Stress and Immunity in Humans: A Meta-Analytic Review

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This article presents a meta-analysis of the literature on stress and immunity in humans. The primary analyses include all relevant studies irrespective of the measure or manipulation of stress. The results of these analyses show substantial evidence for a relation between stress and decreases in functional immune measures (proliferative response to mitogens and natural killer cell activity). Stress is also related to numbers and percents of circulating white blood cells, immunoglobulin levels, and antibody titers to herpesviruses. Subsequent analyses suggest that objective stressful events are related to larger immune changes than subjective self-reports of stress, that immune response varies with stressor duration, and that interpersonal events are related to different immune outcomes than nonsocial events. We discuss the way neuroendocrine mechanisms and health practices might explain immune alteration following stress, and outline issues that need to be investigated in this area.

Key words: Stress, immunity, stressor duration, interpersonal events.

INTRODUCTION

Several recent review articles conclude that stress is associated with changes in human immunity (1–5). In this article we use meta-analytic procedures (6, 7) to more closely evaluate this literature. We estimate the strength of association between stress and each immune outcome, and examine whether key characteristics of stressor measures or manipulations influence the strength of association. Stressor characteristics we evaluate include whether a stressor is an objective discrete event or based on self-reported events or distress, stressor duration, and whether the event is interpersonal or nonsocial. When we include all relevant studies irrespective of the measure or manipulation of stress in the analyses, we find substantial evidence for a relation between stress and both functional and enumerative immune measures. There is also evidence that objective events are related to larger immune changes than subjective self-reports of stress, stressor duration is important for some immune outcomes, and interpersonal events are related to different immune outcomes than nonsocial events.

We begin by describing what we mean by stress and discuss three stressor characteristics that have implications for stress-immunity associations. This is followed by a brief explanation of tests of the immune system used in the studies we review, as well as a description of the physiologic and behavioral mechanisms that provide plausible explanations for a link between stress and immunity. We then present our meta-analysis, an integration of the results, and a discussion of issues that should be considered in future research on this topic.

STRESS

The focus of the work we review is the association between negative life events (i.e., stressors) and alterations in human immunity. Negative life events have been operationalized in two primary ways, objective discrete events (e.g., bereavement, examinations), or self-report checklists of cumulative stressful events (e.g., life events, daily hassles). The theoretical model we adopt assumes that negative events (stressors) lead to negative affective states (distress) that then relate to alterations in human immunity.

We categorize the literature in three ways that may have implications for immune associations. First, we differentiate between discrete objective events and self-reported checklists of events. Self-reported checklists cumulatively assess the occurrence of events over a standard time frame (usually 1 year). Because events are cumulative, the types of events being associated with immune alteration vary across subjects in the sample. Moreover, each subject may experience a heterogeneous mix of events over the time frame. The reliability of subject recall over the time frame is also an issue with self-report measures, as is whether the measure is more reflective of stable individual difference variables than life events (8). Assessing immune alteration in a sample of individuals who have experienced a

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common objective life event circumvents these issues. The events that have been studied tend to be salient and stressful, and usually occur at a time relatively close to the immune assessment. We recognize that negative events do not always trigger negative affective states or psychological distress. Distress results only when the demands of the stressor are perceived to exceed one's own ability to cope (9). Nonetheless, because objective events in the existing literature tend to be intense and contiguous with immune assessment, the overall association of stress with immune alteration may be stronger.

A second dimension of theoretical interest is whether there are differences in immune alteration depending upon the duration of the stressor (3, 5). The studies reviewed include stressors that we have termed "acute laboratory" (lasting less than a half hour), "short-term naturalistic" (lasting between several days and 1 month, e.g., medical school examinations), and "long-term naturalistic" (lasting more than 1 month, e.g., bereavement, unemployment). Stressor duration may be important because the plausibility of stress-elicited hormones (e.g., catecholamines, cortisol, prolactin, growth hormone) affecting immune outcomes depends on the duration of the stressor (10). For example, because the rise in blood levels of cortisol takes approximately 30 minutes following exposure to a stressor (11), insufficient amount of time is allowed between stressor exposure and immune assessment for cortisol to reach its peak levels in most experimental laboratory studies. In comparison, cortisol may exert substantial impact on the immune system in the context of short- or long-term naturalistic stressors. Stressor duration, then, may be important in terms of immune alteration because differences exist in the neuroendocrine responses associated with stressors differing in duration. Another reason that stressor duration is of interest in terms of immune alteration is that people often habituate with prolonged and/or repeated exposure to stressors (12). Thus, *less* immune alteration might be seen with long-term than with short-term naturalistic stressors. However, chronic stress does not always lead to psychological, neuroendocrine, or immunologic habituation (13–15). Some chronic stressors (e.g., bereavement) encompass repetitive intermittent aspects such that stress "boosters" occur at relatively frequent intervals (e.g., seeing pictures), which might inhibit habituation. Long-term stressors might also be associated with relatively enduring changes in behavior, such as eating and sleeping habits after losing a spouse. The behavioral changes themselves may inhibit habituation, or alter hormone levels or other physiologic factors that then influence immune response.

A third issue of theoretical interest is if differences exist in immune alteration depending upon whether a stressor is an interpersonal event or not (3, 16). In this article, we refer to noninterpersonal events as nonsocial events. Stressful events that are interpersonal in nature (i.e., social exits and losses) are more likely to trigger depressive affect and clinical depression than other kinds of events (17, 18). Because affective responses may play a key role in triggering immune alterations (19, 20), we are interested in determining whether interpersonal events are related more strongly to alterations in the immune system than nonsocial events.

THE IMMUNE SYSTEM

The immune system protects people from disease-causing microorganisms and other harmful materials. Foreign materials are called *antigens*, which is short for "antibody generators." Organs of the body where most cells of the immune system are located are the bone marrow, thymus, lymph nodes, spleen, tonsils, appendix, and Peyer's patches (clumps of immune tissue in the small intestines). Because there is no easy way to access cells from these organs, psychoimmunologic work with humans focuses on immune processes occurring in circulating peripheral blood. Circulating blood transports immune components between organs of the immune system and sites of inflammation. Components of the immune system that circulate in blood also survey and combat against invading antigens (e.g., some types of white blood cells, antibody). Therefore, peripheral blood plays a key role in inflammatory and immune processes. Because the body's defensive processes are complex, we do not attempt a comprehensive description of the immune system (21, 22). What follows instead is a brief description of the immune components important in the studies included in the meta-analyses. Descriptions of the immune system for the naive reader are provided by O'Leary (5) and Calabrese et al. (1), and descriptions for the more advanced reader are provided by Male et al. (21) and Stites and Terr (22). We refer to these references as background and provide only brief descriptions of immune measures and tests included in the meta-analyses.

