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REGULAR ARTICLE

Social Support and Antibody Responses to Vaccination: A Meta-Analysis

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Abstract

Background Social support and social integration have been linked to lower rates of morbidity and mortality. However, the biological mechanisms responsible for such links need greater attention. Vaccine paradigms provide an integrative window into immune system involvement in the protective influence of social support/integration.

Purpose The main aim of this article was to conduct a meta-analytic review of the association between social support/social integration and antibody responses to vaccines. Exploratory analyses also examined effect sizes and confidence intervals as a function of several factors to inform future research.

Method A literature search was conducted using the ancestry approach and with PsycInfo, Medline, and the Psychology and Behavioral Science Collection by crossing the exact keywords of social support or social integration with vaccine or antibodies. The review identified nine studies with a total of 672 participants.

Results The omnibus meta-analysis showed that social support/social integration was related to higher antibody levels following vaccination, but the average effect size was small and the lower bound of the confidence interval included zero (Zr = 0.06 [−.04, .15]). These results did not appear to differ much as a function of the operationalization of social relationships, participant age, or follow-up period, although effect sizes appeared larger for studies using a primary antigen.

Conclusions These data provide some evidence that social support may be linked to antibody responses to vaccines. However, effect sizes are mostly small and zero overall effect cannot be ruled out. Future studies would benefit from larger sample sizes and greater consideration of methodological issues associated with secondary immune responses to antigen.

Keywords: Antibody titers · Social support · Relationships · Vaccination

The quality and extent of one's social relationships have been related to lower disease morbidity and mortality [1–3]. More specifically, both structural (e.g., social integration) and functional (e.g., perceived support) measures of social support have been linked to better health outcomes [1, 4, 5]. Thus, the link between social support and health is on strong ground, which sets the stage for theoretical questions on mechanisms.

One area of strong interest is the physiological mechanisms linking social support to disease outcomes. Prior research has examined a number of health-relevant biological pathways including neural, cardiovascular, neuroendocrine, and immune processes [6–8]. Such biological modeling is important because it can highlight important pathways that could be monitored or targeted for psychological and/or pharmacological interventions [9, 10].

Much research linking social support to biological outcomes has focused on the immune system, which is the bodies' defense against infectious and malignant disease [11, 12]. These studies mostly focused on isolated measures of immune function starting with early work examining immune cell counts and their functional response to challenges in vitro [13, 14]. More recent work in the area has examined inflammatory cytokines given their link to numerous health outcomes such as cardiovascular disease and cancer [15–17]. Consistent with the epidemiological evidence linking social support to diverse health outcomes, a recent meta-analysis found that social support was associated with lower levels of

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inflammation [18]. In general, immune system involvement is consistent with the groundbreaking common cold studies by Cohen et al. who have showed that social network diversity is a predictor of lower infection rates following inoculation [19].

Given that most prior work has focused on isolated immune measures, a complementary approach would be to examine an integrative immune response to challenges. Vaccine paradigms (e.g., flu vaccine) provide a strong test of such processes as the immune response they trigger is a clinically significant outcome and there are numerous (and complex) steps that ultimately result in protective antibody titers to an antigen. In a typical immune response to infectious viruses, antigen-presenting cells (e.g., macrophages, dendritic cells) capture and process the antigen [11]. The antigen-presenting cells then present the antigen to the T-cell receptor of helper T cells in the context of major histocompatibility complex class II molecules (a genetic region in all mammals that signals between lymphocytes and cells that have major histocompatibility complex molecules). In response to antigen recognition, helper T cells undergo clonal expansion and secrete a variety of cytokines such as IL-2 and IL-4 that aide in the proliferation of B cells into plasma cells. These plasma cells then secrete antibody specific for the antigen. Upon initial exposure to antigen, the primary antibody response is IgM, which is effective as an immediate response given it has five active binding sites. However, there is an isotype switching from IgM to IgG later in the antibody response to promote longer-term immunity. A hallmark of the immune system is memory, and a subset of memory T and B cells are maintained that promote a more vigorous immune response (e.g., IgG is produced earlier and with greater affinity) upon subsequent exposure [11]. Given prior work linking social support to aspects of immune function, one might expect that this would translate to a stronger, more effective integrative immune response to vaccination.

