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Psychosocial Interventions and Immune System Function
A Systematic Review and Meta-analysis of Randomized Clinical Trials

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Supplemental content

IMPORTANCE Recent estimates suggest that more than 50% of all deaths worldwide are currently attributable to inflammation-related diseases. Psychosocial interventions may represent a potentially useful strategy for addressing this global public health problem, but which types of interventions reliably improve immune system function, under what conditions, and for whom are unknown.

OBJECTIVE To address this issue, we conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) in which we estimated associations between 8 different psychosocial interventions and 7 markers of immune system function, and examined 9 potential moderating factors.

DATA SOURCES PubMed, Scopus, PsycInfo, and ClinicalTrials.gov databases were systematically searched from February 1, 2017, to December 31, 2018, for all relevant RCTs published through December 31, 2018.

STUDY SELECTION Eligible RCTs included a psychosocial intervention, immune outcome, and preintervention and postintervention immunologic assessments. Studies were independently examined by 2 investigators. Of 4621 studies identified, 62 were eligible and 56 included.

DATA EXTRACTION AND SYNTHESIS Data were extracted and analyzed from January 1, 2019, to July 29, 2019. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline was followed. Data were extracted by 2 investigators who were blind to study hypotheses and analyses, and were then analyzed using robust variance estimation. Analysis included 8 psychosocial interventions (behavior therapy, cognitive therapy, cognitive behavior therapy [CBT], CBT plus additive treatment or mode of delivery that augmented the CBT, bereavement or supportive therapy, multiple or combined interventions, other psychotherapy, and psychoeducation), 7 immune outcomes (proinflammatory cytokine or marker levels, anti-inflammatory cytokine levels, antibody levels, immune cell counts, natural killer cell activity, viral load, and other immune outcomes), and 9 moderating factors (intervention type, intervention format, intervention length, immune marker type, basal vs stimulated markers, immune marker measurement timing, disease state or reason for treatment, age, and sex).

MAIN OUTCOMES AND MEASURES The primary a priori outcomes were pretest-posttest-control (ppc) group effect sizes (ppc g) for the 7 immunologic outcomes investigated.

RESULTS Across 56 RCTs and 4060 participants, psychosocial interventions were associated with enhanced immune system function (ppc g = 0.30, 95% CI, 0.21-0.40; $t_{50.9}$ = 6.22; P < .001). Overall, being randomly assigned to a psychosocial intervention condition vs a control condition was associated with a 14.7% (95% CI, 5.7%-23.8%) improvement in beneficial immune system function and an 18.0% (95% CI, 7.2%-28.8%) decrease in harmful immune system function over time. These associations persisted for at least 6 months following treatment and were robust across age, sex, and intervention duration. These associations were most reliable for CBT (ppc g = 0.33, 95% CI, 0.19-0.47; $t_{27.2}$ = 4.82; P < .001) and multiple or combined interventions (ppc g = 0.52, 95% CI, 0.17-0.88; $t_{5.7}$ = 3.63; P = .01), and for studies that assessed proinflammatory cytokines or markers (ppc g = 0.33, 95% CI, 0.19-0.48; $t_{25.6}$ = 4.70; P < .001).

CONCLUSIONS AND RELEVANCE These findings suggest that psychosocial interventions are reliably associated with enhanced immune system function and may therefore represent a viable strategy for improving immune-related health.

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A large body of research demonstrates that the immune system is involved in a wide variety of mental and physical health problems that cause substantial morbidity and mortality,[1,2] including anxiety disorders, depression, suicide, schizophrenia, cardiovascular disease, certain cancers, stroke, and autoimmune and neurodegenerative disorders.[3-6] Indeed, a recent analysis of mortality data collected from 195 countries from 1980 to 2017[7] indicated that more than 50% of all deaths in the world today are attributable to inflammation-related disease conditions.[8] Although pharmacological interventions represent a logical choice for addressing this serious public health problem, such interventions can be costly and have adverse biobehavioral and clinical effects. As a result, several prominent groups, including the World Health Organization, National Academy of Medicine, and National Institutes of Health, have recently emphasized the goal of reducing global disease burden using psychosocial interventions when possible.[9-11]

The ability of psychosocial interventions to enhance immunity and improve immune-related health outcomes is grounded in research showing that immune system processes are influenced by social, neurocognitive, and behavioral factors.[12,13] Indeed, although immune system function was historically thought to be regulated primarily by pathogen exposure, physical injury, and internal physiological processes, numerous studies have now shown that immunologic activity is also related to psychosocial factors, such as life stress, negative emotions, and social support.[14-17] Whereas chronic stress has been reported to suppress cellular and humoral immunity[18] and to increase nonspecific inflammation,[5] for example, psychosocial resilience factors, such as social support and connection, have been found to mitigate the negative effect that life stress has on immune function and health.[16,19-21]