Tests of the Immune System

Two kinds of immune assays are used in the studies included in this article, enumerative and functional. The primary enumerative assay simply counts the numbers or percentages of different kinds of white blood cells in the peripheral blood. Blood includes a number of different kinds of white blood cells. Those relevant to this paper are monocytes and lymphocytes. There are also several different types of lymphocytes, including natural killer (NK), T, and B cells. Quantifying the number of circulating cells is important both because a certain number of each type of immune cell is needed in order to respond adequately to antigenic challenge, and because a balance of the different cell types is needed for the optimal immune response. Interpreting this quantification is difficult for several reasons, however. First, the numbers of different cell types do not necessarily correlate with the functional capacity of the immune system (22). Second, a variety of different mechanisms may explain a change in the number of a specific cell type in peripheral blood (e.g., cell migration to or from the lymph nodes or spleen and the peripheral blood). Finally, the health consequences of small changes in the absolute numbers or percent of lymphocytes in peripheral blood (which is normally what is seen in healthy subjects) have not been determined. Nonetheless, it is a relatively easy assay and is frequently included in studies.

A second enumerative technique is to quantify the amount of antibody (or immunoglobulin) in the saliva (salivary immunoglobulin A [IgA]) or circulating in the peripheral blood (serum IgA, IgG, and IgM). Immunoglobulins are protein molecules produced by B cells that recognize and bind to a specific antigen. They attach to this antigen, mark it for destruction and prevent it from causing infections. IgA, IgG, and IgM represent different types of antibody molecules, each with a specific function. IgA is primarily present in mucous secretions (e.g., salivary, nasal, genital) to combat entry of antigen into the body, while IgM and IgG are found primarily in peripheral blood. The half-lives of serum IgA, IgM, and IgG are 6 to 8 days, 9 to 11 days, and 25 to 35 days, respectively. Therefore, the timing of samples with respect to the occurrence of the stressor is very important for interpretation of the data. In addition, interpreting the meaning of the total levels of serum immunoglobulins is difficult because antibody needs to be specific for an antigen in order for it to function. Thus, for example, only some small portion of serum IgG would be effective in protecting against a particular antigen. It may be, however, that a rise in *total* serum antibody indicates the system's ability to respond to antigens by producing antibody and, therefore, provides a rough marker of antigen-specific activity.

A third enumerative technique is to quantify the amount of antibody (Ab) in serum to herpesviruses (23, 24). Almost everyone has been exposed to the common herpesviruses. These viruses differ from most other known viruses in that after exposure, they are present in the body all of the time, although often in latent states. Latent virus sometimes replicates, creating antigens the immune system sees. Ab is produced in response, and the amount of Ab produced fluctuates in relation to the amount of virus produced. Higher levels of Ab to latent viruses are interpreted as poorer outcomes because they indicate higher levels of virus replication. Two herpesviruses whose Ab levels are assessed in the reviewed studies are herpes simplex virus type 1 (HSV-1; responsible for cold sores) and Epstein-Barr Virus (EBV; responsible for infectious mononucleosis).

In terms of testing the *functional* capacity of human immune cells, two assays have been used in the reviewed studies: lymphocyte proliferative response and NK cell cytotoxic activity. They are in vitro assays, that is, the functions of the cells are studied outside the body in the laboratory. Lymphocytes are the focus of both of these assays, as these types of cells perform some of the most important immunologic functions when the body is battling invading organisms. The first assay, lymphocyte proliferation, examines how effectively stimulated lymphocytes divide (i.e., proliferate). Lymphocytes are stimulated by incubating them with substances (called mitogens) capable of nonspecifically inducing T or B lymphocytes to divide. It is assumed that the more proliferation that occurs, the more effectively the cells are functioning. Commonly used mitogens include phytohemagglutinin (PHA) and concanavalin A (Con A), and the proliferative responses to these mitogens are usually highly correlated.

The purpose of the second assay, NK cell cytotoxic activity, is to determine how effectively NK cells kill damaged or altered (e.g., infected, cancerous) cells. This is done by incubating immune cells with tumor cells. In immunologic terms, the immune cells are "effectors" (i.e., they affect the killing outcome), and the tumor cells are "targets" (i.e., they are the targets for the NK cells). This assay is typically performed at several effector-to-target cell ratios (e.g., 50 immune effector cells to 1 tumor target cell; common ratios are 5:1, 10:1, 25:1, 50:1, and

100:1). With higher ratios, more killing is expected to occur because there are more effector cells available for every tumor target cell. The results of the NK cell assay are often expressed as "lytic units (LU)," defined as the number of effector cells required to kill a certain percentage of target cells (25). Expressing the outcome in this way provides a quantitation of NK activity that is independent of the particular effector-to-target ratios included in a study, rendering comparable results across studies that included different ratios.

Mechanisms Linking Stress and Immunity: Physiology and Behavior

How might stressor exposure result in immune alteration? Both neuroendocrine and behavioral mechanisms provide plausible explanations (5, 19, 20, 26). First, stress is associated with the activation of several neuroendocrine systems, including the hypothalamic-pituitary-adrenal [HPA] axis and the sympathetic nervous system [SNS] (27). The activation of these two particular pathways results in elevated serum levels of cortisol and catecholamines (28). Immune cells have receptors for these hormones (10, 29–31), implying that they play a role in immune system modulation. Serum levels of cortisol, epinephrine, and norepinephrine are also directly associated with various indicators of immunity (5, 10). Recent evidence suggests, however, that the SNS is associated with alterations in human immune function before the HPA axis has had enough time to respond with an increase in cortisol. Support for this view comes from two laboratory studies that find SNS-associated immune alteration in the absence of changes in serum cortisol (32, 33). A study of individuals living near Three Mile Island also suggests that there are SNS-associated immune alterations in the absence of differences in serum levels of cortisol (34). Thus, in the case of certain immune responses (e.g., lymphocyte proliferation) it may be that the SNS plays a greater role in stress-induced immune alteration than the HPA axis. It is also possible that other endocrine systems activated by stress play roles in altering immune responses following stressor exposure. These systems include prolactin, growth hormone, and the opioids (29).

An alternative kind of pathway that could account for the relation between stress and immunity involves the association of stress with specific behaviors that modulate immune response. Distressed persons sleep less, exercise less, have poorer diets, smoke more, and use alcohol and other drugs more often than nondistressed people (35, 36). These behaviors have all been shown to alter immune response (37–41). The association of stressor exposure with immunity might, therefore, be accounted for by the health practices of stressed subjects being different from those of controls.

THE META ANALYSIS

Meta-analysis refers to the "statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" (6, p. 3). The primary analyses we conduct focus on immune system relations with stress using studies with any measure or manipulation of stress in the analyses. In addition, wherever data are available, we address differences in immune outcomes depending upon whether stressors are self-reported or objective events, stressor duration, and whether events are characterized as interpersonal or nonsocial. In each case, four groups of meta analyses are done to assess associations between stress and 1) indicators of cellular immune function, 2) the numbers and/or percents of circulating white blood cells, 3) immunoglobulin levels, and 4) herpesvirus antibody titers. The number and percent of white blood cells are analyzed separately because they represent different things. For example, a decrease in the percent of T cells in peripheral blood can reflect one of two things: a decrease in the number of T cells, or an increase in the number of another type of white blood cell (ensuring that the percent of T cells decreased). Moreover, a recent meta-analysis indicates that this distinction is important because alterations in the number, and not percent, of specific kinds of lymphocytes were associated with the clinical diagnosis of depression (19).[1]

[1] Because several recent reviews of the depression-immunity literature show that age moderates depression-immunity associations (19–20,56), we explored age effects with the available data in these studies. However, no consistent pattern of reliable effects was found. The mean age of subjects in the majority of these studies, however, was under 30 years old, and it may be that age-driven immune system effects will be most evident when samples include older individuals (e.g., over 40) (42).

