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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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

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 5 K + 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

TABLE 1. Study Characteristics and Effect Sizes

No.	Authors	Year	n[1]	% Females	Follow-Up Time (wks)	URI[2,3] Indep.	URI[4] Preexp.	Major Life Events Effect Size		Minor Life Events (Hassles) Effect Size		Perceived Stress Effect Size		Other Effect Size	
								ESR[5]	p	ESR	p	ESR	p	ESR	p
1	Meyer et al. (3)	1962	100	n.r.[6]	52	−	−							B[7]:0.53[8]	.001
2	Totman et al. (34)	1977	47	73	1	+	+							C[7]:0.36[9]	.012
														B[7]:0.15[9]	.32
3	Totman et al. (35)	1980	52	67	1	+	+	C:0.19 B:0.22	.18 .12						
4	Graham et al. (11)	1986	116	n.r.	26	−	−	S:0.29 C:0.21	.002 .02						
5	Linville (40)	1987	106	59	2	+	−	S:0.25	.01						
6	Stone et al. (41)	1987	30	0	12	+	−			S:0.29	.20				
7	Evans et al. (44)	1988	30	66	1	+	−			S:0,00	1.00				
8	Chapar et al. (10)	1988	49	n.r.	4	+	−	S:0.29	.04						
9	Clover et al. (12)	1989	246	n.r.	n.r.	−	−	B:0.00	1.00						
10	Evans & Edgarton (39)	1991	97	n.r.	1	+	−			S:0.13	.21				
11	Kiecolt-Glaser et al. (48)	1991	138	71	52	+	−							S:−0.01[10]	.91
12	Cohen et al. (14)	1991	162	63	1	+	+							C:0.17[11]	.03
														B:0.41[11]	.001
13	Stone et al. (15)	1992	17	65	1	+	+	C:0.26	.32			C:0.13	.63		
14	Stone et al. (42)	1993	79	0	12	+	−			S:−0.04	.73				
15	Lyons & Chamberlain (27)	1994	144	65	2	+	−			S:0.27	.001				

(Continued)

TABLE 1. Continued

No.	Authors	Year	n[1]	% Females	Follow-Up Time (wks)	URI[2,3] Indep.	URI[4] Preexp.	Major Life Events Effect Size		Minor Life Events (Hassles) Effect Size		Perceived Stress Effect Size		Other Effect Size	
								ESR[5]	p	ESR	p	ESR	p	ESR	p
16	Lee et al. (33)	1995	38	0	4	−	−					S:0.00	1.00		
17	Sheffield et al. (30)	1996	48	60	1	+	−	S:0.29	.045						
18	Evans et al. (29)	1996	35	69	7	+	−	S:0.38	.024						
19	Cobb & Steptoe (31)	1996	107	51	15	−	−	C:0.71	.001	C:0.00	1.00	C:0.46	.001		
20	Cohen et al. (16)	1998	276	55	1	+	+	B:0.14	.017						
21	Turner-Cobb & Steptoe (32)	1998	62	53	15	−	−			C:0.34	.007				
22	Deinzer & Schüller (49)	1998	66	52	2	+	−					S:−0.08	.53		
23	Cohen et al. (17)	1999	55	52	1	+	+					C:0.33	.013		
24	Takkouche et al. (38)	2001	448	46	52	+	−	S:0.20	.001			S:0.31	.001		
25	Lutgendorf et al. (50)	2001	45	62	6	+	−							S:0.46[12]	.001
26a	Cohen et al. (36)	2002	114	53	12	+	+					C:0.00	1.00		
26b	Hamrich et al. [13] (37)	2002	115	53	12	+	+	S:0.13 C:0.33	.17 .001						
27	Smolderen et al. (43)	2007	5404	51	4	+	−					S:0.07	.001		
	Total: K=27		8110			21+ 6 −	7+ 20 −	K(S) = 7 K(C) = 5 K(B) = 3 K = 15		K(S) = 5 K(C) = 2 K(B) = 0 K = 7		K(S) = 4 K(C) = 4 K(B) = 0 K = 8		K(S) = 2 K(C) = 2 K(B) = 3 K = 7	
	Average		300.4 104.1[14]	53.3[15]	11.5										