Given these findings, numerous studies have examined whether interventions that reduce stress or bolster psychological resources can improve immune system function. However, research on this topic has been mixed: although some studies have found that psychosocial interventions clearly enhance immunity,[22] others have not.[23] Meta-analyses have made some progress in identifying factors contributing to these mixed results, but this work has also had several limitations. First, rather than comparing findings across different types of interventions, existing reviews and meta-analyses have primarily focused on only 1 intervention type, such as cognitive behavior therapy (CBT),[24] meditation,[25,26] mind-body interventions,[27] lifestyle interventions,[28] mind-body therapies,[29] stress management interventions,[30] or non-therapy-specific interventions.[31] Consequently, it remains unknown whether certain interventions are more reliably associated with improved immunity than others, which is critical for informing policy. Second, existing meta-analyses have been largely restricted to populations with specific disorders, such as HIV-positive adults,[24,30] adults with depression,[32] patients with breast cancer,[33] or populations with other chronic illnesses.[29] The resulting data are therefore informative but do not address the important question of whether the effectiveness of various psychosocial interventions differs across disease condition or patients' reasons for seeking treatment. Finally, rather than examining a variety of immune markers, existing meta-analyses have either collapsed across different markers, thus obscuring potential marker-specific effects, or have evaluated only a few markers, thus preventing an examination of whether different psychosocial interventions are associated with some immunologic markers more consistently than others.[30,32,33]

To address these issues, we conducted what we believe is the first systematic review and meta-analysis of randomized clinical trials (RCTs) that have examined the effects of a psychosocial intervention on immune system outcomes. We focused on 8 psychosocial intervention types: behavior therapy, cognitive therapy, CBT, CBT plus additive treatment or mode of delivery that augmented the CBT (eg, CBT plus benzodiazepines or phone/video sessions), bereavement or supportive therapy, multiple or combined interventions, other psychotherapy, and psychoeducation. In addition, we examined 7 immune outcomes that could be influenced by these interventions: proinflammatory cytokines (eg, interleukin-6) and markers (eg, C-reactive protein), anti-inflammatory cytokines (eg, interleukin-10), antibodies (eg, IgA), immune cell counts (eg, CD4), natural killer cell activity (eg, cytotoxicity), viral load (eg, HIV RNA), and other immune outcomes (eg, blastogenesis, number of postoperative infectious diseases). Finally, we investigated 9 factors that could potentially moderate associations between psychosocial interventions and immune system function: type of psychosocial intervention, intervention format (no group vs group sessions), intervention length, type of immune marker, whether the immune marker represented basal or stimulated levels, time from treatment cessation to immune marker measurement, participants' disease state or reason for receiving treatment, age, and sex. This meta-analysis thus addresses the critical question of

Key Points

Question How consistently are psychosocial interventions associated with changes in immune system function, and which immunologic, demographic, or clinical factors moderate these associations?

Findings In this systematic review and meta-analysis of 56 unique randomized clinical trials and 4060 participants, psychosocial interventions were associated with positive changes in immunity over time, including improvements in beneficial immune system function and decreases in harmful immune function that persisted for at least 6 months following treatment for participants randomly assigned to a psychosocial intervention vs a control group. These associations were most reliable for cognitive behavior therapy and multiple or combined interventions and for studies that assessed proinflammatory cytokines or markers.

Meaning These findings suggest that psychosocial interventions may enhance immune system function and may thus represent a viable strategy for improving immune-related health.

which types of psychosocial interventions are most consistently associated with enhanced immune system function, under what conditions, and for whom, which may in turn inform research efforts and public policy aimed at using psychosocial interventions to improve immune-related health.

Methods

Literature Review

We performed a comprehensive search of articles published in PubMed, Scopus, PsycInfo, and ClinicalTrials.gov, following the recommended Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[34] and using the search string presented in the eMethods in the Supplement. The search was performed from February 1, 2017, to December 31, 2018, and included all articles published through December 31, 2018. Consistent with recommended procedures and prior meta-analyses,[34,35] 2 independent reviewers (including C.M.S.) who were blind to study hypotheses and analyses screened titles and abstracts from each database, and each reviewer then read the full text of each study that included a potentially relevant effect (eg, the study was an RCT that included a psychosocial intervention or immune outcome). If an article did not include sufficient information for analysis, the article was marked as such, and after all databases were searched by both reviewers, we contacted the corresponding authors of those articles to obtain the necessary details. In addition, we reviewed the reference lists of all relevant articles to identify other potentially eligible trials. Given the early start date of this research (June 1, 2016), this protocol was not preregistered. The meta-analysis was conducted and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

Inclusion Criteria

Each relevant study was independently examined by all authors. To be included, studies had to have randomized participants to a psychosocial intervention condition or a control condition (ie, any condition lacking a psychosocial intervention component, such as a treatment as usual or waitlist control condition). In addition, studies had to have assessed immune system function and have included both preintervention and postintervention immunologic assessments. These inclusion criteria yielded a data set of RCTs assessing the effects of 8 different psychosocial interventions on 7 immune system outcomes. No studies were excluded based on any participant characteristics, although all of the RCTs included sampled adults.

Coding of Studies and Moderators

We coded for several intervention, immunologic, and participant-based factors that could potentially moderate the association between psychosocial interventions and immune system function. Categorical moderators were dummy coded with appropriate reference groups, and continuous moderators were centered for analyses at the lowest obtained value to make the interpretation of the intercept (ie, the effect size) for the association between psychosocial interventions and immune system function at that lowest value of the covariate. If the mean participant age was not reported, the median participant age was used if available; if neither of these statistics were reported, the midpoint of the reported participant age range was used.