There have been a number of studies that have examined the link between social support and vaccine responses. Most of these have examined if social support predicts antibody titers to the influenza vaccine [20–23]. In general, results of these studies are mixed. For instance, Phillips et al. [21] found no link between perceived social support and antibody titers to the flu vaccine, whereas Pressman et al. [23] found that social integration was associated with higher antibody titers to the flu vaccine indicating a beneficial response. However, the study by Pressman et al. [23] only found a link to one strain of the trivalent flu vaccine (i.e., New Caledonia) and not the other two strains. Thus, a meta-analysis that looks at composite results across studies is needed in order to draw stronger inferences. This is especially important given the logistic challenges and invasive nature of such studies, which typically examine antibody responses from blood over several time points. The main aim of this meta-analytic review was thus to examine whether social support was related to a stronger antibody response to vaccination as might be expected given the epidemiological evidence to date.

An exploratory aim was to characterize the effect sizes and confidence intervals (CI) associated with several factors that might influence the link between social support and antibody titers to vaccines. This would help inform future research as an inferential moderation test (i.e., meta-regression) involving significance tests would likely be underpowered given the small number of studies identified in this review. One important conceptual question that can be explored relates to the different ways of measuring relationships, which have distinct theoretical implications [24, 25]. The classic review by Cohen and Wills [26] made the distinction between structural and functional measures of support. Social integration reflects the extent of one's social connections and access to support (e.g., marriage, friendships, volunteer organizations [24]). Importantly, structural and functional measures of support are empirically and conceptually separable [1, 24, 27]. Functional measures of support can further be distinguished as perceived or received support. Perceived support reflects the perception that support would be available if needed whereas received support is the reported receipt of support during a particular time frame [28]. This distinction is also significant because perceived support is more consistently related to better health outcomes compared with received support [25, 28]. In fact, received support often has variable links to health as it might not be a good match to the needs or motivations of the recipient and can threaten a person's sense of independence [29, 30]. For these reasons, it is possible that the effects of perceived support on antibody responses to vaccines might be stronger than the effects of received support.

There are several methodological aspects of studies that are important to consider as well. One is the age of participants as aging is associated with decreases in the number of naive T and B cells, the function of memory T cells, and changes in inflammation that negatively affect vaccine responses [31, 32]. For instance, the efficacy of the annual flu vaccine is only 30%–50% for adults over 65 compared with up to 90% in children and younger adults [31]. A second methodological factor is whether a study included multiple follow-up periods. This is important as associations might become stronger over time given the potential positive cumulative impact of social support on antibody production. Finally, an important methodological factor is whether the vaccine evokes a primary or secondary immune response. A primary immune response involves antigens that an individual has

no prior exposure to, in contrast to a secondary immune response that is characterized by immunologic memory [11]. As a result, the secondary immune response is more vigorous and efficient as it can rely on memory T and B cells, which are "primed" to respond to the antigen. Secondary immune responses might be more difficult to find an association with social support given potential ceiling effects in antibody titers. Thus, an exploratory aim of this review was to examine these factors to inform future work in the area.

Method

Identification and Inclusion/Exclusion of Studies

The review protocol used in this meta-analysis is detailed below. A literature search was first conducted using the major databases of PsycInfo, Medline, and the Psychology and Behavioral Science Collection by crossing the exact keywords of social support or social integration with vaccine or antibodies. This search was run up to March of 2019 and identified 242 records, with 200 remaining after duplicates were removed (see Fig. 1). One hundred and eighty-five articles were rejected based on a review of titles/abstracts as they did not contain any quantitative data or did not include measures of social support or antibody responses to vaccines. Of the remaining 14 records, 5 were excluded for various reasons, the most common being that no direct link between social support and antibody titers was examined given it was not a primary aim of the study. The ancestry approach was also used which searched the reference list of all eligible articles and review papers on the topic (e.g., Whittaker [33]). This resulted in a final count of nine articles. A search of EMBASE resulted in no additional articles being flagged.