[1]n = the number of participants, the effect size is based on; [2]URI = upper respiratory infection; [3]URI Indep. = URI cases assumed to be independent; [4]URI preexp. = control for preexposure, e.g., control for antibodies against vira used in experimentally induced colds; [5]ESR = effect size correlation (positive=in the hypothesized direction); [6]n.r. = not reported; [7]S = self-reported URI symptoms; C = clinically verified URI; B = biologically verified URI; [8]hronic familial stress; [9]experimental stressor; [10]natural stressor (caregiving); [11]Stress index; [12]natural stressor (moving); [13]same sample as Cohen et al. 2002; [14]excluding study 27 (Smolderen et al.); [15]based on studies (K = 23) where information on gender was available.

TABLE 2. Results of Meta-Analyses of Associations Between Psychological Stress and Upper Respiratory Infection (URI) and Possible Moderators of the Associations: URI Assessment Method, Independence, and Control for Preexposure

	Sample Size		Heterogeneity[1]			Global Effect Sizes			Fail-Safe n[3]	Criterion[4]
	k	*n*	Q	*df*	*p*	ESR[2]	95% CI	*p*		
A. Main effects										
All stress types	27	8110	97.0	26	<.001	0.21[5]	(0.15–0.27)	<.001	850	145
						0.17[5,6]	*(0.11–0.23)*	*<.001*		
Major Life Events	12	1612	63.0	11	<.001	0.28[5]	(0.16–0.40)	<.001	279	70
Minor Life Events	7	549	10.7	6	.099	0.14[5]	(0.02–0.25)	.022	11	45
Perceived stress	8	5801	49.2	7	<.001	0.17[5]	(0.03–0.31)	.018	89	50
Between groups[7]	22	7617	2.42	2	.30	—	—	—	—	—
B. URI assessment										
A. Self-reported	16	6985	47.1	15	<.001	0.17[5]	(0.09–0.25)	<.001	229	90
B. Verified[5]	12	1354	33.4	11	<.001	0.26[5]	(0.16–0.35)	<.001	255	70
B1. Biologically ver.	6	938	34.1	5	<.001	0.25[5]	(0.12–0.36)	.001	63	40
B2. Clinically ver.[8]	9	625	5.7	8	.68	0.26[9]	(0.19–0.33)	<.001	105	55
Between groups [7](A and B)	27	8109	2.71	1	.10	—	—	—	—	—
Between groups [7](A, B1, and B2)	27	7993	2.92	2	.23	—	—	—	—	—
C. Independence										
Nonindependent[7]	6	669	31.7	5	<.001	0.27[5]	(0.07–0.44)	.009	57	40
Independent[7, 10]	21	7648	56.2	20	<.001	0.19[5]	(0.12–0.25)	<.001	452	110
						0.16[5,6]	*(0.10–0.22)*	*<.001*		
Between groups[7]	27	8317	0.64	1	.42	—	—	—	—	—
D. Preexposure										
Control for preexposure[11]	7	724	3.55	6	.74	0.22[9]	(0.15–0.29)	<.001	53	45
No control for preexposure	20	7386	84.8	19	<.001	0.20[5]	(0.12–0.28)	<.001	460	120
Between groups[7]	27	8109	0.23	1	.63	—	—	—	—	—