Intervention type was coded based on the intervention type description provided by the study authors, with 3 exceptions. First, we coded a study as "CBT plus additive" whenever it included CBT and an additional treatment or mode of delivery that augmented standard CBT (but not another psychosocial intervention). Second, we coded a study as "multiple interventions" whenever several different psychosocial interventions were administered. Third, we coded a study as "other psychotherapy intervention" when a study included an unambiguous psychotherapeutic intervention that was not covered by the other categories (ie, nonspecific stress management therapies, internal family systems therapy, narrative exposure therapy, and nonspecific counseling). Psychoeducation was not included in this category because it is not a form of psychotherapy. All recognized psychotherapies were considered; therefore, if a particular psychotherapy is not represented (eg, psychoanalysis), it means that the literature review did not yield any RCTs that have examined how those psychotherapies are associated with changes in immune system function. All study information was coded by 2 independent reviewers (including C.M.S.), and disagreements were resolved by a consensus discussion led by a third reviewer (G.M.S.).

Effect Size Calculation

To examine how consistently psychosocial interventions were associated with changes in immune system function, we calculated the pretest-posttest-control (ppc) group effect size (ppc Cohen *d*),[36] which increases the statistical power and precision of effect size estimates relative to estimates of effect size from posttest measurement alone.[36] We then converted effect sizes from ppc Cohen *d* to ppc Hedges *g* using the standard transformation. We used baseline samples as the pretest values and follow-up samples as the posttest values for each follow-up time point that was available. This effect size provides a relatively unbiased index of how immune system function changes in an intervention vs a control group. The ppc group effect size incorporates the pretest-posttest correlation in calculating the variance of this effect size, which we obtained from the studies that reported it and all the authors we contacted for data. As such, we set the pretest-posttest correlation as the meta-analytic point estimate of the pretest-posttest correlation for calculation of the ppc effect sizes (see below). Importantly, sensitivity analyses using the lower and upper bounds of the 95% CI of the estimated pretest-posttest correlation indicated no differences in reported results with high or low correlations that were used to derive the variance of the effect sizes.

Analytic Strategy

Data were analyzed from January 1, 2019, to July 29, 2019, and are available on the Open Science Foundation website (https://osf.io/xcz7s). The primary a priori effect size outcome of interest was the standardized mean difference between the psychosocial intervention and control groups from preintervention to postintervention. We used ppc *g* rather than ppc *d* as the effect size for analysis because ppc *g* is a less biased estimate of the population-standardized mean difference effect size than ppc *d*. Whenever possible, we calculated ppc *g* from the means, SDs, and sample sizes that were reported. Pretest-posttest correlations between time points for each immune marker were provided in several studies and by some authors over email. Correlations were transformed to *z* scores using the Fisher *z* transformation, meta-analyzed to obtain a point estimate and 95% CI, and then back-transformed to a correlation using the Fisher *z*-to-*r* transformation. This back-transformed correlation coefficient of pretest with posttest immune markers was used as the pretest-posttest correlation for all calculated effect sizes. If the means and SDs were not reported but graphed, we used the figure extraction program DataThief to extract data from figures with 1 × 1-pixel accuracy. If none of this information was available, we requested the required statistics from the relevant corresponding author. If the corresponding author did not respond (5 studies), the study was excluded.

Many studies reported more than 1 type of immunologic outcome, which poses a challenge for conventional meta-analytic methods because calculating mean effect sizes within studies without accounting for their correlations can alter or obscure true effect size estimates.[37,38] In addition, because only a limited number of studies have examined the effects of psychosocial interventions on immune system function, analyzing each immune system outcome separately would substantially reduce power because the studies differ in the outcomes assessed. To address these issues, we used the meta-analytic technique of robust variance estimation, a random-effects meta-regression that accounts for dependence between effect size estimates.[39,40] This technique robustly estimates effect size weights and standard errors for the given effects, allowing for multiple outcomes within studies. We used the robumeta package in R, version 3.6.0 (R Project for Statistical Computing), to conduct these analyses using the correlated weights given by Hedges et al,[39] with analyses using the small sample corrections suggested by Tipton.[41] To partially account for this dependency, ρ was set to the recommended 0.80.[40] Heterogeneity was quantified as τ^2, which represents between-study variance in this meta-analytic method.[39,40]

Degrees of freedom for all primary analyses were estimated using the Satterthwaite approximation, where $df = 2/cv^2$ and cv represents the coefficient of variation, because simulation studies have indicated that this method of estimating degrees of freedom is most analytically valid with study set sizes of 40 or less (which was the case in moderator analyses) using the robust variance estimation meta-analytic technique.[41] Because of how the degrees of freedom are estimated, if $df<4$, then the risk of type I error is increased and the analysis results cannot be trusted to represent population values.[41] However, because this estimation of degrees of freedom is very sensitive to outliers (since degrees of freedom are a function of the coefficient of variation), one can be relatively confident that when $df>4$, outlying studies are not driving observed significant effects. To assess publication bias, we conducted the Egger test for funnel plot asymmetry[42] as well as a risk of bias assessment for each study (described below).

