weisse et al., 1990						
Willemsen et al., 1998						
Winzer et al., 1999						
Zakowski, 1995						
Zakowski et al., 1992, 1994						
Zeier et al., 1996						

Table 3

Meta-Analysis of Immune Responses to Acute Time-Limited Stress in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
Leukocytes	25	1,129	.17	.04	.10, .25	.001	34.61
Granulocytes	12	397	.08	.06	minus;.04, .19	.18	31.77
Neutrophils	3	86	.30	.12	.08, .50	.009	2.13
Eosinophils	3	81	−.10	.16	−.39, .21	.53	2.99
Monocytes	15	590	.04	.05	−.05, .13	.43	15.43
Lymphocytes	24	828	.18	.05	.09, .26	.001	31.77
T lymphocytes	33	1,452	.07	.03	.01, .12	.01	25.48
T-helper lymphocytes	42	1,678	.01	.03	−.05, .05	.86	23.72
T-cytotoxic lymphocytes	42	1,678	.20	.03	.15, .25	.001	34.05
T-helper:T-cytotoxic ratio	19	920	−.23	.10	−.40, −.04	.02	17.98
Naive T lymphocytes	3	241	−.09	.11	−.29, .12	.41	2.46
B lymphocytes	18	739	−.07	.04	−.14, .01	.08	16.23
Activated B lymphocytes	4	60	−.15	.14	−.40, .14	.31	0.48
Natural killer cells	41	1,635	.43	.06	.33, .51	.001	172.75***
Large granular lymphocytes	8	362	.53	.30	.00, .83	.05	165.64***
Leukocyte subset percentage							
Granulocytes	5	295	−.13	.10	−.31, .07	.20	7.24
Neutrophils	5	217	.04	.07	−.10, .18	.56	3.75
Monocytes	7	277	.06	.09	−.12, .23	.55	10.82
Lymphocytes	7	350	.06	.06	−.05, .16	.30	1.34
T lymphocytes	10	497	−.05	.09	−.22, .13	.62	28.05***
T-helper lymphocytes	14	642	−.24	.04	−.31, −.16	.001	13.61
T-cytotoxic lymphocytes	15	692	.09	.04	.01, .16	.03	9.28
B lymphocytes	5	248	−.11	.07	−.24, .02	.09	1.46
Natural killer cells	15	693	.24	.11	.03, .42	.02	90.19***
Total immunoglobulins							
Serum IgA	4	91	.12	.11	−.10, .33	.30	0.95
Serum IgM	3	67	.14	.13	−.12, .37	.30	0.61
Secretory IgA secretion rate	6	293	.22	.08	.06, .37	.008	6.92
Secretory IgA concentration	8	337	.22	.09	.05, .38	.01	13.05
Basal cytokine levels							
Interleukin-1β	4	89	−.01	.11	−.23, .21	.91	0.25
Natural killer cell function							
Natural killer cell cytotoxicity	37	1,398	.30	.05	.20, .39	.001	108.85***
Per-cell cytotoxicity	8	287	.12	.11	−.09, .32	.26	18.12*
Lymphocyte proliferation							
Proliferation to ConA	17	706	−.17	.04	−.24, −.09	.001	14.12
Proliferation to PHA	26	1,120	−.17	.04	−.23, −.10	.001	35.36
Proliferation to PWM	10	480	−.10	−.05	−.19, −.01	.03	5.84
Cytokine production							
Interleukin-1β	3	78	.01	.12	−.23, .23	.98	5.78
Interleukin-4	3	136	−.19	.11	−.39, .03	.08	2.38
Interleukin-6	3	143	.28	.09	.13, .44	.001	12.84**
Interferon-γ	3	96	.21	.11	.01, .40	.05	0.24

Note. CI = confidence interval; IgA = immunoglobulin A; IgM = immunoglobulin M; ConA = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 4