[1]$p \leq .1$ were taken to suggest heterogeneity; [2]ESR = effect size correlation. A positive value indicating an effect size in the hypothesized direction, i.e., a positive association between stress and increased risk of URI; [3]fail-safe n = number of nonsignificant studies that would bring the p value to nonsignificant ($p > .05$); [4]a fail-safe n exceeding the criterion ($5 \times k + 10$) indicates a robust result; [5]random effects model; [6]if analyses indicated the possibility of publication bias, missing values were imputed and an adjusted ESR calculated (italics); [7]to maximize statistical power while ensuring independency of results, results from studies with multiple results were either combined or excluded in the result category with the largest number of studies; [8]number of biologically verified (B1) and clinically verified (B2) URI-studies exceed total number of verified URI-studies (B) since a number of studies provided data for both biologically and clinically verified colds; [9]fixed effects model; [10]assumed independence of URI cases; [11]control for preexposure, e.g., controlling for antibodies against the virus used in experimentally induced colds.

living in dorms. Preexposure to the antigen was controlled for in seven studies.

Association Between Stress, Stress Type, and URI

A simple vote count revealed statistically significant results for ten of 14 studies of major life events, two of seven studies of minor life events or hassles, and four of eight studies of perceived stress. Three nonsignificant studies reported effect sizes in the opposite of the hypothesized direction (42,48,49), whereas the remaining results were either in the hypothesized direction or reported as "nonsignificant." As seen in Table 2*A*, there were clear signs of heterogeneity, and a random effects model was therefore chosen. The results showed an overall main effect relationship between stress and URI, regardless of stress or URI assessment methods (ESR = 0.21) (Fig. 1).

A funnel plot indicated a risk of publication bias in the direction of stronger positive results, which was confirmed by Eggers' test ($p < .001$). When imputing results from missing studies with Duval and Tweedie's trim and fill method (60), the effect size was reduced to 0.17 (95% confidence interval [CI], 0.11–0.23). The result could be considered robust, as indicated by the large fail-safe number, which considerably exceeded the criterion (52).

When analyzing the three major stress assessment methods separately, all pooled effect sizes reached statistical significance. The results for minor life events or hassles, however, could be considered less robust, as indicated by the small fail-safe number, which did not exceed the criterion. When comparing the effect sizes, the between-group difference did not reach statistical significance. There were no clear indications of publication bias for any of the three stress types (Eggers' test: $p = .24–0.85$).

Comparing URI Assessment Methods

A vote count showed statistically significant results for nine of 18 assessments of URI based on self-report, and 11 of 19 assessments of clinically or biologically verified URI. Of the 13 studies using clinically verified URI, eight had statistically significant results, whereas three of six using biologically verified URI were statistically significant. When analyzing the results for self-reported and verified URI separately, both reached statistical significance (Table 2*B*). Although verified URI studies showed a larger pooled effect size (0.26) than self-report studies (0.17), the difference did not reach statistical significance. There were no indications of publication bias, and the fail-safe numbers indicated robust results for both URI assessment methods. When