METHOD

Selection of Studies for Inclusion

In order to identify studies for inclusion in the meta-analysis, a computerized search was conducted (Medline), the reference lists from existing reviews were inspected, as were the reference lists of articles retrieved from the reviews. Key words used in the computer search included stress, life events, daily hassles, bereavement, examinations, psychoimmunology, and psychoneuroimmunology; however, the majority of the articles were retrieved through reference lists of recent reviews. These searches were conducted in December 1991. We included only those English studies published in peer-review journals that reported data from independent samples. Therefore, two studies reported by Irwin and colleagues were not included here (43, 44). To be included in the meta-analyses, a study had to meet three criteria: a self-report measure of stress had to be used or the study population had to be experiencing one common stressor; the participants had to be physically healthy (e.g., not cancer or AIDS patients); and the immune outcome had to be shared by at least two other studies. The three criteria yielded a total of 38 studies which are listed in the "Appendix." Articles meeting the first two criteria, but not sharing an immune outcome with at least two other studies are listed separately in the "Appendix."

For the analyses investigating effects of stressor duration, we defined three levels: acute laboratory stressors (lasting less than a half hour), short-term naturalistic stressors (lasting between several days and 1 month; medical school examinations), and long-term naturalistic stressors (lasting more than 1 month; divorce, caregiving, bereavement, living near Three Mile Island [TMI], unemployment). Studies are coded for duration based on the average time since the stressful event reported for the sample. For analyses of self-reported stress, the stress measures include assessments of life events (PERI Life Events Scale - 45; Geriatric Social Readjustment Rating Scale - 46; Social Readjustment Rating Scale - 47), daily hassles (Hassles and Uplifts - 48), perceived stress (a list of adjectives - 49), and job strain (50). Types of events include bereavement, divorce, caregiver stress, examination stress, living near TMI, and unemployment. Finally, we categorized bereavement, caregiving, and divorce as interpersonal events, and laboratory stress, examinations, living near TMI, and unemployment as nonsocial events. We recognize that some of these events (e.g., unemployment) may be both interpersonal and nonsocial in nature, but have categorized them in terms of what we believe is their most salient feature. The coding of each study for these three distinctions is indicated in the "Appendix."

Meta-Analytic Techniques

We used the product-moment correlation coefficient (r) as the effect size estimate. An effect size indicates how large an association is between two variables, disregarding sample size. Whenever a study used a between-subjects design, effect sizes were calculated from means and standard deviations provided in the article. If these data were not provided or if a study used a within subjects design, effect sizes were calculated from the results of a statistical test (e.g., a t or F value). Because the procedures of meta-analysis rest on the assumptions of independence of effect sizes (7, 51), each study was allowed to contribute only one effect size per immune outcome (although studies did contribute more than one effect size to the review if they had more than one immune outcome). Therefore, in analyses including all stress studies, the mean of the relevant effect sizes was used for studies that assessed more than one type of stressor (e.g., life events and daily hassles).

Combined or mean effect sizes were computed by: transforming each r into a Fisher's z coefficient, summing these Fisher's z's, dividing the sum by the number of studies, and transforming the resulting Fisher's z back into an r (7, 51). We used the weighted mean effect size, which assigns more weight to studies with larger numbers of subjects. This is important because correlations become more stable as sample size increases and effect sizes based on large sample sizes deviate less from the population effect size than those from smaller samples (although the pattern of results remains essentially the same when the unweighted effect size is used). There is no consensus on how to determine whether an effect size differs significantly from zero. However, two relevant pieces of information are whether the confidence interval includes the value zero (based on the random effects model; 51), whereas another is the size of the z statistic (based on a fixed effects model).

One common criticism of meta-analysis is that an inherent bias exists in the studies selected for inclusion in the analysis because studies with significant findings are more likely to be published than studies with nonsignificant findings. This bias is referred to as the "file-drawer problem." It is assumed that an unknown number of studies with effect sizes of zero remain unpublished somewhere in file drawers. Rosenthal (7) suggests calculating a "fail-safe N" to address this bias. The fail-safe N reflects the number of file-drawer studies required before the combined effect size is no longer significant. If the fail-safe N is relatively small, a file-drawer problem might exist. Rosenthal (51) provides a formula for computing the fail-safe N. He also provides a rule of thumb for determining whether the fail-safe N is small enough to suggest an inclusion bias in the meta-analysis. Specifically, if the fail-safe N for the analysis is less than five times the number of included studies plus 10, a file-drawer problem may be present. For example, if seven studies are included in an analysis, and the fail-safe N is below 45, an inclusion bias might exist. For each analysis where a reliable effect was found, therefore, we compute a fail-safe N.

Three studies used in the meta-analysis failed to report means and standard deviations, the actual effect size, or probability value obtained, but indicated that results were statistically significant with p less than .05. In these cases, the probability levels were assumed to actually be .05, and transformations to r were done. This is a conservative approach because the actual effect size would most likely have been larger than the value that was used. Another six studies failed to report means and standard deviations, the actual effect size, or probability value obtained, but stated that the results were not statistically significant for certain parameters. In these cases, the effect sizes were assumed to be equivalent to a zero correlation, again a conservative approach.

Functional immune parameters included as outcomes are lymphocyte proliferation in response to PHA and Con A, and NK cell cytotoxic activity. Enumerative parameters include salivary IgA and serum levels of IgA, IgG, and IgM, the helper:suppressor ratio, antibody titers to HSV-1 and EBV, and white blood cell types. The types of cells used as enumerative outcomes included total white blood cells, two kinds of white blood cells (monocytes and lymphocytes), three kinds of lymphocytes (NK, B, and T cells), and two kinds of T cells (helper and suppressor/cytotoxic T cells).

TABLE 1. Meta-Analysis of Associations Between Stress and Cellular Immune Function

	No. of studies	N	Mean effect size (r)	95% Confidence interval	Z	Fail-safe N	File drawer issue?
PHA							
All stress	10	483	−.204	−.29–−.11	4.51***	65	No
Events	9	458	−.192	−.28–−.10	4.14***	48	Yes
Long-term	4	222	−.247	−.37–−.12	3.72***	16	Yes
Interpersonal	7	395	−.201	−.30–−.10	4.03***	35	Yes
Nonsocial	3	88	−.280	−.46–−.07	2.64**	5	Yes
Con A							
All stress	7	443	−.237	−.32–−.15	5.04***	58	No
Events	7	443	−.237	−.32–−.15	5.04***	58	No
Long-term	3	229	−.191	−.31–−.06	2.91**	6	Yes
Interpersonal	6	403	−.126	−.22–−.03	2.52*	8	Yes
NK Cell Activity							
All stress	11	497	−.245	−.33–−.16	5.53***	114	No
Self-report	7	382	−.231	−.33–−.13	4.58***	47	No
Events	5	190	−.358	−.48–−.22	5.07***	43	No
Short-term	3	149	−.401	−.53–−.25	5.07***	25	No
Nonsocial	4	172	−.295	−.43–−.15	3.93***	19	Yes

* $p < .05$; ** $p < .01$; *** $p < .001$ (two-tailed).