Analysis Plan and Data Extraction

Major details regarding studies (e.g., sample, type of support measure, outcomes) were first characterized and examined in tabular form. The subsequent meta-analysis was performed using a commercially available software package (MetaWin, Rosenberg et al. [34]) that provided results regarding effect sizes, CI, tests of variability regarding effect sizes, and a fail-safe number for any significant associations. These analyses were based on a random effects model, so that inferences can be made to studies on the topic more generally [35]. Correlation coefficients (r) were used as the common metric for data entry. When correlations were not presented, measures of effect size were converted to r values. Standardized regression weights were converted using the formula: $r = \beta + .05\ \lambda$ where $\lambda = 1$ when β is not negative and $\lambda = 0$ when β is negative [36]. When p-values were the only source of data, they were transformed using the equation $r = \frac{z}{\sqrt{N}}$ based on the one-tailed z-score. Results reported as nonsignificant utilized a conservative significance level of .50 [37]. To reduce the problem of nonindependence in omnibus analyses, when multiple effects were reported (e.g., different vaccine strains, assessment points), they were first transformed to a common metric (i.e., z-scores), averaged into a single effect, then entered into the meta-analysis. Publication bias for the omnibus meta-analysis was done at the outcome level by calculating Kendall's Tau and the fail-safe number. Kendall's

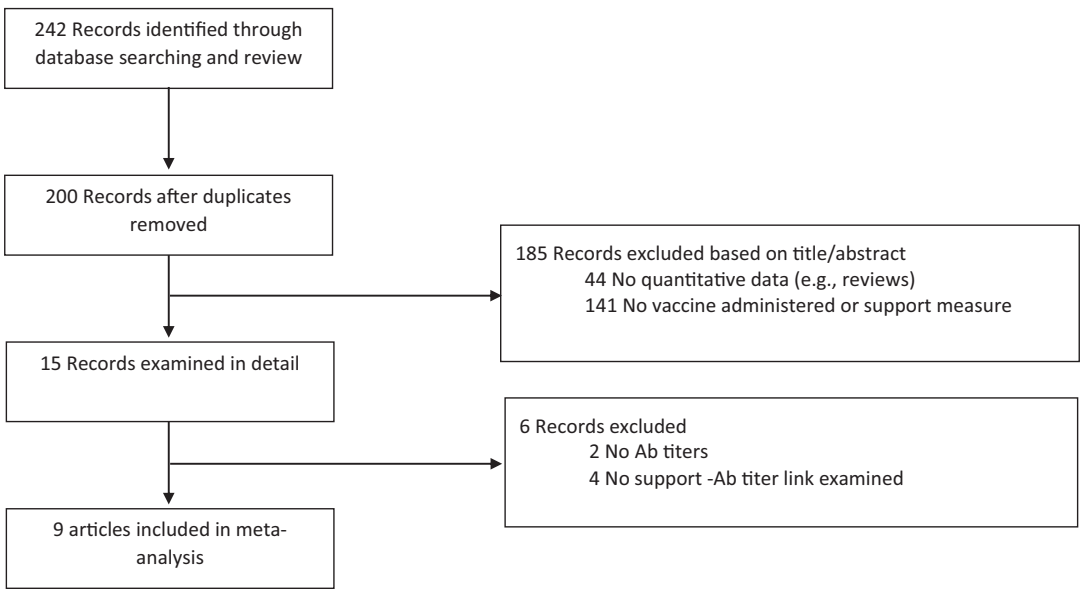

Fig. 1. Meta-analytic flow chart describing selection of studies.

Tau examines the association between effect sizes and sample sizes, whereas the fail-safe number estimates the number of nonsignificant studies needed to make the results nonsignificant [37]. Finally, exploratory analyses were done to characterize the effect sizes and CI for the different types of support (i.e., structural, perceived support, received support), participant age (i.e., young, older), follow-up period (first, second), and type of immune response (i.e., primary, secondary).

Results

Overview of Studies

The main characteristics of these studies are shown in Table 1. At least two authors verified the accuracy of the details listed in the table that was subsequently also used in the exploratory analyses. In total, 672 participants were included in the meta-analysis. Most of these studies used relatively young, healthy samples under the age of 25 (67%). Several studies had multiple support assessments (33%), and the most common measures examined were perceived support (77%), followed by social integration (57%), and received support (22%).

What Is the Overall Link Between Social Support, Social Integration, and Antibody Titers?

As shown in Table 1, 67% of the studies showed a positive association between social support/integration and antibody titers. Across nine studies, the weighted random effect size was in the expected direction (i.e., social support being linked to higher antibody titers to vaccination), but the CI included 0 (Zr = .06, 95% CI [−0.04, 0.16]). The test of study-level heterogeneity was not significant (Q [8] = 8.52, p = .38), but given the likelihood of true study heterogeneity in biomedical research [40], a random effects analysis was used. A direct test of the association between effect sizes and sample sizes revealed a nonsignificant link suggesting no sample size bias (Kendall's Tau = .03, p = .92).

