

Influence of Psychological Stress on Upper Respiratory Infection—A Meta-Analysis of Prospective Studies

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Objective: To quantify the available evidence for the hypothesis that reduced resistance caused by psychological stress may influence the development of clinical disease in those exposed to an infectious agent. **Methods:** We conducted a systematic review and meta-analysis of 27 prospective studies examining the association between psychological stress and subsequent upper respiratory infection (URI). **Results:** The results revealed a significant overall main effect of psychological stress on the risk of developing URI (effect size correlation coefficient, 0.21; 95% confidence interval, 0.15–0.27). Further analyses showed that effect sizes for the association did not vary according to type of stress, how URI was assessed, or whether the studies had controlled for preexposure. **Conclusions:** The meta-analytical findings confirmed the hypothesis that psychological stress is associated with increased susceptibility to URI, lending support to an emerging appreciation of the potential importance of psychological factors in infectious disease. **Key words:** meta-analysis, moderators, psychological stress, psychoneuroimmunology, upper respiratory infection.

ESR = effect size correlation coefficient; URI = upper respiratory infection.

INTRODUCTION

Upper respiratory infections (URIs), often caused by rhino-, corona-, or influenza viruses, constitute a major public health problem (1). The emergence of novel influenza types, such as “severe acute respiratory distress syndrome,” avian influenza A H5N1, and latest pH1N1 flu (“swine flu”) has led to increased attention to influenza viruses as a possible threat to global health (2). Of those exposed to an infectious agent, only a proportion develop clinical disease, and it has long been suggested that at least a part of this variability could be due to reduced resistance to infection caused by psychological stress (3,4). This possibility is supported by the growing evidence that psychological stress is associated with changes in relevant immunological parameters (5). Psychological stress is believed to influence immune function locally through autonomic innervation of lymphoid tissues, as well as systemically through hormone-mediated effects on leukocytes (6), but it may also influence immunity indirectly through behavioral changes induced by the stressful situation, e.g., increased alcohol consumption, increased smoking, poor diet, and reduced physical activity (7).

Over the last four decades, results from more than 50 studies of psychological stress and susceptibility to URIs have been published. As demonstrated in the last major systematic review (8), simple vote counting of the results of the available studies may not provide a sufficiently clear picture of the association between stress and increased risk of URI. One reason could be that many of the studies are characterized by relatively small samples, which could lead to limited statistical power and increased risk of Type 2 error. Other reasons could

be related to the methodological heterogeneity of the available studies.

First, psychological stress has been assessed in different ways. In some studies, stress has been conceptualized as exposure to significant environmental stressors. Examples of this approach are studies investigating the role of major life events, e.g., death of spouse, divorce, and changes in employment, or the role of minor events or daily hassles, e.g., argument with a spouse, problems at work, and issues with children. Other studies have used an appraisal approach, which defines stress as subjective judgments of a situation as challenging or threatening, i.e., perceived stress.

Second, there is considerable methodological diversity concerning how URI has been assessed. In some studies, URI has been defined by the self-report of common URI-related symptoms. In others, the presence of infection has been verified, either clinically by a health professional or biologically through isolation of virus from nasal secretion or by increases in specific antibody titers. All three methods involve issues of reliability. For instance, stress may both be associated with increased awareness of bodily sensations, perhaps due to decreased threshold for anxiety, and with decreased awareness, e.g., if being sick would interfere with important plans and activities (9). Although some individuals may therefore report symptoms without actually being infected, others may be infected with an URI, as confirmed by the detection of a pathogen, without reporting symptoms (7). Another concern is the difficulty of demonstrating the presence of an unknown pathogen, which only succeeds in about 15% to 28% of the cases (8).

A third issue concerns possible shared exposure among participants. Several studies (3,10–12) of stress and URI have used families as targets of the investigation, and the occurrence of a contagious disease in one family member cannot be treated as independent of the occurrence in other family members, which could increase the risk of Type 1 error when concluding that it is the effect of stress that is responsible for the increased susceptibility to infectious diseases, whereas, in reality, it could be that the family membership itself is responsible as a result of increased exposure (13).

