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

ANETTE PEDERSEN, PHD, ROBERT ZACHARIAE, DMSCI, AND DANA H. BOVBJERG, PHD

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

From the Department of Psychology (A.P., R.Z.), University of Aarhus, Aarhus, Denmark; Department of Oncology (R.Z.), Aarhus University Hospital, Århus, Denmark; and the University of Pittsburgh Cancer Institute (D.H.B.), and Departments of Psychiatry, Psychology, and Behavioral and Community Health Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence and reprint requests to Robert Zachariae, Professor, MDSci, Psychooncology Research Unit, Jens Chr. Skous Vej 4, 8000 Århus C, Denmark. E-mail: bzach@aarhus.rm.dk

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