Effect sizes for the studies ranged from Zr = −.19 to Zr = .49 (see Fig. 2). Of these, only one study showed a negative correlation (i.e., social support being related to lower antibody titers, Moynihan et al. [20]). In addition, this was one of the only studies that did not control or take into account baseline antibody titers which could influence post-vaccine analyses. As a result, this study was deleted to examine whether the links were stronger across the remaining studies. However, the effect size only increased slightly and was still not significant although

Table 1. Main study characteristics

Study	*n*	Age	Vaccine type	Periods	Support measure	Main outcome	Effect size *Zr*	Var(*Zr*)
Snyder et al. (1990) [38]	89	21	KLH	Baseline, 3 weeks, 8 weeks	RSS	IgG Ab titers	.000	.011
Glaser et al. (1992) [39]	35	23.3	Hep B	Baseline, 1 month, 6 m months	PSS	Composite of HBsAg Ab titers and T-cell response from 2nd to 3rd periods	.485	.031
Moynihan et al. (2004) [20]	37	84	Flu: NC, HK, Pan	Baseline, 3 weeks	PSS	HAI Ab titers	-.192	.029
Phillips et al. (2005) [21]	57	19.8	Flu: NC, Pan, Shan; Mening A, C	Baseline, 5 weeks, 5 months	PSS/SI	HAI/IgG Ab titers	.023	.018
Pressman et al. (2005) [23]	83	18–25	Flu: NC, Pan, Yam/Vict	Baseline, 1 month, 4 months	SI	HAI Ab titers	.090	.013
Phillips et al. (2006) [23]	104	74.6	Flu: NC, Pan, Shan	Baseline, 1 month, 12 months	SI, PSS	HAI Ab titers	.000	.010
Li et al. (2007) [41]	119	57.1	Tetanus	Baseline, 4 weeks	RSS	IgG Ab titers	.131	.009
Gallagher et al. (2008) [42]	74	23	Pneum	Baseline, 5 days	PSS	IgM Ab titers	.070	.014
Gallagher et al. (2008) [43]	74	22.9	Primary (Pneum), Hep A	Baseline, 4 weeks, 18 weeks	PSS, SI	IgG Ab titers	.030	.014

Cumulative Z*r* = .06, 95% CI [−0.04, 0.16]. *PSS* perceived social support; *RSS* received social support; *SI* social integration.

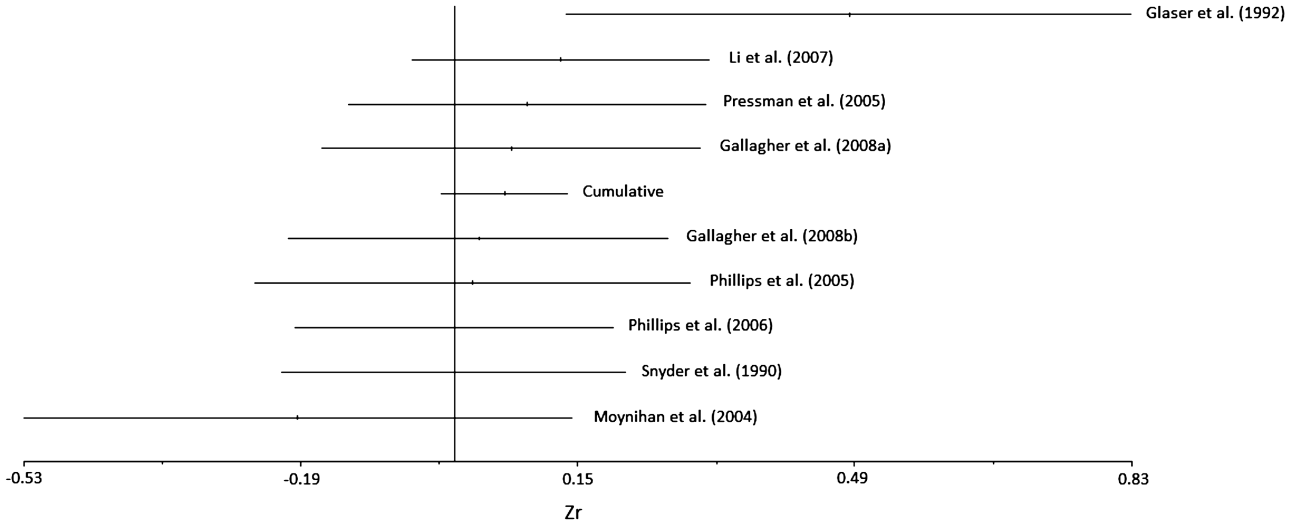

Fig. 2. Forest plot of effect sizes and confidence intervals.

it pointed in the expected direction (*Zr* = .08, 95% CI [−0.02, 0.17]).