RESULTS

Tables 1 through 5 present the results of the meta-analyses. Each table includes information on the number of studies assessing specific immune parameters, the total number of subjects across studies, the mean effect size, the 95% confidence interval, the corresponding Z in a normal distribution, the fail-safe N, and whether there is a file-drawer problem associated with the effect. Interpreting the effect size is equivalent to interpreting a correlation; the range is −1 to 1, with higher values indicating a stronger effect. Effect sizes have positive signs when stress is related to *increases* in an immune parameter and negative signs when stress is related to *decreases*. When there is a file-drawer problem, it is probably best to think of it as reflecting a marginal effect that needs additional confirmation. We report the results of all analyses addressing whether stress is self-reported or is an objective event, stressor duration, and whether events are interpersonal or nonsocial. Where it is possible, we also test for differences between correlations to determine whether one of the effect sizes within a particular category (i.e., self-report vs. objective events) is reliably different from the other.

Meta-Analysis of Associations Between Stress and Cellular Immune Function

The results of the meta-analyses addressing whether stress is related to cellular immune function are presented in Table 1. Stress is negatively related to the proliferative response of lymphocytes to PHA (−.204) and Con A (−.237), as well as NK cell activity (−.245). There is a reliable decrease in proliferative response to PHA when stressful events are either interpersonal (−.201) or nonsocial (−.280), but the interpersonal-nonsocial distinction does not differentiate lymphocyte proliferation in response to PHA ($p < .10$). There is a reliable decrease in NK cell activity when stress is assessed by self-report (−.231) and following objective events (−.358), and the effect is marginally stronger in the case of objective events than it is for self-reports of stress ($p < .06$).

Meta-Analysis of Associations Between Stress and Numbers and Percents of White Blood Cells

Tables 2 and 3 present the results of the meta-analyses addressing whether an association exists between stress and the number and/or percent of different kinds of circulating white blood cells. Data in Table 2 show that stress is positively related to the number of circulating white blood cells (.361). In addition, stress is negatively related to the number of circulating B cells (−.243), T cells (−.256), helper T cells (−.204), suppressor/cytotoxic T cells (−.387), and large granular lymphocytes (−.319; NK cells are a subset of large granular lymphocytes). Data in Table 3 show that stress is also reliably associated with the percent of lymphocytes that are T cells (−.130), helper T cells (−.174), and suppressor/cytotoxic T cells (−.160). The fail-safe Ns suggest that only the effect for the number of suppressor/cyto-

TABLE 2. Meta-Analysis of Associations Between Stress and Numbers of Circulating White Blood Cells

	No. of studies	N	Mean effect size (r)	95% Confidence interval	Z	Fail-safe N	File drawer issue?
Total white blood cells							
All stress	5	143	.361	+.20–+.50	4.43***	31	Yes
Monocytes							
All stress	4	80	−.134	−.36–+.10	1.19		
Total lymphocytes							
All stress	8	198	−.063	−.20–+.08	.88		
Events	3	53	−.084	−.36–+.21	.60		
B Cells							
All stress	9	259	−.243	−.36–−.12	3.95***	43	Yes
Events	6	196	−.246	−.38–−.10	3.48***	21	Yes
Acute laboratory	3	63	−.233	−.46–+.03	1.83*		
Long-term	5	144	−.330	−.47–−.17	4.04***	25	Yes
Interpersonal	3	76	.016	−.22–+.25	.14		
Nonsocial	6	183	−.343	−.47–−.20	4.76***	44	No
T cells							
All stress	8	234	−.256	−.38–−.13	3.97***	38	Yes
Events	6	196	−.303	−.43–−.16	4.32***	35	Yes
Long-term	5	144	−.402	−.54–−.25	5.00***	44	No
Interpersonal	3	76	−.004	−.24–+.23	.04		
Nonsocial	5	158	−.368	−.50–−.22	4.76***	37	No
Helper T cells							
All stress	7	192	−.204	−.34–−.06	2.84**	14	Yes
Events	4	129	−.237	−.40–−.06	2.70**	15	Yes
Acute laboratory	3	63	−.135	−.38–+.13	1.06		
Long-term	4	129	−.237	−.40–−.06	2.70**	15	Yes
Suppressor/cytotoxic T cells							
All stress	7	192	−.387	−.51–−.25	5.54***	72	No
Events	4	129	−.669	−.76–−.56	8.67***	107	No
Acute laboratory	3	63	.392	+.15–+.59	3.18***	8	Yes
Long-term	4	129	−.669	−.76–−.56	8.67***	107	No
Helper:suppressor ratio							
All stress	8	394	.103	+.01–+.20	2.04*	4	Yes
Events	7	366	.098	−.01–+.20	1.87*		
Long-term	5	292	.171	+.05–+.28	2.92**	11	Yes
Interpersonal	4	217	.228	+.09–+.35	3.38***	13	Yes
Nonsocial	3	149	−.097	−.26–+.07	1.17		
Large Granular Lymphocytes							
All stress	3	68	−.319	−.53–−.08	2.65**	5	Yes

* $p < .05$; ** $p < .01$; *** $p < .001$ (two-tailed).

toxic T cells does not suffer from the file-drawer problem.

Four parameters were assessed in a sufficient number of studies to compare the stress effect sizes for numbers and percents: B, T, helper T, and suppressor/cytotoxic T cells. Testing for differences between correlations, we find that in two cases, the effect for number of cells is reliably stronger than the effect for percent of cells (B cells, −.243 vs. .000; suppressor/cytotoxic T cells, −.387 vs. −.160) ($p < .01$). For the other two parameters no reliable differences between effect sizes are evident.