For all analyses, positive effect sizes indicate that a psychosocial intervention was associated with improved immune function relative to the control condition (eg, by reducing circulating proinflammatory cytokine levels or increasing anti-inflammatory cytokine levels, immune cell counts, natural killer cell activity or cytotoxicity, or lymphocyte or antibody responses to antigens). In contrast, negative effect sizes indicate that an intervention was associated with impaired immune function relative to the control condition (eg, by increasing circulating proinflammatory cytokine levels or decreasing immune cell counts, natural killer cell toxicity, stimulated anti-inflammatory cytokine production, or lymphocyte or antibody responses to antigens).

To further investigate any significant main findings, we examined the extent to which the following 9 a priori–selected factors moderated associations between psychosocial interventions and immune system function: intervention type, intervention format, intervention length, type of immune marker, whether the immune marker represented basal or stimulated levels, immune marker assessment timing, participants' disease state or reason for receiving treatment, age, and sex. Because the outcome of these analyses is the standardized mean difference between groups (ie, the effect size), a significant continuous moderator means that the effect size estimate differs based on the levels of that continuous moderating factor. Given that most studies used CBT, secondary analyses paralleling those described above were conducted to examine this intervention type in greater detail. All of the *t* tests conducted were unpaired, 2-tailed *t* tests.

Results

Search Results

The search of PubMed returned 2941 results; Scopus, 537 results; PsycInfo, 515 results; and ClinicalTrials.gov, 628 results. Of these studies, our inclusion criteria yielded 62 RCTs. Five studies did not present means and standard errors, SDs, or 95% CIs from both preintervention and postintervention in the text, a table, or a figure, and the authors did not respond to emails requesting these data, leaving 57 studies available for preliminary analysis. The publication bias analysis revealed that 1 study should be excluded because of potential bias, leaving a final sample of 56 RCTs[23,43-96] available for all primary analyses. The PRISMA flow diagram is presented in **Figure 1**, and the included RCTs are described in eTable 1 in the Supplement.

Preliminary Analyses

Study Characteristics

The initial sample included 57 studies and 4076 participants. From these studies, we obtained 265 effect sizes, which is simi-

lar to the number of effect sizes obtained per study in the social sciences[38] and in similar meta-analyses.[97]

Publication Bias

The result of the Egger test examining evidence of publication bias was significant (t_{55} = 3.84; P < .001), indicating evidence of publication bias. Importantly, however, a trim-and-fill analysis indicated that even when the estimated missing (eg, file-drawer) studies were included (n = 12), the overall beneficial effect of psychosocial interventions on immune system function remained significant (z = 3.00, P = .003; see below). Investigating the cause of this publication bias revealed 1 outlying study with a study-average effect size that was substantially greater than the others (ie, the study-average effect size was more than 6 SDs from the mean study-average effect size (eFigure in the Supplement). To prevent the findings of this study from unduly biasing the results, following Uttal et al,[98] we excluded this study and conducted all primary analyses on the final sample of 56 studies and 4060 participants. A detailed risk of bias assessment and the coding explanation for each study is presented in eTable 2 in the Supplement. In brief, most studies exhibited low-to-unclear risk for most sources of bias, with the exception of blinding of participants and personnel, which was high-risk for most studies because of the nature of the intervention and control groups.

Primary Analyses

Overall Effect Size

The overall effect size (56 studies; 263 effect sizes; 4060 participants) revealed that psychosocial interventions as a whole were significantly associated with enhanced immune system function (ppc g = 0.30, 95% CI, 0.21-0.40; $t_{50.9}$ = 6.22; P < .001). There was relatively low between-study heterogeneity in these effect sizes (τ^2 = 0.14), indicating that this association of psychosocial interventions with immunity was relatively consistent across studies and conditions (**Figure 2**). If calculated as a percentage difference, being randomly assigned to a psychosocial intervention condition vs a control condition was associated with a statistically significant 14.7% (95% CI 5.7% to 23.8%) improvement in beneficial immune system function and a statistically significant 18.0% (95% CI 7.2% to 28.8%) decrease in harmful immune system function over time.

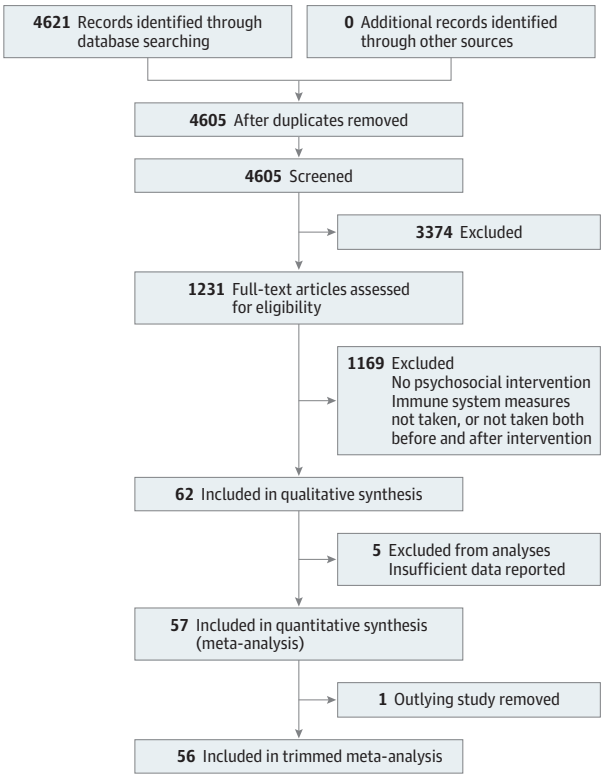
Intervention Type

Analyses examining whether this overall association was moderated by the type of intervention administered indicated significant differences between the interventions studied ($F_{6, 54}$ = 3.40; P = .006) (**Table 1**). Of the 8 interventions examined, only 2 were significantly associated with changes in immune system outcomes: CBT (31 studies; ppc g = 0.33, 95% CI, 0.19-0.47; $t_{27.2}$ = 4.82; P < .001) and multiple or combined interventions (7 studies; ppc g = 0.52, 95% CI, 0.17-0.88; $t_{5.7}$ = 3.63; P = .01).