Exploratory analyses were conducted to descriptively characterize the effect sizes based on several conceptual and methodological variables. First, the type of support was examined. The effect size appeared only slightly larger for received support (*Zr* = .07, 95% CI [−0.88, 1.02]) compared with perceived support (*Zr* = .04, 95% CI [−0.10, 0.18]) and social integration (*Zr* = .04, 95% CI [−0.15, 0.23]). Second, older individuals tend to have lower seroconversion rates to vaccines given age-related declines in immune functioning [31]. The effect size for younger individuals (i.e., less than 30 years) appeared only slightly larger compared with older individuals (*Zr* = .08, 95% CI [−0.06, 0.23] vs. *Zr* = .03, 95% CI [−0.29, 0.35]). Variations based on the follow-up assessment periods were also examined. In total, five studies included an early and later follow-up of antibody titers and related them to social support. The effect sizes appeared comparable for the first (*Zr* = .04, 95% CI [−0.10, 0.18]) and second (*Zr* = .02, 95% CI [−0.12, 0.16]) assessment periods in these studies. Finally, a distinction was also made between primary and secondary vaccine responses. This classification produced the largest absolute difference as associations were larger for primary versus secondary responses (*Zr* = .15, 95% CI [−1.16, 1.45] vs. *Zr* = .04, 95% CI [−0.08, 0.16], respectively). Of course, the relatively large CI for primary responses suggests some caution in making conclusions.

Discussion

The main aim of this meta-analytic review was to examine whether social support predicted higher antibody titers to vaccination. Such an association would be consistent with epidemiological research that has linked support to lower overall mortality rates (Holt-Lunstad [3]). Indeed, respiratory infections are one of the leading cause of death globally, especially in low-income countries [44]. Across all studies to date, the effect size linking social support to antibody titers following vaccination was small (*Zr* = .06) and its CI included zero [−0.04, 0.16]. Although the bulk of the plausible values are positive, more evidence is needed on the topic [45].

It is important to note that the number of studies included in this meta-analysis was small. However, small meta-analyses are frequently conducted, especially when they ask a specific question with similar approaches [45]. It is also important to conduct such an analysis given the logistics and costs of running such studies. Vaccine protocols are time intensive and relatively invasive compared with other common biological assessments. They involve longitudinal designs with multiple intravenous blood draws and assays to quantify antibody titers. The expense and difficulty of doing such studies is reflected by the fact that these nine studies were published over an 18-year period (1990–2008), with the last one published over 10 years ago. It is thus unlikely that this literature will grow considerably in the foreseeable future and this review can inform current theory and future work in the area.

A second, exploratory aim was to examine effect sizes and CI to guide future research. Effect sizes appeared to vary little as a function of support type, participant age, and follow-up period. Effect sizes appeared to vary more considerably for primary challenges (*Zr* = .15) versus secondary challenges (*Zr* = .04). Primary antigens are new to the body and hence prior exposure is limited as a complicating factor. This is an important issue as social support is associated with greater social contact [46], which is a primary mode of infectious disease transmission.

This might make it more difficult to detect links between social support and Ab titers due to ceiling effects and/or reduced variability. The use of a primary antigen reduces such concerns and hence may be a stronger test of links between social support and vaccine responses. Of course, there were only two studies that examined a primary immune response and the CI around this estimate was relatively large [39, 47]. If this trend is correct, future studies examining secondary immune responses might need larger samples sizes to detect smaller associations.

The exploratory analyses also suggested that the effect size for perceived support was small, which appears inconsistent with prior epidemiological work. One possible area for future work is to examine the stress-buffering model of support [26]. Although several studies assessed both stress and support, only one study directly examined the stress-buffering hypothesis. This study found preliminary evidence that social support buffered the influence of anxiety on antibody responses to the vaccine [47]. Future research examining the stress-buffering model will not only aide in a conceptual understanding of how social support operates in vaccine models but also potentially explain additional variance in outcomes as the above study did not find a significant main effect of social support.