We compared event duration for five parameters: the number of circulating B cells, helper T cells, and suppressor/cytotoxic T cells, and the percent of lymphocytes that are helper T cells and suppressor/cytotoxic T cells. First, comparing acute laboratory stressors to long-term naturalistic stressors, the strength of association is not reliably different for either the number of B cells or helper T cells ($p > .05$). In the case of suppressor/cytotoxic T cells, however, there is a reliable difference between acute laboratory and long-term naturalistic stressors, with an *increase* in their number following acute laboratory stressors (+.392) and a *decrease* in their number following long-term naturalistic stressors (−.669) ($p < .001$). Second, comparing short- to long-term naturalistic stressors, the strength of association is not reliably different for the percent of lymphocytes that are suppressor/cytotoxic T cells. In the case of the percent of helper T cells, however, short-term naturalistic stressors are related to larger

TABLE 3. Meta-Analysis of Associations Between Stress and Percents of Circulating White Blood Cells

	No. of studies	N	Mean effect size (r)	95% Confidence interval	Z	Fail-safe N	File drawer issue?
B cells							
All stress	3	176	.000				
T cells							
All stress	5	284	−.130	−.25–−.01	2.19*	4	Yes
Events	4	261	−.141	−.26–−.02	2.29*	4	Yes
Long-term	3	221	−.084	−.22–+.05	1.25		
Interpersonal	3	221	−.084	−.22–+.05	1.25		
Helper T cells							
All stress	10	555	−.174	−.26–−.09	4.12***	52	Yes
Events	7	443	−.121	−.21–−.03	2.55**	10	Yes
Short-term	3	97	−.319	−.49–−.12	3.18***	8	Yes
Long-term	4	346	−.063	−.17–+.04	1.17		
Interpersonal	4	346	−.063	−.17–+.04	1.17		
Nonsocial	4	120	−.392	−.54–−.22	4.42***	25	Yes
Suppressor/cytotoxic T cells							
All stress	10	555	−.160	−.24–−.08	3.79***	43	Yes
Events	7	443	−.234	−.32–−.14	4.99***	58	No
Short-term	3	97	−.267	−.45–−.07	2.65**	5	Yes
Long-term	4	346	−.225	−.32–−.12	4.22***	22	Yes
Interpersonal	4	346	−.225	−.32–−.12	4.22***	22	Yes
Nonsocial	4	120	−.056	−.24–+.13	.61		
NK cells							
All stress	4	305	−.079	−.19–+.04	1.37		
Long-term	3	282	−.132	−.25–−.01	2.22*	3	Yes
Interpersonal	3	282	−.132	−.25–−.01	2.22*	3	Yes

* $p < .05$; ** $p < .01$; *** $p < .001$ (two-tailed).

decreases than long-term natualistic stressors (−.319 vs. −.063; $p < .01$).

We also compared interpersonal with nonsocial events for five immune parameters: the helper: suppressor ratio, the number of circulating B and T cells, and the percent of lymphocytes that are helper and suppressor/cytotoxic T cells. In the case of the helper:suppressor ratio, a reliable difference exists between the effect size for interpersonal events (+.228) and nonsocial events (−.097) ($p < .001$). This is also true of the number of circulating B cells (+.016 vs. −.343; $p < .01$), and the number of circulating T cells (−.004 vs. −.368; $p < .01$), as well as the percent of lymphocytes that are helper T cells (−.063 vs. −.392; $p < .001$) and suppressor/cytotoxic T cells (−.225 vs. −.056; $p < .05$). It should be pointed out that for each of these parameters, the studies that involve long-term naturalistic stressors are the *same* as those that involve interpersonal events.

Meta-Analysis of Associations Between Stress and Immunoglobulin Levels

Table 4 presents the results of the meta-analyses addressing whether associations exist between stress and immunoglobulin levels. Stress is negatively related to two of the four immune parameters, including salivary IgA (−.144) and serum IgM (−.125). In the case of salivary IgA, the effect size is reliably larger when the outcome is assessed following an objective event (−.229) rather than related to subjective self-reports of stress (−.074) ($p < .05$).

There is a problem in the s-IgA literature, however, that raises doubt as to whether any of these relations are supportive of stress-elicited change in s-IgA level. Many of these studies assess the concentration of s-IgA (amount of s-IgA in a given volume of saliva, μg/ml) without controlling for the amount of saliva produced during the sampling period. The problem is that salivary flow itself is associated with both changes in stress and changes in concentration of s-IgA (52, 53). In order to get an uncontaminated measure of s-IgA production, other studies calculate a *synthesis rate* (divide the concentration of s-IgA by the volume of saliva and report amount of s-IgA produced in a given time, μg/min). We conducted two additional analyses (also reflected in Table 4) to compare the results of studies that report the concentration of s-IgA vs. those that report the synthesis rate. Of the eight studies included in the total salivary IgA analysis, two reported synthesis rate, four reported concentration, and two were not specific about the outcome they reported. As apparent from

Table 4, analysis of the synthesis rate studies yields an effect size of −.044, whereas analysis of the concentration studies yields a reliably stronger effect size of −.236 ($p < .05$). Our failure to find an association between stress and s-IgA in the two studies using synthesis rate raises serious questions as to the interpretability of the s-IgA results and suggests that additional studies using synthesis rate are needed before a more definitive conclusion can be made.

Meta-Analysis of Associations Between Stress and Herpesvirus Antibody Titers

Table 5 presents the results of the meta-analyses addressing whether associations exist between stress and herpesvirus antibody titers. Strong positive associations exist between stress and titers of EBV-VCA (.528) and HSV-1 (.848). Strong positive associations also exist between titers of EBV-VCA and long-term naturalistic (.535) and interpersonal stressors (.535). Again, however, the studies that involve long-term naturalistic stressors are the same as those that involve interpersonal events.

DISCUSSION

We find substantial evidence for a relation between stress and both functional and enumerative immune measures in humans. In terms of functional parameters, stress is associated with reliable decreases in the proliferative response to PHA and Con A, as well as NK cell activity. Although the size of these effects are considered low to moderate (−.20 to −.25) (see Ref. 54 for evaluation of effect sizes),

TABLE 4. Meta-Analysis of Associations Between Stress and Immunoglobulin Levels

	No. of studies	N	Mean effect size (r)	95% Confidence interval	Z	Fail-safe N	File drawer issue?
Total salivary IgA							
All stress	8	481	−.144	−.23–−.05	3.10**	21	Yes
Self-report	5	348	−.074	−.18–+.03	1.38		
Events	5	262	−.229	−.34–−.11	3.73***	21	Yes
Short-term	4	187	−.214	−.35–−.07	2.94**	9	Yes
Nonsocial	5	262	−.229	−.34–−.11	3.73***	21	Yes
Synthesis rate	2	178	−.044	−.19–+.11	.58		
Concentration	4	163	−.236	−.38–−.09	3.03**	10	Yes
Total serum IgA							
All stress	5	255	<.001	−.13–+.13	.01		
Short-term	3	105	.274	+.08–+.45	2.83**	6	Yes
Nonsocial	3	105	.274	+.08–+.45	2.83**	6	Yes
Total serum IgG							
All stress	7	317	−.003	−.12–+.11	.05		
Events	6	268	+.053	−.07–+.18	.87		
Short-term	3	98	+.277	+.08–+.46	2.77**	6	Yes
Nonsocial	4	118	+.265	+.08–+.43	2.90**	8	Yes
Total serum IgM							
All stress	6	275	−.125	−.24–−.01	2.08**	4	Yes
Short-term	3	105	.147	−.05–+.33	1.50		
Nonsocial	4	125	−.053	−.23–+.13	.59		

* $p < .05$; ** $p < .01$; *** $p < .001$ (two-tailed).