Intervention Format

Given the known association between social support, immunity, and health,[19] it is possible that interventions involving group therapy or discussion might enhance immune system function more reliably than those without a group component. This possibility was partially confirmed. Interventions that included a group component were more consistently associated with enhanced immune function (ppc g = 0.38, 95% CI, 0.24-0.53; $t_{29.0}$ = 5.35; P < .001) than those that did not (ppc g = 0.20, 95% CI, 0.08-0.33; $t_{20.9}$ = 3.36; P = .003), although this difference did not reach statistical significance ($F_{1, 55}$ = 3.70; P = .06).

Figure 1. PRISMA Flow Diagram Depicting Selection of Studies



Intervention Length

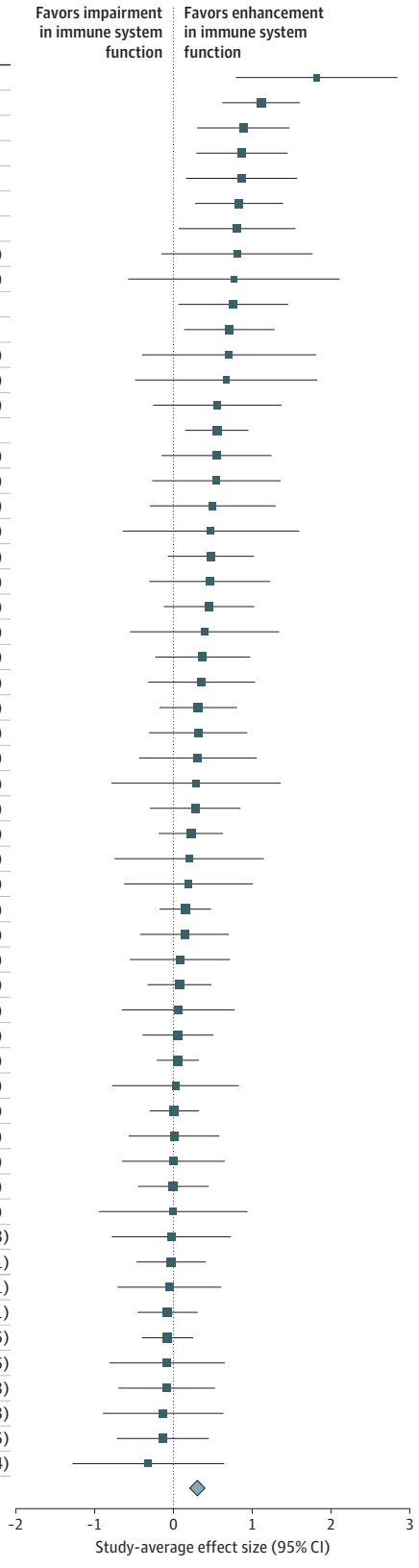
Analyses examining intervention length revealed that, contrary to what might be expected, intervention length (in weeks) did not moderate the association between psychosocial interventions and immune system function (B = .001, β = .005, $t_{4.4}$ = 0.10; P = .93) (**Table 2**).

Type of Immune Marker

Analyses examining the types of immune markers assessed revealed that psychosocial interventions had significantly different associations with the immune markers studied ($F_{6, 55}$ = 3.13; P = .01). As shown in Table 1, of the 7 types of immune outcomes investigated, only proinflammatory cytokine or marker levels (33 studies; ppc g = 0.33, 95% CI, 0.19-0.48; $t_{25.6}$ = 4.70; P < .001) and immune cell counts (27 studies; ppc g = 0.29, 95% CI, 0.14-0.43; $t_{24.0}$ = 4.03; P < .001) were significantly associated with the psychosocial interventions examined. In contrast, the effect sizes obtained did not differ

Figure 2. Forest Plot Depicting Study-Average Effects of Psychosocial Interventions on Immune System Function