A fourth issue is related to possible preexposure to the URI antigen. If participants have developed immunity against a

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The authors have not disclosed any potential conflicts of interest.

Received for publication November 18, 2009; revision received July 5, 2010.

DOI: 10.1097/PSY.0b013e3181f1d003

particular antigen through preexposure, they are less likely to develop a URI, stressed or not, and a possible effect of stress on susceptibility to the URI could thus be underestimated, increasing the risk of Type 2 error. This issue has been addressed in so-called viral inoculation studies, exposing participants to specific infectious antigens at the same time excluding individuals with the presence of serum-neutralizing antibody titers to the specific antigen (14–17). In addition, these studies have controlled for exposure by administering predefined doses of antigen.

Finally, several of the available studies (18–20) have assessed URI cross sectionally or retrospectively. This approach could potentially introduce recall bias, thereby increasing the risk of Type 1 error, as stressed individuals could be more prone to selective recall of negative physical symptoms (8). There are, however, a growing number of prospective studies, which have investigated the possible association between stress and URI by using prospective assessment of URI.

On this background, we therefore conducted a meta-analysis of the available prospective studies of stress and URI. Our primary aim was explanatory, i.e., to investigate the support in the current literature for the hypothesis of a general association between stress and increased susceptibility to URI. Furthermore, given the methodological heterogeneity of the available studies, we also wished to explore 1) whether the association varies according to a) the type of stress assessment and b) the type of URI assessment; 2) whether the influence of stress varies according to the possible dependency/independency among participants; 3) whether the results differ according to whether serologic status at baseline was included in the analysis or not; 4) to the extent possible, the moderating roles of the time-to-follow-up and the sex of the participants.

METHODS

Search Strategy

Articles for this meta-analysis were identified through a computerized literature search of the database PubMed. We used the following PubMed query: (stress OR hassles OR "life events") AND ("upper respiratory infection" OR "common cold" OR influenza OR "infectious illness"). Medline was searched for the period January 1, 1960 to June 30, 2009. The search was limited to include only articles published in English and humans as study subjects. This search identified 269 papers, and 33 papers were found potentially relevant and retrieved for more detailed evaluation. Of these, nine studies were either editorial letters or reviews and were excluded. Four studies had examined URI retrospectively, e.g., at the end of a follow-up period and were also excluded (21–24). Hence, the computerized literature search identified 20 relevant papers. Six additional studies were located from the reference sections of the publications identified through the electronic search and from reference sections of qualitative reviews that we were aware of (14,25,26). Four more studies, which we were already familiar with from having conducted previous work in this area, were added (27–30). Hence, the literature search identified a total of 30 relevant papers.

Selection Criteria

Dependent Variable

To be included, studies had to use a measure of URI, either a) as self-reported symptoms, preferably assessed with a standardized measure; b) as clinically verified by a nurse or physician; or c) verified biologically, e.g., by microbiological assays for specific types of bacteria or virus, or by assessment of elevated antibody titers for a specific antigen. Furthermore, it

was required that the assessment of URI was prospective, i.e., done after the assessment of stress.

Independent Variable

To be included, the identified article had to report results for a measure of psychological stress. This criterion was met a) if participants who had been exposed to a naturally occurring or an experimental stressor were compared with a nonstressed sample, e.g., caregivers and controls; b) if participants were compared at different time points with varying exposure to stress; or c) if stress levels of the participants were assessed with a standard measure of stress (e.g., a measure of perceived stress, major life events, and minor life events or daily hassles). Studies focusing on physical stressors (e.g., physical exhaustion) were excluded.