TABLE 5. Meta-Analysis of Associations Between Stress and Herpesvirus Antibody Titers

	No. of studies	N	Mean effect size (r)	95% Confidence interval	Z	Fail-safe N	File drawer issue?
EBV-VCA							
All stress	6	421	.528	+.45–+.60	11.70***	298	No
Long-term	4	332	.535	+.45–+.61	10.53***	160	No
Interpersonal	4	332	.535	+.45–+.61	10.53***	160	No
HSV-1							
All stress	3	112	.848	+.78–+.89	11.80***	151	No

* $p < .05$; ** $p < .01$; *** $p < .001$ (two-tailed).

their magnitude is consistent across functional parameters. In terms of cell numbers, stress is reliably associated with a higher number of circulating white blood cells and lower number of circulating B cells, T cells, helper and suppressor/cytotoxic T cells, and large granular lymphocytes. Stress is also reliably associated with a lower percent of lymphocytes that are T cells, helper T cells, and suppressor/cytotoxic T cells. These findings are in contrast to an earlier paper, where we found that only the number, and not the percent, of different cell types were reliably associated with depression (19). With respect to immunoglobulin levels, stress is reliably associated with decreases in total serum IgM (−.13) and the concentration of total salivary IgA (−.24), although the latter association is difficult to interpret because of methodological shortcomings. Finally, large increases in antibody titers to EBV-VCA and HSV-1 are also associated with stress (effect sizes are .53 and .85).

One potential limitation of this review is that 11 of the 38 studies included in the review (29%) come from the laboratory of Glaser, Kiecolt-Glaser, and colleagues. Thus, there is a question regarding how strongly the results of the meta-analysis might be influenced by results from a single laboratory. To address this issue, we generated effect sizes that excluded all data from their lab. Of the 23 immune outcomes included in the review, Glaser, Kiecolt-Glaser, and colleagues had contributed data to 14 of them. Four of the 14 outcomes could not be reanalyzed because once Glaser, Kiecolt-Glaser data were excluded, an insufficient number of studies remained for a meta-analysis. These include percent of lymphocytes that are T cells and NK cells, and antibody titers to the two herpesviruses. Effect sizes for 6 of the 10 immune parameters that were reanalyzed were not reliably different when data from the Glaser, Kiecolt-Glaser lab were dropped. These include proliferative response to PHA, NK cell activity, the helper:suppressor ratio, total salivary IgA, total serum IgA, and total serum IgG. However, effect sizes for four of the immune parameters changed significantly when data from the Glaser, Kiecolt-Glaser lab were dropped: proliferative response to Con A (−.24 when the Glaser, Kiecolt-Glaser data are included vs. −.34 when they are not, $p < .01$), percent of lymphocytes that are helper T cells (−.18 vs. −.31, $p < .01$), percent of lymphocytes that are suppressor/cytotoxic T cells (−.16 vs. +.12, $p < .01$), and total serum IgM (−.13 vs. −.26, $p < .01$). Three of these differences suggest that when the Glaser, Kiecolt-Glaser data are included the effect size is simply attenuated—the direction of the effect is the same. The fourth immune parameter, however, shows an effect in the opposite direction. Of the 23 immune outcomes, then, four (17%) are significantly affected by data being generated by the Glaser, Kiecolt-Glaser laboratory. In the case of only one of 23 effects (4%), however, would a different conclusion have been made had the Glaser, Kiecolt-Glaser data not been available.

Although we find several associations between stress and both functional and enumerative measures of the immune system, interpreting these outcomes with respect to health is difficult. The health consequences of changes in the enumerative immune parameters (e.g., numbers of lymphocytes in peripheral blood) have not been determined in otherwise healthy populations. Nothing is known about the health consequences of relatively small changes in the level of serum immunoglobulins or antibody titers to herpesviruses. Although decreased NK cell activity has been implicated in certain human diseases (e.g., progression of cancer, chronic viral infection, autoimmune diseases) (55), the direct health consequences of a decrease in this parameter have not been established. A decreased proliferative response to mitogens is associated with increased levels of mortality and an increased number of hospitalizations among the elderly (56, 57). There seems to be no correlation, though, between the decreased proliferative responses to mitogens and mortality or hospitalization because of specific disease entities (56, 57). At this point, therefore, it is difficult to say whether stressor-induced immune alterations have substantial implications for health (19, 20, 58).

Stressor Characteristics

What did we learn about the characteristics of stressors that may be most related to immune alteration? It seems that immune alteration is greater when *objective* events are assessed compared when *self-reported* stress is measured. In both cases where it was possible to make this comparison (NK cell activity and salivary IgA), the effect was stronger for objective events. Earlier we raised several issues in regard to the cumulative self-report measures that might explain this effect, including the heterogeneity of stressors within a sample (both within and between subjects), and recall bias and error. Also, in contrast to the 1-year time frame that cumulative checklists of life events often utilize, the occurrence of objective events tend to be proximal to immune assessments (or the time can at least be pinpointed). This is important because recent negative events

will more likely be related to negative affect than distant events. Although the occurrence of negative life events does not guarantee negative affect in all people, the objective events used in these studies may have been salient and/or stressful enough to elicit at least some distress, and hence immune alteration.

Our examination of the effect of stressor *duration* on immune alteration showed two things. First, acute laboratory stressors *increase* the number of circulating suppressor/cytotoxic T cells whereas long-term naturalistic stressors *decrease* their number. It is interesting to note that although both short- and long-term naturalistic stressors are negatively related to NK cell function, a laboratory study shows a positive association (.445) between exposure to an acute stressor and NK cell function (data not shown because it was the only laboratory study to assess this immune outcome) (59). Why would acute stressors result in different immune effects than more prolonged naturalistic stressors? It is likely that the processes responsible for the observed alterations differ. Immune outcomes assessed after a laboratory stressor are probably altered by the *acute* secretion of stress-elicited hormones (e.g., catecholamines). The sudden change in circulating levels of hormones then results in the immune system showing an immediate, but short-lived, deviation from baseline levels. On the other hand, exposure to more prolonged stressors may lead to relatively stable changes in the baseline levels themselves. The secretion of stress-elicited hormones (e.g., cortisol, catecholamines) over the long-term has a lasting physiologic impact, probably by altering neuroendocrine receptor numbers, densities, or availabilities (28, 60). Physiologic feedback loops then result in the system operating at different baseline levels. Because these are two different processes then, it would be possible for an individual who has experienced a long-term naturalistic stressor (e.g., bereavement) to show an altered immune baseline level, but to simultaneously show a temporary rapid immune fluctuation when exposed to an acute laboratory stressor.