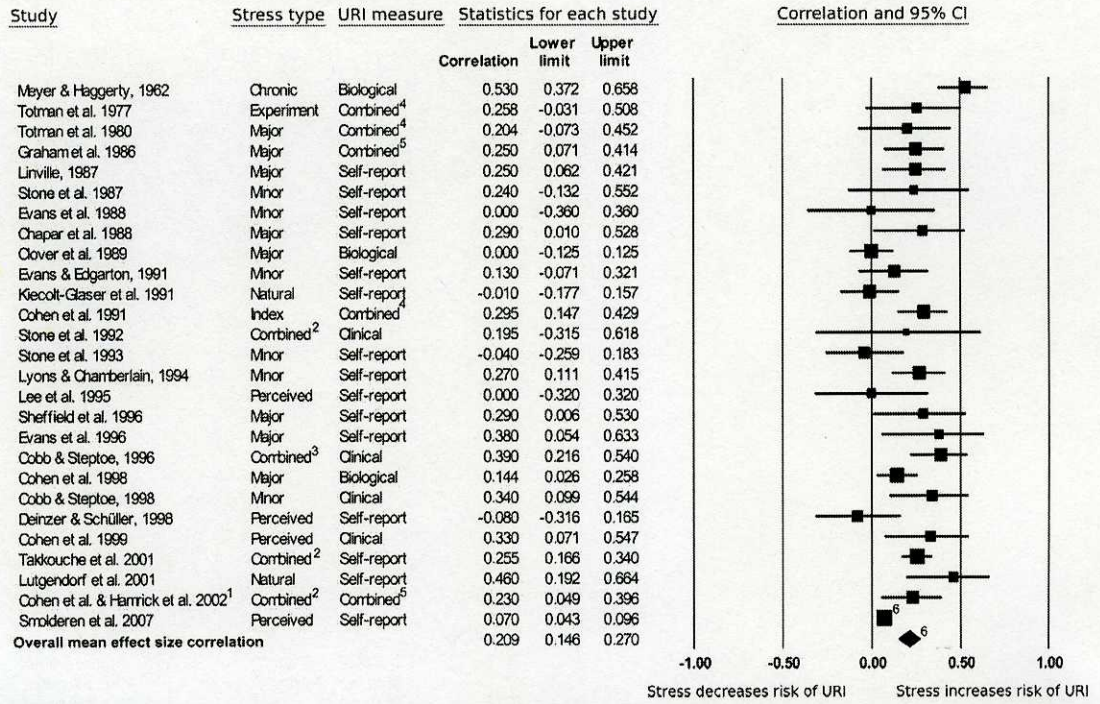

Figure 1. Effect size correlations and 95% confidence intervals of included studies. [1]Results from the work of Cohen et al. (2002) and Hamrick et al. (2002) are based on the same sample. [2]The stress type is a combination of major stressful events and perceived stress. [3]The stress type is a combination of major and minor stressful events and perceived stress. [4]The upper respiratory infection (URI) measure is a combination of biological and clinical evaluations. [5]The URI measure is a combination of self-reported symptoms and clinical evaluation. [6]*Error bars* are hidden behind the primary symbol.

analyzing biologically and clinically verified URI studies separately, both types of studies showed similar (0.25 and 0.26) and statistically significant pooled effect sizes. There were no indications of publication bias, although the fail-safe number for biologically verified studies only slightly exceeded the criterion.

Independent Versus Nondependent URI

A vote count showed statistically significant results for 12 of 21 studies where URI could be assumed independent, and four of six, where URI was assumed to be nonindependent. As seen in Table 2*C*, the effect sizes for both independent and nonindependent studies reached statistical significance. The effect size for nonindependent studies (ESR = 0.27) was larger than for studies assumed to be independent (0.19), but the difference did not reach statistical significance. There was an indication of publication bias for independent studies (Eggers' test: $p = .002$), but imputing missing results only reduced the effect size slightly from 0.19 to 0.16. The fail-safe number for nonindependent studies only just exceeded the criterion.

Control for Preexposure

A vote count showed statistically significant results for four of seven studies that statistically controlled for preexposure to the antigen, and 12 of 20 that had not controlled for preexposure. As seen in Table 2*D*, when comparing studies having controlled for preexposure with studies without control, both results were statistically significant with relatively similar effect sizes (0.22 and 0.20). There were no clear indications of publication bias, but the fail-safe number for the relatively small number of preexposure controlled studies only just exceeded the criterion.

Sex and Time-to-Follow-Up

The percentage of females among participants varied, and a meta-regression with that percentage included as independent, continuous variable, and the effect sizes as dependent variable was conducted. The results indicated no moderating effect of percent females on the association between stress and URI (slope, 0.003; SE, 0.002; $p = .17$ [mixed effects regression]). The time to follow-up varied considerably, and we therefore also analyzed the possible moderating effect of this variable. Again, there was no indication of a moderating effect (slope, 0.002; SE, 0.002; $p = .43$ [mixed effects regression]).