Meta-Analysis of Immune Responses to Brief Naturalistic Stress in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
Leukocytes	9	249	.20	.07	.07, .32	.002	12.95
Granulocytes	3	56	.01	.15	−.27, .29	.93	0.01
Neutrophils	5	103	.11	.11	−.07, .34	.18	2.33
Monocytes	6	120	.06	.10	−.13, .25	.52	3.90
Lymphocytes	9	236	.06	.08	−.10, .23	.46	10.46
T lymphocytes	5	110	.03	.10	−.18, .22	.81	0.05
T-helper lymphocytes	7	197	.06	.08	−.09, .21	.43	1.08
T-cytotoxic lymphocytes	6	185	.05	.08	−.10, .20	.50	1.74
T-helper:T-cytotoxic ratio	12	351	.01	.07	−.11, .14	.84	13.68
B lymphocytes	5	126	.48	.56	−.51, .92	.35	99.48***
Natural killer cells	5	103	−.15	.11	−.35, .06	.16	2.06
Leukocyte subset percentage							
Monocytes	4	98	.11	.11	−.10, .32	.30	2.33
Lymphocytes	3	97	−.13	.11	−.33, .08	.23	2.05
T lymphocytes	5	160	−.16	.18	−.47, .19	.36	13.67**
T-helper lymphocytes	11	350	−.11	.10	−.29, .09	.28	26.56**
T-cytotoxic lymphocytes	12	362	−.03	.06	−.14, .08	.60	8.84
B lymphocytes	3	121	.07	.53	−.74, .80	.89	42.48***
Natural killer cells	5	163	−.02	.19	−.38, .35	.93	18.20**
Total immunoglobulins							
Serum IgA	6	243	.11	.07	−.02, .24	.10	1.28
Serum IgG	7	290	.06	.06	−.06, .17	.37	2.54
Serum IgM	7	290	.02	.10	−.17, .21	.83	13.41*
Secretory IgA rate	4	139	.09	.33	−.50, .63	.78	31.31***
Secretory IgA concentration	9	350	.19	.18	−.20, .46	.40	66.97***
Specific immunoglobulin							
Epstein-Barr virus	7	359	.20	.04	.10, .30	.001	6.56
Herpes simplex virus	4	225	.18	.08	−.02, .34	.08	4.97
Complement molecule							
C3	3	116	−.16	.10	−.34, .03	.09	1.77
Natural killer cell function							
Natural killer cell cytotoxicity	14	468	−.11	.05	−.21, −.01	.04	14.55
Lymphocyte proliferation							
Proliferation to ConA	9	220	−.32	.15	−.56, −.03	.03	27.08***
Proliferation to PHA	14	443	−.19	.09	−.35, −.02	.03	33.38***
Proliferation to PWM	3	106	−.17	.15	−.43, .12	.24	4.75
Cytokine production							
Interleukin-1β	6	149	.11	.08	−.05, .27	.17	15.07***
Interleukin-2	4	107	−.17	.36	−.71, .49	.63	27.34***
Interleukin-4	3	81	−.10	.12	−.32, .13	.39	0.69
Interleukin-6	3	100	.26	.11	.06, .44	.01	0.79
Interleukin-10	3	95	.41	.11	.21, .57	.001	1.65
Interferon-γ	8	314	−.30	.13	−.51, .05	.02	28.76***
Tumor necrosis factor-α	3	100	.18	.19	−.19, .51	.34	5.10

Note. CI = confidence interval; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; ConA = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 5

Meta-Analysis of Immune Responses to Brief Naturalistic Stress in Participants With Asthma

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Neutrophil function							
Superoxide release with FMLP	3	216	.20	.07	.06, .32	.004	0.39
Superoxide release with PHA	3	216	.37	.07	.24, .49	.001	0.68
Natural killer cell function							
Natural killer cell cytotoxicity	3	216	−.33	.07	−.45, −.21	.001	0.50
Lymphocyte proliferation							
Proliferation to PHA	3	216	.32	.07	.19, .43	.001	0.35

Note. CI = confidence interval; FMLP = *N*-formyl-met-leu-phe; PHA = phytohemagglutinin.