Our examination of the effect of stressor duration on immune alteration also showed that long-term naturalistic stressors continue to be related to alterations in immune outcomes. Specifically, a reliable association between exposure to a long-term stressor and the immune system was found for 10 of the 12 immune outcomes where the effect was examined. Thus, these data support the suggestion made earlier that habituation may not occur when stressors are long-term. Rather, it may be that the longer an individual is exposed to a particular stressor, the more likely it will be that there will be a change in baseline immune values. In addition to long-term physiologic changes associated with the excretion of stress hormones, immune alteration might result from behavior changes that arise in response to the stressor. These behaviors might be adaptive and encompass active and effortful coping, or might be somewhat self-destructive (e.g., drinking alcohol, smoking) (61). Either way, behavioral adaptations may themselves lead to physiologic changes that lead to additional immune alteration. Alternatively, individuals may not have difficulty adjusting to the stressor itself, but over the long term, may evidence immune alteration associated with secondary effects of the stressor. For example, an individual's social network can react in particularly unhelpful or hurtful ways after a naturalistic stressor (e.g., by placing blame), in effect creating new stressors to cope with (62). Even when negative reactions are not experienced, long-term stressors seem to erode the social support available to individuals experiencing them (63).

Finally, we were able to compare the strength of the effect for *interpersonal* and *nonsocial* events for six immune outcomes. Results indicated that for two immune outcomes interpersonal events are related to greater immune alteration than nonsocial events (the helper:suppressor ratio, and the percent of suppressor/cytotoxic T cells), although for three immune outcomes nonsocial events are related to greater immune alteration than interpersonal events (the number of B cells and T cells and the percent of helper T cells). As we pointed out earlier, the studies that comprise interpersonal events in these cases overlap with those that comprise long-term naturalistic stressors. It may be the nature of interpersonal events that they do not resolve quickly, though, and this may be part of the reason they can have substantial impact on individuals (3, 5, 16). Nonetheless, even where it seems that interpersonal events may have more impact on immune outcomes, this conclusion needs to be made with caution because of the overlap with stressor duration. Although interpersonal stressful events are more likely to trigger depressive affect and clinical depression than other kinds of events (17, 18), then, it is not clear that they are more strongly related to immune outcomes than nonsocial events. It does seem, however, that interpersonal events are related to alterations in *different* immune outcomes than nonsocial events.

Other Issues Needing to Be Addressed

This is the first article to document the strength of association between stress and various indicators of immunity in humans. It is clear that relatively strong and consistent associations exist for both functional and enumerative immune measures. However, there are several areas where existing knowledge is limited. First, we know relatively little about the specific characteristics of stressors that are relevant to immune alteration. We were able to investigate three parameters. However, of the 23 immune outcomes included in this paper, only two could be compared in terms of self-report vs. objective events, only six could be compared in terms of stressor duration, and only six could be compared in terms of interpersonal vs. nonsocial events. Thus, we need a more comprehensive picture of immune effects associated with specific stressor characteristics. Moreover, there are several other stressor characteristics that warrant investigation, including the controllability and predictability of a stressor (64), its uniqueness for the individual, and number of concomitant stressors.

In addition to understanding more about the qualities or characteristics of stressors that are related to immune alteration, we need to determine the personal and social characteristics of individuals that render them more or less susceptible to stress-induced immune alteration (65–68). Personal resources that have been the focus in other stress and coping research include locus of control and self-esteem (65). An important social resource for individuals experiencing stress is the availability and receipt of social support (66, 69–70). A recent study of cynomolgus monkeys, for example, found that affiliating with fellow monkeys was protective against decreases in lymphocyte response to mitogens elicited by a chronic and repetitive social stressor lasting over 2 years (14).

We suggested earlier that both neuroendocrine and behavioral responses after stress might explain the immune changes found in these studies (5, 19, 20, 26). An additional point with respect to the impact of health practices on immunity needs to be made. Although the majority of the reviewed studies run a health screen and presumably include only healthy subjects, relations between health behaviors and stress or immunity are rarely assessed. Exceptions are studies conducted by Kiecolt-Glaser, Glaser and colleagues (15, 71–78), who typically assess serum protein levels (which indicate severe malnutrition), sleep, weight changes, medications taken, caffeine and alcohol intake, and exercise. Although group differences are often found on particular measures, the health practices themselves are neither related to immune parameters (e.g., 14, 70) nor to psychological variables (75). Other evidence suggests, however, that stress may be related to many of these health behaviors (35, 36). Moreover, evidence exists for associations between immunity and specific health practices such as objective measures of sleep (79), exercise (41), smoking (80), alcohol (40), and drugs (38). Health practices, therefore, provide a plausible pathway through which stressor exposure might influence some immune parameters. There are several possible reasons that Kiecolt-Glaser, Glaser, and colleagues do not find immune associations with the health behaviors they assess, including that most of these studies are of medical students who tend to be homogenous on these behaviors (39). Alternatively, data showing relations between health practices and immunity primarily show that immune alterations occur when the frequency of engaging in these behaviors is high (e.g., trained athletes, alcoholics). It is not clear whether engaging in these behaviors on a less frequent basis will result in detectable immune alteration. Nonetheless, we believe that future studies need to carefully investigate the immune effects of these life style variables in order to fully understand the immune alteration associated with stress.

We have presented evidence for relations between stress and both functional and enumerative immune measures. Furthermore, objective stressful events are related to larger immune changes than subjective self-reports of stress, stressor duration is important for immune outcomes, and interpersonal events are related to alterations in different immune parameters than nonsocial events. A more comprehensive understanding of the conditions and properties of individuals under which particular stressor characteristics are most relevant for immune alteration is needed. This goal can best be met by designing studies that address the impact of specific stressor characteristics in stressor-immune relations.

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74. Kiecolt-Glaser JK, Fisher LD, Ogrocki P, et al: Marital quality, marital disruption, and immune function. Psychosom Med 49:13–34, 1987
75. Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, et al: Chronic stress and immunity in family caregivers of alzheimer's disease victims. Psychosom Med 49:523–535, 1987
76. Kiecolt-Glaser JK, Garner W, Speicher CE, et al: Psychosocial modifiers of immunocompetence in medical students. Psychosom Med 46:7–14, 1984
77. Kiecolt-Glaser JK, Glaser R, Strain EC, et al: Modulation of cellular immunity in medical students. J Behav Med 9:5–21, 1986
78. Kiecolt-Glaser JK, Kennedy S, Malkoff S, et al: Marital discord and immunity in males. Psychosom Med 50:213–229, 1988
79. Irwin M, Smith TL, Gillin JC: Electroencephalographic sleep and natural killer activity in depressed patients and control subjects. Psychosom Med 54:10–21, 1992
80. Holt PG: Immune and inflammatory function in cigarette smokers. Thorax 42:241–249, 1987

APPENDIX

Studies Used in the Meta-Analyses

Arnetz BB, Wasserman J, Petrini B, Brenner SO, Levi L, Eneroth P, Salovaara H, Hjelm R, Salovaara L, Theorell T, Petterson IL: Immune function in unemployed women. Psychosom Med 49:3–12, 1987 [Event/Long-term naturalistic stressor/Nonsocial]**

** Codes indicate the way each study was used in subsequent analyses addressing 1) self-report vs. objective events; 2) acute laboratory, short-term naturalistic, or long-term naturalistic stressors; and 3) interpersonal vs. nonsocial events. If an article did not provide information or could not be coded on a particular dimension, this is indicated by the phrase "not coded."