Study	Study-average effect size (95% CI)
Carrico et al,[49] 2005	1.82 (0.79 to 2.84)
McCain et al,[76] 2008	1.11 (0.62 to 1.61)
Goodkin et al,[62] 1998	0.89 (0.30 to 1.47)
Hosaka et al,[65] 2002	0.87 (0.29 to 1.45)
Irwin et al,[66] 2015	0.86 (0.16 to 1.57)
Shadick et al,[87] 2013	0.83 (0.27 to 1.39)
Thornton et al,[94] 2009	0.81 (0.06 to 1.55)
McGregor et al,[78] 2004	0.81 (-0.15 to 1.77)
Doering et al,[57] 2007	0.76 (-0.58 to 2.11)
Grossarth–Maticek and Eysenck,[63] 1989	0.76 (0.06 to 1.46)
Chen et al,[51] 2011	0.71 (0.13 to 1.28)
Mohr et al,[82] 2001	0.71 (-0.40 to 1.81)
Janelsins et al,[68] 2011	0.67 (-0.49 to 1.83)
Larson et al,[71] 2000	0.56 (-0.26 to 1.37)
Mikocka–Walus et al,[80] 2017	0.55 (0.15 to 0.95)
Antoni et al,[45] 1991	0.54 (-0.15 to 1.24)
Castés et al,[50] 1999	0.54 (-0.27 to 1.36)
Savard et al,[85] 2006	0.50 (-0.30 to 1.30)
Dolsen et al,[58] 2018	0.47 (-0.65 to 1.60)
Kéri et al,[69] 2014	0.47 (-0.07 to 1.02)
Gonzalez–Garcia et al,[61] 2014	0.46 (-0.31 to 1.23)
Irwin et al,[66] 2014	0.45 (-0.12 to 1.03)
Chen et al,[52] 2008	0.39 (-0.55 to 1.34)
Shen et al,[90] 2018	0.37 (-0.23 to 0.97)
Taylor et al,[92] 2009	0.36 (-0.32 to 1.03)
Moore et al,[22] 2013	0.31 (-0.18 to 0.80)
Cruess et al,[56] 2000	0.31 (-0.31 to 0.94)
Zautra et al,[95] 2008	0.31 (-0.44 to 1.06)
Mohr and Genain,[81] 2004	0.29 (-0.79 to 1.36)
Lopez et al,[73] 2013	0.27 (-0.30 to 0.85)
Parsons et al,[84] 2007	0.22 (-0.19 to 0.63)
McCain et al,[77] 1996	0.20 (-0.75 to 1.15)
Zgierska et al,[96] 2016	0.19 (-0.63 to 1.01)
Memon et al,[79] 2017	0.15 (-0.18 to 0.48)
Antoni et al,[47] 2000	0.14 (-0.42 to 0.70)
Sharpe et al,[89] 2001	0.08 (-0.55 to 0.72)
Lumley et al,[74] 2014	0.08 (-0.33 to 0.48)
Koh and Lee,[70] 2004	0.06 (-0.66 to 0.77)
Cohen et al,[55] 2011	0.06 (-0.39 to 0.51)
Hasson et al,[64] 2005	0.06 (-0.21 to 0.32)
Morath et al,[83] 2014	0.02 (-0.78 to 0.83)
Andersen et al,[43] 2010	0.01 (-0.30 to 0.32)
Coates et al,[54] 1989	0.01 (-0.57 to 0.58)
Sharpe and Schrieber,[88] 2012	0.00 (-0.65 to 0.65)
Berger et al,[48] 2008	0.00 (-0.45 to 0.45)
Kang and Yoo,[23] 2007	0.00 (-0.95 to 0.94)
Antoni et al,[44] 2005	-0.03 (-0.78 to 0.73)
Antoni et al,[46] 2009	-0.03 (-0.47 to 0.41)
Mackay et al,[75] 2009	-0.05 (-0.71 to 0.61)
Laudenslager et al,[72] 2015	-0.08 (-0.46 to 0.31)
Claesson et al,[53] 2006	-0.08 (-0.40 to 0.25)
Simoni et al,[91] 2013	-0.08 (-0.82 to 0.65)
Savard et al,[86] 2005	-0.09 (-0.70 to 0.53)
Garand et al,[60] 2002	-0.13 (-0.90 to 0.63)
Euteneuer et al,[59] 2017	-0.14 (-0.72 to 0.45)
Theeke et al,[93] 2016	-0.32 (-1.28 to 0.64)
Pooled effect size	0.30 (0.21 to 0.40)



A positive effect indicates an intervention-related enhancement in immune system function, whereas a negative effect indicates an intervention-related impairment in immune system function. The size of each square represents the weight assigned to that study in the meta-analysis. The error bars represent the 95% CIs for each study-average effect. Overall, psychosocial interventions were associated with a significant beneficial effect on immune system outcomes (pretest-posttest-control $g = 0.30$, 95% CI, 0.21-0.40; $t_{50.9} = 6.22$; $P < .001$).

Table 1. Categorical Moderators of the Association Between All Psychosocial Interventions and Immune System Function