Table 6

Meta-Analysis of Immune Responses to Stressful Event Sequences in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
Monocytes	3	113	−.02	.10	−.21, .17	.87	0.39
Lymphocytes	5	223	.05	.07	−.09, .18	.49	2.65
T lymphocytes	5	213	−.02	.07	−.16, .12	.82	0.37
T-helper lymphocytes	9	566	.03	.11	−.19, .25	.81	39.29***
T-cytotoxic lymphocytes	8	544	−.14	.15	−.41, .15	.35	58.22***
T-helper:T-cytotoxic ratio	6	296	.06	.08	−.09, .21	.44	7.54
B lymphocytes	5	185	.02	.08	−.13, .17	.76	0.35
Natural killer cells	4	370	.17	.09	.00, .34	.05	5.06
Leukocyte subset percentage							
T lymphocytes	3	129	.02	.09	−.16, .19	.85	0.11
T-helper lymphocytes	5	279	.00	.06	−.12, .12	.94	0.00
T-cytotoxic lymphocytes	5	279	−.05	.06	−.17, .07	.43	3.65
B lymphocytes	3	129	−.04	.09	−.22, .14	.67	0.57
Specific immunoglobulin							
Epstein-Barr virus	3	198	.21	.07	.07, .34	.003	1.18
Natural killer cell function							
Natural killer cell cytotoxicity	13	698	−.03	.17	−.29, .34	.87	164.40***
Lymphocyte proliferation							
Proliferation to ConA	6	297	−.04	.06	−.15, .08	.53	2.53
Proliferation to PHA	11	675	.10	.10	−.09, .28	.32	42.25***
Proliferation to PWM	7	284	.12	.16	−.19, .40	.45	28.72***

Note. CI = confidence interval; ConA = concanavalin A; PHA = phytohemagglutinin; PWM = pokeweed mitogen.

*** $p < .001$.

Table 7

Meta-Analysis of Immune Responses to Chronic Stress in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
Leukocytes	4	240	.07	.07	−.06, .19	.32	2.12
Neutrophils	3	124	.36	.36	−.33, .79	.31	20.45***
Eosinophils	3	124	−.07	.22	−.47, .35	.75	8.07*
Monocytes	4	240	−.04	.17	−.36, .29	.83	14.33**
Lymphocytes	4	240	−.06	.10	−.25, .13	.54	5.24
T lymphocytes	5	470	−.03	.05	−.12, .06	.55	2.75
T-helper lymphocytes	10	786	−.05	.04	−.12, .03	.22	8.54
T-cytotoxic lymphocytes	10	786	−.08	.08	−.23, .08	.34	33.44***
T-helper:T-cytotoxic ratio	6	528	−.11	.08	−.29, .08	.26	17.47**
Activated B lymphocytes	3	138	−.02	.09	−.19, .15	.82	0.03
Natural killer cells	4	158	−.14	.32	−.65, .45	.65	33.61***
Leukocyte subset percentage							
Monocytes	3	224	.08	.10	−.11, .26	.42	3.18
T lymphocytes	5	522	−.03	.05	−.13, .07	.59	4.93
T-helper lymphocytes	10	860	−.07	.06	−.18, .03	.19	19.45*
T-cytotoxic lymphocytes	10	860	.02	.05	−.08, .11	.75	13.72*
Natural killer cells	6	246	.04	.09	−.13, .21	.64	7.85
Specific immunoglobulin							
Antibody to herpes simplex virus 1	3	185	.44	.34	−.19, .81	.17	20.78***
Antibody to influenza after vaccination	3	304	−.22	.05	−.33, −.11	.001	0.38
Natural killer cell function							
Natural killer cell cytotoxicity	8	563	−.12	.05	−.20, −.01	.04	11.58
Lymphocyte proliferation							
Proliferation to ConA	4	486	−.13	.06	−.24, −.02	.02	4.06
Proliferation to PHA	6	636	−.16	.06	−.27, −.05	.004	8.75
Cytokine production							
Interleukin-2	3	355	−.21	.05	−.31, −.11	.001	1.50

Note. CI = confidence interval; ConA = concanavalin A; PHA = phytohemagglutinin.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 8

Meta-Analysis of Immune Responses to Distant Stressors and Posttraumatic Stress Disorder in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Natural killer cell cytotoxicity	3	94	−.05	.25	−.49, .41	.84	7.67*

Note. CI = confidence interval.

* $p < .05$.