More generally, this research also suggests the importance of examining other indicators of immune responses to vaccination in order to examine which aspects of the integrative immune system may be compromised by low social support. For instance, the first study in this area by Snyder et al. [47] did not find that social support was significantly related to antibody titers to keyhole limpet hemocyanin (a primary antigen). However, a subsequent paper did show social support to predict a greater proliferative response of immune cells to stimulation by keyhole limpet hemocyanin with effect sizes ranging from r = .13 to .23 [38]. This is consistent with early studies showing that social support predicts proliferative lymphocyte responses to mitogens [48–50]. This is important because although antibody titers do confer protection, the immune system has other mechanisms of protection depending on the challenge at hand. For instance, the T-cell response is also critical for the resolution of intracellular pathogens such as viruses and some bacteria [11].

Research in this domain should also examine potential neuroendocrine mediators. Prior work has linked social support to lower levels of catecholamines, cortisol, and higher oxytocin levels [7, 51]. Importantly, many immune cells (e.g., lymphocytes) have functional receptors for neuroendocrine hormones, which provide a direct route for neuroimmune modulation [52, 53]. Recent research is also highlighting the role of the parasympathetic nervous system (as reflected by respiratory sinus arrhythmia) on social/regulatory functioning [54, 55]. Future work will be needed to directly model these neuroendocrine pathways as mediators of the link between social support and vaccine responses.

Given the correlational nature of the links between social support and vaccine responses in this review, future research should consider alternative designs that could produce larger effect sizes and stronger inferences. For instance, support interventions that include the involvement of family, peers, and individuals with experiential similarity could be conducted over time following vaccination and compared with relevant control conditions [3, 56]. In addition, although largely untested in the health domain, compassion-based practices (e.g., loving-kindness meditation) could be used as they appear to positively influence health-relevant psychological outcomes such as depression and positive affect [57, 58]. Finally, daily life protocols might also be possible using text-based short message services to enhance support although such research is in its infancy [59, 60]. Relatedly, results suggested a positive effect of received support, although the CI around this estimate was wide. Nevertheless, given mixed evidence regarding links between received support and health, future work may benefit from examining this association in greater detail.

It should be emphasized that the conclusion of this meta-analysis is *not* that researchers should abandon using vaccine protocols for social support studies given the nonsignificant link. The CI associated with the omnibus test highlights the importance of more research on this topic given the larger range for a protective link [45]. Indeed, meta-analytic evidence exists linking other psychosocial processes such as chronic and perceived stress to lower antibody titers to the flu vaccine [61]. It is likely that the increased social contact associated with social support complicates many such studies that often rely on secondary immune responses. Future research will need to consider this issue and carefully consider how to take them into account in future studies (e.g., assessments of social contact, prior vaccine history, etc.). In addition, the overall effect size is relatively small, so larger sample sizes will be needed to potentially detect associations (n's for the current studies ranged from 35 to 154), with potentially even larger sample sizes for detecting antibody responses to secondary antigen. Modeling stress-buffering influences or implementing social support manipulations over time as part of the vaccination protocol may also be useful to increase effect sizes as noted earlier.

In summary, the link between social support and antibody responses during vaccination appears to be small and positive, but is statistically inconclusive and hence is in need of more research. The relatively small effect size appears inconsistent with the epidemiological evidence

showing an association between social support and all-cause mortality given that infectious diseases are among the leading causes of death worldwide. This review also raised several important issues that will need to be considered in future work including sample size, type of immune response, and the incorporation of other indicators of immune system function. Nevertheless, the vaccination protocol remains an important paradigm for this area (and others in psychoneuroimmunology) given its ability to test an integrative and clinically significant immune response to potential pathogens.

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards The authors declare that they have no conflict of interest.

Authors' Contributions B.N.U. produced a draft of the manuscript, conducted the literature review, and performed the primary meta-analysis. J.L. provided comments on earlier and the final drafts of the paper. He also served as a reliability check for the main study characteristics. K.Z. provided comments on earlier and final drafts of the paper. She also served as a reliability check for the main study characteristics. N.B. provided comments on both earlier and final drafts of the paper. He also served as a consultant on the meta-analytic procedures.

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