Moderator	No. of studies	Effect size estimate, ppc *g* (95% CI)	*F* or *t* value (*df*)[a]	*P* value
Intervention type			3.40 (6, 54)	.006
Behavior therapy	2	0.21 (−2.34 to 2.75)	1.03 (1.0)	.49
Cognitive therapy[b]	2	0.39 (−0.95 to 1.74)	3.71 (1.0)	.17
CBT	31	0.33 (0.19 to 0.47)	4.82 (27.2)	<.001
CBT plus additive	6	0.05 (−0.10 to 0.20)	0.82 (4.7)	.45
Bereavement or supportive therapy[c]	3	0.57 (−0.80 to 1.93)	1.95 (1.8)	.20
Multiple or combined interventions	7	0.52 (0.17 to 0.88)	3.63 (5.7)	.01
Other psychotherapy intervention	6	0.19 (−0.21 to 0.58)	1.24 (4.8)	.27
Psychoeducation	1	−0.13 (NA)	NA	NA
Intervention format			3.70 (1, 55)	.06
No group session(s)	23	0.20 (0.08 to 0.33)	3.36 (20.9)	.003
Group session(s)	33	0.38 (0.24 to 0.53)	5.35 (29.0)	<.001
Immune marker			3.13 (6, 55)	.01
Proinflammatory cytokines or markers	33	0.33 (0.19 to 0.48)	4.70 (25.6)	<.001
Anti-inflammatory cytokines[b]	4	−0.23 (−0.88 to 0.41)	−1.69 (1.8)	.24
Antibodies[c]	4	0.70 (−1.69 to 3.08)	1.43 (1.8)	.30
Immune cell counts	27	0.29 (0.14 to 0.43)	4.03 (24.0)	<.001
Natural killer cell activity	10	0.24 (−0.43 to 0.91)	1.00 (4.0)	.37
Viral load	4	0.05 (−0.25 to 0.36)	0.56 (2.8)	.62
Other immune outcome[c]	5	0.32 (−0.41 to 1.05)	1.51 (2.6)	.24
Basal or stimulated immune marker			0.10 (1, 55)	.75
Basal	45	0.29 (0.19 to 0.39)	5.82 (39.1)	<.001
Stimulated	24	0.33 (0.07 to 0.60)	2.69 (16.4)	.02
Disease state or reason for treatment			2.40 (9, 55)	.02
Autoimmune disorder	8	0.37 (0.08 to 0.66)	3.06 (6.5)	.02
Cancer[b]	7	0.31 (−0.05 to 0.68)	2.16 (5.5)	.08
Depression	5	0.28 (−0.19 to 0.75)	1.64 (4.0)	.18
HIV	13	0.41 (0.14 to 0.68)	3.35 (11.5)	.006
Insomnia[b]	3	0.60 (−0.08 to 1.28)	4.11 (1.9)	.06
Other physical health condition[c]	7	0.26 (−0.11 to 0.63)	1.77 (5.4)	.13
Other psychiatric disorder(s)[b]	3	0.09 (−0.10 to 0.28)	2.13 (1.9)	.17
Physical and mental health issues	4	0.14 (−0.32 to 0.60)	1.00 (3.0)	.39
Stress (caregiving)	3	0.05 (−0.58 to 0.67)	0.33 (1.9)	.78
Stress (other)	3	0.31 (−1.03 to 1.66)	1.10 (1.8)	.40

Abbreviations: CBT, cognitive behavior therapy; ppc, pretest-posttest-control; NA, not applicable.

[a] If *df* < 4.0, the results should be considered preliminary. *F* values are given for categorical moderation analysis; *t* values, for test of effect significance.

[b] This effect size was significant when small sample corrections were not used.

[c] This effect size was marginal when small sample corrections were not used.

Table 2. Continuous Moderators of the Association Between Psychosocial Interventions and Immune System Function for All Psychosocial Interventions and CBT Only

	All psychosocial interventions					CBT only				
Moderator	Mean (SD) [range]	Unstandardized regression slope (*B*)	Standardized regression slope (β)	*t* Value (*df*)[a]	*P* value	Mean (SD) [range]	Unstandardized regression slope (*B*)	Standardized regression slope (β)	*t* Value (*df*)[a]	*P* value
Participant age, y	46.7 (12.1) [11.5-75.0]	−0.004	−0.047	−1.06 (17.2)	.30	49.5 (11.2) [22.6-75.0]	−0.006	−0.071	−1.12 (10.7)	.29
Participant sex, % male	40.8 (33.9) [0-100]	0.001	0.020	0.38 (23.9)	.71	32.3 (32.1) [0-100]	0.003	0.106	1.37 (11.7)	.20
Length of psychosocial intervention, wk	11.6 (9.0) [1-56]	0.001	0.005	0.10 (4.4)	.92	10.4 (4.9) [1-28]	−0.002	−0.012	−0.17 (4.2)	.88
Time from treatment cessation to immune measurement, mo	1.8 (3.7) [0-24]	0.002	0.006	0.19 (3.7)	.86	2.6 (4.7) [0-24]	−0.002	−0.011	−0.19 (2.9)	.86

Abbreviations: CBT, cognitive behavior therapy; *df*, degrees of freedom.

[a] If *df* < 4.0, the results should be considered preliminary.

Table 3. Categorical Moderators of the Association Between CBT and Immune System Function