Comparing Research Groups

Three research groups had published at least three independent articles. They were the Cohen group (14,16,17,36,37), the Evans group (29,39,44), and the Stone group (15,41,42). The pooled effect sizes were 0.22 (95% CI, 0.14–0.29; $p < .001$), 0.16 (95% CI, 0.01–0.31; $p = .04$), and 0.05 (95% CI, −0.13–0.23; $p = .56$) respectively. All studies by the Cohen group and one study by the Stone group controlled for preexposure, whereas the remaining studies did not. There were no indications of heterogeneity within research groups (Q = 1.9–3.5; $p = .27$–$.38$), and between-group differences did not reach statistical significance (Q = 2.5; $df = 2$; $p = .28$).

Cumulative Analysis

To investigate the pattern of effect sizes over time of publication, a so-called cumulative analysis (64) was conducted with year of publication as criterion. In the studies published from 1962 through 1989, the cumulated effect size diminished gradually from 0.53 (3) to 0.24 (12). For the studies published from 1991 through 2007, the cumulative effect size remained stable around 0.21 (random effects model). Within-group analyses showed a pooled effect size for studies published until the year of the systematic review of Cohen and Williamson (8) of 0.23 (95% CI, 0.12–0.34; $p < .001$) (random effects), and a slightly smaller pooled effect size for the subsequent studies of 0.20 (0.12–0.34; $p < .001$) (random effects). The between-group difference did not reach statistical difference ($Q = 0.27$; $df = 1$; $p = .60$).

DISCUSSION

Our results confirmed the primary study hypothesis that psychological stress is associated with increased susceptibility to subsequent URI. Further analyses showed that effect sizes for the stress association did not vary significantly according to how the URIs were assessed, or by the type of stress that was assessed, or by whether the studies used natural exposure to pathogens or experimental exposure to virus with control for preexposure antibody levels.

When the results were analyzed separately for self-reported versus verified URI, each of the assessment methods revealed statistically significant associations with psychological stress. The effect size of that association with regard to self-reported URI was smaller than the effect size concerning verified URI, but the difference was not significant. As it has been documented that persons with higher levels of psychological stress express more symptoms of URI, self-report URI scales have been criticized for potentially overestimating the influence of stress on susceptibility on URI (8). On the other hand, evaluation studies have supported the validity of self-report URI scales. For example, self-reported symptoms reaching the criteria for a clinical cold have been shown to correlate with use of healthcare services (65), and the pattern of self-reported symptoms has been shown to follow the known seasonal variation in the frequency of URIs and to be associated with the number of URI events registered in the National Health Survey (66). In addition, biological studies (17) have shown that psychological stress can affect aspects of the actual underlying disease. For instance, chronic stress reduces the ability of the immune system to respond to hormonal signals that turn off proinflammatory cytokine production (17,67,68), and overly exuberant cytokine responses may result in increased symptomatic response (17,69). Taken together, these considerations and the results of our meta-analysis do not support the view that self-reported assessments of URI overestimate the influence of stress on susceptibility to URI. Whereas biologically verified URIs provide gold standard outcomes, self-reported URI provide a far more feasible outcome to assess in real world settings and seem to yield consistent results in stress studies.

When comparing studies that relied on natural exposure to pathogens with those that experimentally exposed participants to viruses and controlled for preexposure viral-specific antibody levels, the meta-analysis revealed statistically significant stress associations with similar effect sizes. We had speculated that studies without control for preexposure could underestimate the influence of stress, because participants who have developed immunity against a particular pathogen through preexposure are less likely to develop a URI, stressed or not. However, although the results must be interpreted cautiously given the small number of studies, we found no evidence to support our speculation. Interestingly, viral inoculation studies (14) have reported that the effects of stress on susceptibility to colds are the same for both subjects who were seropositive at baseline and those who were seronegative for the challenge virus, which would suggest that the association between stress and URI is not limited to primary rather than secondary immune responses. Given the importance of this issue to our understanding of the mechanisms by which stress may affect risk of URI, these results highlight the need for additional research.