Moderators

One potential moderator of the association between stress and URI was the dependence versus independence of URI cases. Studies of families, where more than one participant was recruited from the same family (3,11,12,31,32), and a study of military cadets (33), were categorized as nonindependent. Another, preexposure, was controlled for in studies using experimentally induced URI as the dependent variable (14–17,34–37), and these studies were therefore categorized as controlled for preexposure. A third moderator was the follow-up time measured as the number of weeks after stress assessment during which possible URI episodes were recorded. The fourth moderator assessed was the sex of the participants. Since immune function is influenced by age, we considered exploring a possible moderating role of age on the association between stress and URI susceptibility. However, many of the studies provided data concerning participants' ages in formats that precluded such an analysis of moderation. For instance, seven studies (11,14,16,31,34,35,38) included participants with an age range of >30 years, making it difficult to classify the participants as young, middle-aged, or elderly. Two studies (17,39) provided no information concerning the participants' ages and four studies (3,12,33,40) provided qualitative descriptions only (e.g., participants were described as family members, students, or cadets). Finally, three studies described mean ages as approximately 40 years but did not provide data concerning the variance of age (41,42) or provided data that suggested substantial variance (43).

Statistical Power

Before the literature search, we conducted a pilot review of nine prospective studies (3,10–12,34,35,40,41,44) published until 1989 of associations between stress and URI, and included in the review by Cohen and Williamson (8). The mean sample size of these studies was 86 (range, 30–246). A statistical power analysis was conducted, following the procedures suggested by Hedges and Pigott (45). The analysis revealed that, using a fixed effects model, an α of 5% (two-tailed), and a sample size of 86 participants in each study, a total of ten studies would be sufficient to detect a small pooled effect size (effect size correlation coefficient [ESR] = 0.10) (46) with a statistical power of 83%. Similarly, if using a random effects model, a total of 16 studies would be required to detect a small effect size (ESR = 0.10) with a statistical power of 82%.

Study Coding

Following a structured coding protocol developed on basis of the pilot review, two of the authors reviewed the retrieved articles and independently coded the sample characteristics, the independent and the dependent variables, and whether the study fulfilled the inclusion criteria. Differences were discussed, and a final assessment was negotiated for each study.

Computing Effect Sizes

As suggested by Rosenthal and Rubin (47), we used the ESR as the global effect size, with positive values indicating that stress is associated with subsequent development of URI, i.e., an association in the hypothesized direction. The average effect size was calculated as a weighted mean using the inverse variance method giving studies with larger sample size greater weight than studies with small sample size. Two researchers computed the effect

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sizes independently. If differences in results were found, the results and methods were discussed until agreement about the most appropriate method was reached. When one or more effect sizes had been computed for each study, they were combined to provide a global effect size for the outcome variable at interest: URI.

In some articles (10,17,30,35,40), effect sizes (Pearson's r) were directly available. For other studies, we calculated the effects sizes from means and standard deviations or standard errors (SE), e.g., as mean stress scores of infected and noninfected participants (15,29,42,43,48), or from proportions, e.g., as the number of infected stressed and nonstressed participants (3,37,38,49,50). In some articles, the results were presented as other types of statistics, e.g., odds ratios (16) or B coefficients derived from logistic regression (14,31). In other work, only the sample size, F statistic (31), t statistic (32,34,39,41), or p value (11) were available, and the effect size was estimated using the appropriate formulas provided in the literature (51,52). In one article (27), providing the β coefficient from linear regression, the effect size was estimated using the formula suggested by Peterson and Brown (53). Generally, when direct results, e.g., proportions or means, were available, these were preferred over other types of statistics for the effect size calculation. Where the results were based on comparisons between subsamples, the sample size was adjusted accordingly. In four articles (12,33,36,44), data to calculate the effect size were only presented as "nonsignificant," and the effect size was set to 0.0. When several results were available for the same association, e.g., for different measures of the same type of stress, or for several time points, combined average effect sizes were used. When investigating minor life events, some studies (15,41) had investigated both desirable and undesirable events. In these cases, we chose the effect size for undesirable events.

Independence of Results

If an article reported results for more than one type of stress or URI assessment, an average effect size across stress types and/or URI assessment type was calculated, so that only one result per study was used in each model. If different results for the same sample of participants were reported in different articles (36,37), the same procedure was used when appropriate. When comparing effect sizes between different stress or URI assessment types, only one of the results was included in the analysis.