Baker GHB, Irani MS, Byrom NA, Nagvekar NM, Wood RJ, Hobbs JR, Brewerton DA: Stress, cortisol concentrations, and lymphocyte subpopulations. Br Med J 290:1393, 1985 [Self-report/Short-term naturalistic stressor/Not coded]

Baron RS, Cutrona CE, Hicklin D, Russel DW, Lubaroff DM: Social support and immune function among spouses of cancer patients. J Pers Soc Psychol 59:344–352, 1990 [Self-report, Event/Not coded/Interpersonal]

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Glaser R, Kiecolt-Glaser JK, Speicher CE, Holliday JE: Stress, loneliness, and changes in herpesvirus latency. J Behav Med 8:249–260, 1985 [Event/Short-term naturalistic stressor/Nonsocial]

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Glaser R, Mehl VS, Penn G, Speicher CE, Kiecolt-Glaser JK: Stress-associated changes in plasma immunoglobulin levels. Int J Psychosom, in press [Event/Short-term naturalistic stressor/Nonsocial]

Glaser R, Rice J, Speicher CE, Stout JC, Kiecolt-Glaser JK: Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. Behav Neurosci 100:675–678, 1986 [Event/Short-term naturalistic stressor/Nonsocial]

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Halvorsen R, Vassend O: Effects of examination stress on some cellular immunity functions. J Psychosom Res 31:693–701, 1987 [Event/Short-term naturalistic stressor/Nonsocial]

Irwin M, Daniels M, Bloom E, Smith TL, Weiner H: Life events, depressive symptoms, and immune function. Am J Psychiatry, 144:437–441, 1987 [Self-report/Not coded/Not coded]

Irwin M, Daniels M, Smith TL, Bloom E, Weiner H: Impaired natural killer cell activity during bereavement. Brain Behav Immun 1:98–104, 1987 [Event/Short-term naturalistic stressor/Interpersonal]

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Jemmott JB, Borysenko JZ, Borysenko M, McClelland DC, Chapman R, Meyer D, Benson H: Academic stress, power motivation, and decrease in secretion rate of salivary secretory immunoglobulin A. Lancet 1:1400–1402, 1983 [Self-report, Event/Not coded, Short-term naturalistic stressor/Not coded, Nonsocial]

Jemmott JB, Magloire K: Academic stress, social support, and secretory immunoglobulin A. J Pers Soc Psychol 55:803–810, 1988 [Event/Short-term naturalistic stressor/Nonsocial]

Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R: Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. Psychosom Med 53:345–362, 1991 [Event/Long-term naturalistic stressor/Interpersonal]

Kiecolt-Glaser JK, Fisher LD, Ogrocki P, Stout JC, Speicher CE, Glaser R: Marital quality, marital disruption, and immune function. Psychosom Med 49:13–34, 1987 [Event/Long-term naturalistic stressor/Interpersonal]Kiecolt-Glaser JK, Garner W, Speicher CE, Penn GM, Holliday JE, Glaser R: Psychosocial modifiers of immunocompetence in medical students. Psychosom Med 46:7–14, 1984 [Self-report, Event/Not coded, Short-term naturalistic stressor/Not coded, Nonsocial]

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Kiecolt-Glaser JK, Glaser R, Strain EC, Stout JC, Tarr KL, Holliday JE, Speicher CE: Modulation of cellular immunity in medical students. J Behav Med 9:5–21, 1986 [Event/Short-term naturalistic stressor/Nonsocial]

Kiecolt-Glaser JK, Kennedy S, Malkoff S, Fisher L, Speicher CE, Glaser R: Marital discord and immunity in males. Psychosom Med 50:213–229, 1988 [Event/Long-term naturalistic stressor/Interpersonal]

Kubitz KA, Peavey BS, Moore BS: The effect of daily hassles of humoral immunity: An interaction moderated by locus of control. Biofeedback and Self-Regulation 11:115–123, 1986 [Self-report/Not coded/Not coded]

Landmann RMA, Muller FB, Perini CH, Wesp M, Erne P, Buhler FR: Changes of immunoregulatory cells induced by psychological and physical stress: Relationship to plasma catecholamines. Clin Exp Immunol 58:127–135, 1984 [Not coded/Acute laboratory stressor/Nonsocial]

Levy SM, Herberman RB, Simons A, Whiteside T, Lee J, McDonald R, Beadle M: Persistently low natural killer cell activity in normal adults: Immunological, hormonal and mood correlates. Nat Immun Cell Growth Regul 8:3–186, 1989 [Self-report/Not coded/Not coded]

Linn MW, Linn BS, Jensen, J: Stressful events, dysphoric mood, and immune responsiveness. Psychol Rep 54:219–222, 1984 [Event/Not coded/Interpersonal]

Locke SE, Kraus L, Leserman J, Hurst MW, Heisel JS, Williams RM: Life change stress, psychiatric symptoms, and natural killer cell activity. Psychosom Med 46:441–453, 1984 [Self-report/Not coded/Not coded]

Manuck SB, Cohen S, Rabin BS, Muldoon MF, Bachen EA: Individual differences in cellular immune response to stress. Psychol Sci 2:111–115, 1991 [Not coded/Acute laboratory stressor/Nonsocial]

McClelland DC, Alexander C, Marks E: The need for power, stress, immune function, and illness among male prisoners. J Abnorm Psychol 91:61–70, 1982 [Self-report/Not coded/Not coded]

McClelland DC, Ross G, Patel V: The effect of an academic examination on salivary norepinephrine and immunoglobulin levels. J Hum Stress 11:52–59, 1985 [Event/Short-term naturalistic stressor/Nonsocial]

Moss RB, Moss HB, Peterson R: Microstress, mood, and natural killer-cell activity. Psychosomatics 30:279–283, 1989 [Self-report/Not coded/Not coded]

Naliboff BD, Benton D, Solomon GF, Morley JE, Fahey JL, Bloom ET, Makinodan T, Gilmore SL: Immunological changes in young and old adults during brief laboratory stress. Psychosom Med 53:121–132, 1991 [Not coded/Acute laboratory stressor/Nonsocial]

Schaeffer MA, McKinnon W, Baum A, Reynolds CP, Rikli P, Davidson LM, Fleming I: Immune status as a function of chronic stress at Three Mile Island. Psychosom Med 47:85, 1985 [Event/Long-term naturalistic stressor/Nonsocial]

Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M: Suppression of lymphocyte stimulation following bereavement

JAMA 250:374–377, 1983 [Event/Long-term naturalistic stressor/Interpersonal]

Spratt ML, Denney DR: Immune variables, depression, and plasma cortisol over time in suddenly bereaved parents. J Neuropsychiatry Clin Neurosci 3:299–306, 1991 [Event/Long-term naturalistic stressor/Interpersonal]

Theorell T, Orth-Gomer K, Eneroth P: Slow-reacting immunoglobulin in relation to social support and changes in job strain: A preliminary note. Psychosom Med 52:511–516, 1990 [Self-report/Not coded/Not coded]

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