It has long been known that males are more susceptible to infections than women. For instance, more males than females died in the 1917 to 1918 influenza epidemic; and in many free-living mammals, males are more likely to harbor parasites and to suffer more intensely from their effects (70). The mechanism responsible for this difference in susceptibility to infections is unknown, but estrogen could be an important factor. First, research has shown that women report more infectious symptoms during the perimenstrual period compared with midcycle where estrogen levels are highest (63). Second, the results of a recent study (71) indicated that, through estrogen production, females have a built-in mechanism that prevents Caspase-12, an important effector of innate immunity, from being expressed, favoring more robust inflammatory and immune responses to pathogens. Our results did not, however, reveal any evidence of a moderating effect of percent participating females on the association between stress and susceptibility to URI. Hence, although males may be more vulnerable to infectious diseases in general, males and females may be equally vulnerable to the stress-induced suppression of immune function.

The time to follow-up varied considerably across studies, but there was no evidence of a moderating effect of that variable on the relationship between stress and increased susceptibility to URI. This finding is, on the one hand, surprising because a short follow-up could be anticipated to be associated with reduced statistical power as a consequence of fewer incidences of URI. On the other hand, the studies with shortest follow-up were viral inoculation studies in which participants were experimentally challenged with specific respiratory viruses. Becaise the incubation period of URI is generally 2 to 5 days, a follow-up after 7 days would be expected to be a sufficient follow-up period for full detection of infection and would allow less time for changes in stress levels that would be expected over time.

The results of a cumulative analysis (64) revealed that, in the studies published from 1962 to 1989, the cumulative effect size diminished gradually from 0.53 to 0.24. From 1991 to 2007, the cumulated effect size remained stable around 0.21. In 1991, a major systematic qualitative review (8) was published examining the association between stress and infectious diseases, including URI. In that prior review, it was concluded that there was enough evidence to support a relationship between stress and susceptibility to URI to suggest that further work would be worthwhile, but not enough to draw definitive conclusions. Although the individual studies published after that review did not change the overall evidence of an association between stress and susceptibility to URI, the present study is the first to go beyond simple vote counting methods to include a meta-analysis of these studies.

The complex issues of the mechanisms responsible for the observed association between psychological stress and increased susceptibility to URI are beyond the scope of this meta-analytic review. Possible behavioral mediators were explored in some of the studies, although often cursorily as potential confounders explored in preliminary analyses, or included simply as covariates in the analyses. The results of the majority of these studies did not provide evidence that exercise frequency, cigarette smoking, sleep quality, diet, vitamin use, alcohol use, or coffee consumption mediated the association between stress and URI (14,29,32,43,50). The results of one study (48) showed an association between stress and increased risk of URI and between stress and reduced amount of sleep. The results of another study (16) showed that smoking status, exercise frequency, sleep efficiency, vitamin C, and alcohol consumption partially mediated the association between stress and URI, but including these factors in the statistical model only slightly reduced the association between stress and URI. Possible immunological mediators have yet to receive mediation analyses in one study (17) that suggested that interleukin-6 may act as a major pathway through which stress was associated with increased symptoms of illness. However, increases in interleukin-6 may also occur in response to tissue damage associated with illness symptoms and the relationship may be bidirectional. Additional studies with formal testing of the influence of possible behavioral and biological mediators on the relationship between stress and URI are needed.

CONCLUSIONS

Overall, the results of this meta-analytical study revealed statistically significant positive associations between psychological stress and susceptibility to subsequent URI. These results can be considered robust as indicated by the large fail-safe number and the stable effect size found in the cumulative analysis. Further analyses showed that effect sizes did not vary according to the stress assessment method, URI assessment method, or statistical control for an experimental design, including a control for preexposure. Neither sex nor time-to-follow-up had a moderating effect on the association between stress and susceptibility to URI. Future research should explore possible mediating factors, e.g., cytokines, in explaining the association between stress and URI, and attempt to identify possible critical periods during which stress may be most influential regarding susceptibility to URI.

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