Heterogeneity

To quantify levels of heterogeneity, we calculated Q , a χ^2 statistic (54). Due to the risk of low statistical power as a consequence of small sample sizes, we followed statistical recommendations and used a p of .10 to determine statistical significance when assessing heterogeneity. In case of statistical significance, the effect size measures from each individual study were aggregated using a random-effects model (55).

Quality Assessment

As the usefulness of assigning a quality score to each study and use of this score to weight the results in meta-analyses are highly debated (56), we chose not to follow a formal scoring procedure, and we have instead raised apposite methodological concerns in the appropriate section of text.

Publication Bias

Publication bias, a widespread problem when conducting meta-analyses (57), was evaluated using the funnel plot method, the Eggers' method, and calculation of fail-safe numbers (58,59). The fail-safe number addresses the file drawer problem, i.e., the possibility that unknown studies might exist with results that do not confirm the conclusion reached in the meta-analysis, and refers to the minimum number of unpublished studies reporting null findings that would be required to reach another conclusion in a specific meta-analysis. It has been suggested that a reasonable level is achieved if the fail-safe number exceeds $5K + 10$, with K being the number of studies included in the meta-analysis (52). If the results were suggestive of potential publication bias, an adjusted effect size was estimated using Duval and Tweedie's trim and fill method (60), which imputes missing results and recalculates the effect size accordingly.

Analytical Strategy

First, we planned to test the hypothesis of a significant effect of stress on URI by calculating the overall effect size for all studies included, using a fixed or random model approach depending on whether there were signs of heterogeneity ($p < .10$). Our next aim was to explore the role of potential moderators of the association between stress and URI using meta-analyses of variance for categorical moderators and meta-regression for continuous moderators. Finally, we compared the results of research groups having published at least three articles, and we explored the development of effect sizes over time by cumulative analysis. The meta-analysis was conducted using Comprehensive Meta-Analysis, version 2.2 (61) and its results were reported following the criteria stated in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" guidelines (62).

RESULTS

Study Characteristics

The literature search identified 30 prospective studies between 1960 and 2009 investigating associations between psychological stress and URI. Closer examination revealed that, in one study, it was not possible to distinguish URI symptoms from other types of infectious symptoms, and this study was therefore excluded (63). Another study focusing mainly on academic stress and activation of latent virus had also reported results for self-reported URI (28). The data, however, were insufficient to estimate a reliable effect size. Two studies (36,37) presented results for different types of stress but seemed to use the same sample of participants. This resulted in a total of 27 independent, prospective studies reporting results concerning associations between one or more types of stress and URI, assessed as either self-report or clinically or biologically verified. The 27 studies investigated a total of 8,110 participants, with an average sample size of 300, after adjusting the sample sizes according to the number of participants that the effect size calculations were based on. The study characteristics are shown in Table 1.

Major life events were investigated in 12 studies yielding 15 effect sizes (due to more than one URI assessment in some studies), minor life events or daily hassles in seven studies ($n = 7$ effect sizes), and perceived stress in eight studies ($n = 8$ effect sizes). Other types of stress measures were investigated in five studies, with natural stressors, such as moving (50) and caregiving (48) in two studies, chronic stress in one study (3), forced choice experimental stress in one (34) ($n = 2$ effect sizes), and finally a stress index combining major life events, perceived stress, and negative affectivity in one study (14) ($n = 2$ effect sizes). Thirteen studies measured URI by self-report, and 14 studies verified URI clinically or biologically. Five studies, of which two used the same sample (11,15,31,36,37), included more than one type of URI assessment for each stress type assessed. In the remaining 23 studies, there was no significant association between the stress assessment methods and the URI assessment methods (self-report or verified clinically and/or biologically) ($\chi^2 = 3.0$; $p = .40$). Although URI cases were assumed to be the result of independent exposure to pathogens in 21 studies, this could not be assumed in the remaining six studies, where participants had been recruited from families or were military cadets