Table 9

Meta-Analysis of Immune Responses to Major and Minor Life Events of Unknown Duration in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
Lymphocytes	5	537	−.18	.17	−.47, .14	.27	20.28***
T lymphocytes	4	237	.00	.07	−.13, .13	.99	0.00
T-helper lymphocytes	5	227	.00	.07	−.13, .13	.99	0.00
T-cytotoxic lymphocytes	5	227	.05	.07	−.09, .18	.48	3.02
T-helper:T-cytotoxic ratio	3	70	.14	.38	−.54, .71	.71	12.11**
Natural killer cells	4	194	−.08	.07	−.22, .07	.28	2.72
Leukocyte subset percentage							
T lymphocytes	3	151	.20	.21	−.21, .55	.34	7.61*
T-helper lymphocytes	7	285	.01	.06	−.11, .13	.83	0.54
T-cytotoxic lymphocytes	6	205	−.01	.07	−.15, .14	.92	0.07
Natural killer cells	5	261	.00	.06	−.12, .12	.99	0.00
Total immunoglobulins							
Serum IgA	3	124	−.07	.10	−.26, .14	.52	2.19
Serum IgG	3	124	−.06	.10	−.24, .13	.54	2.06
Serum IgM	3	124	.03	.09	−.15, .21	.72	0.72
Secretory IgA rate	3	276	−.08	.10	−.26, .11	.43	3.97
Secretory IgA concentration	4	101	−.16	.14	−.42, .12	.25	4.34
Specific immunoglobulin							
Epstein-Barr virus	3	317	−.02	.11	−.23, .19	.86	5.65
Natural killer cell function							
Natural killer cell cytotoxicity	12	672	−.07	.07	−.20, .07	.35	29.39***
Lymphocyte proliferation							
Proliferation to ConA	3	72	−.13	.15	−.35, .16	.38	2.49
Proliferation to PHA	4	131	−.26	.15	−.50, .03	.08	6.11

Note. CI = confidence interval; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglob-ulin M; ConA = concanavalin A; PHA = phytohemagglutinin.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 10

Meta-Analysis of Immune Responses to Major and Minor Life Events of Unknown Duration in Participants With HIV/AIDS

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
T-helper lymphocytes	11	998	−.01	.03	−.08, .05	.70	7.70
T-cytotoxic lymphocytes	6	669	−.14	.08	−.29, .01	.08	17.92**
T-helper:T-cytotoxic ratio	3	356	−.02	.05	−.13, .09	.70	0.09
Natural killer cells	3	261	−.27	.06	−.38, −.15	.001	0.30
Leukocyte subset percentage							
T-helper lymphocytes	4	1,026	−.02	.06	−.15, .10	.73	7.58
T-cytotoxic lymphocytes	3	223	.00	.07	−.13, .13	.99	0.00

Note. CI = confidence interval.

** $p < .01$.

Table 11

Meta-Analysis of Immune Responses to Global Stress Appraisals in Healthy Participants

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
T lymphocytes	3	241	−.15	.09	−.31, .03	.10	3.15
T-helper lymphocytes	3	241	−.14	.10	−.32, .06	.18	3.80
T-cytotoxic lymphocytes	4	279	−.02	.09	−.19, .15	.80	5.09
Naive T lymphocytes	3	241	−.09	.11	−.29, .12	.41	4.29
Natural killer cells	3	205	−.20	.13	−.42, .04	.10	4.28
Leukocyte subset percentage							
T-helper lymphocytes	3	143	−.02	.09	−.19, .15	.79	0.08
T-cytotoxic lymphocytes	3	143	−.03	.09	−.23, .11	.48	0.60
Total immunoglobulin							
Serum IgG	4	332	.02	.10	−.18, .20	.87	7.51
Natural killer cell function							
Natural killer cell cytotoxicity	4	151	−.11	.09	−.27, .06	.21	1.85

Note. CI = confidence interval; IgG = immunoglobulin G.

Table 12

Meta-Analysis of Immune Responses to Stress Appraisals and Intrusive Thoughts Within Healthy Stressed Populations

Immune marker	*k*	*N*	*r*	SE_r	95% CI	*p*	*Q*
Leukocyte subset count							
T-helper lymphocytes	3	462	−.10	.11	−.31, .11	.35	7.52*
T-cytotoxic lymphocytes	3	462	−.26	.32	−.71, .34	.40	57.99***
Natural killer cell function							
Natural killer cell cytotoxicity	3	566	−.15	.06	−.27, −.02	.02	7.97

Note. CI = confidence interval.

* $p < .05$.

*** $p < .001$.