Moderator	No. of studies	Effect size estimate, ppc *g* (95% CI)	*F* or *t* value (*df*)[a]	*P* value
Intervention format			0.40 (1, 30)	.53
No group session(s)	11	0.28 (0.06 to 0.49)	2.92 (9.7)	.02
Group session(s)	20	0.36 (0.16 to 0.56)	3.77 (17.7)	.001
Immune marker			16.34 (6, 30)	<.001
Proinflammatory cytokines or markers	22	0.34 (0.14 to 0.53)	3.68 (17.1)	.002
Anti-inflammatory cytokines[b]	2	−0.31 (−1.52 to 0.90)	−3.25 (1.0)	.19
Antibodies	2	0.85 (−8.31 to 10.00)	1.18 (1.0)	.45
Immune cell counts	12	0.27 (0.07 to 0.47)	2.96 (9.9)	.01
Natural killer cell activity	4	0.36 (0.03 to 0.68)	4.48 (2.1)	.04
Viral load	3	−0.03 (−0.32 to 0.26)	−0.51 (1.9)	.66
Other immune outcome	3	0.74 (0.29 to 1.20)	9.84 (1.5)	.02
Basal or stimulated immune marker			2.16 (1, 30)	.15
Basal	25	0.25 (0.12 to 0.38)	4.08 (21.5)	.001
Stimulated	14	0.56 (0.12 to 0.99)	2.85 (9.3)	.02
Disease state or reason for treatment			1.19 (6, 29)	.34
Autoimmune disorder[b]	6	0.25 (−0.06 to 0.56)	2.12 (4.7)	.09
Cancer	2	0.30 (−4.91 to 5.52)	0.74 (1.0)	.59
Depression[b]	2	0.42 (−0.33 to 1.16)	7.14 (1.0)	.09
HIV	8	0.46 (0.02 to 0.90)	2.46 (6.8)	.04
Insomnia[b]	3	0.60 (−0.04 to 1.25)	4.20 (1.9)	.06
Other physical health condition	5	0.26 (-0.35 to 0.87)	1.22 (3.7)	.30
Other psychiatric disorder(s)	1	0.15 (NA)	NA	NA
Physical and mental health issues	4	0.15 (−0.31 to 0.61)	1.03 (3.0)	.38
Stress (caregiving)	NA	NA	NA	NA
Stress (other)	NA	NA	NA	NA

Abbreviations: CBT, cognitive behavior therapy; ppc, pretest-posttest-control; NA, not applicable.

[a] If *df* < 4.0, the results should be considered preliminary. *F* values are given for categorical moderation analysis; *t* values, for test of effect significance.

[b] This effect size was significant when small sample corrections were not used.

between basal and stimulated immune system markers ($F_{1, 55}$ = 0.10; P = .75).

Immune Marker Assessment Timing

Analyses examining the amount of time that transpired between treatment cessation and when immune markers were assessed revealed that, contrary to what might be expected, a shorter follow-up period (in months) was not associated with a larger effect size (B = .002, β = .006, $t_{3.7}$ = 0.19; P = .86) (Table 2). On the other hand, sensitivity analyses examining the temporal persistence of these associations revealed that psychosocial interventions were associated with enhancements in immune system function that lasted for at least 6 months following treatment cessation (ppc g = 0.31, 95% CI, 0.17-0.45; $t_{8.4}$ = 5.10; P < .001).

Disease State or Reason for Receiving Treatment

Analyses examining whether participants' disease state or reason for seeking treatment moderated the association between psychosocial interventions and immune system function revealed that disease state or reason for seeking treatment was a significant moderator ($F_{9, 55}$ = 2.40; P = .02). As shown in Table 1, the most reliable intervention-based associations were found for individuals receiving treatment for HIV, autoimmune disorders, cancer, and insomnia.

Demographic Characteristics

Analyses examining whether associations between psychosocial interventions and immune system function were moderated by participants' age or sex revealed no moderating effects for age ($t_{17.2}$ = −1.06; P = .30) or sex ($t_{23.9}$ = 0.38; P = .71) (Table 2).

Secondary Analyses Focusing on CBT

Given that CBT has been reported to be the most empirically well validated of all psychotherapies[99] and that more than half of the studies examined herein (31 [55.4%]) used CBT, we conducted secondary analyses to more fully characterize the effect that CBT had on immune system function. Consistent with the results reported above, CBT was significantly associated with enhanced immunity (ppc g = 0.33, 95% CI, 0.19-0.47; $t_{27.2}$ = 4.82; P < .001; 2181 participants), with moderate between-study heterogeneity (τ^2 = 0.21). If calculated as a percentage difference, being randomly assigned to a CBT condition vs a control condition was associated with a statistically significant 14.8% (95% CI 7.5% to 22.1%) improvement in beneficial immune system function and a statistically significant 33.8% (95% CI 22.5% to 45.0%) decrease in harmful immune system function over time.

As shown in Table 2 and **Table 3**, associations between CBT and immune system function differed by the type of

immune marker assessed ($F_{6, 30}$ = 16.34; P < .001). In brief, CBT was significantly associated with enhanced immune system function as indexed by lower proinflammatory cytokine or marker levels ($t_{17.1}$ = 3.68; P = .002), higher immune cell counts ($t_{9.9}$ = 2.96; P = .01), higher natural killer cell activity ($t_{2.1}$ = 4.48; P = .04), and improved other immune outcomes (eg, blastogenesis, number of postoperative infectious diseases; $t_{1.5}$ = 9.84; P = .02). These associations were not moderated by whether the CBT intervention included a group component ($F_{1, 30}$ = 0.40; P = .53), nor were they moderated by treatment duration ($t_{4.2}$ = −0.17; P = .88; although only 1 CBT study assessed immune system outcomes with a treatment duration of less than 4 weeks). In addition, the benefits of CBT did not differ as a function of whether the immune markers represented basal or stimulated levels ($F_{1, 30}$ = 2.16; P = .15), by participants' disease state or reason for treatment ($F_{6, 29}$ = 1.19; P = .34), by participants' age ($t_{10.7}$ = −1.12; P = .29) or sex ($t_{11.7}$ = 1.37; P = .20), or by the amount of time (in months) between treatment cessation and immune marker assessment ($t_{2.9}$ = −0.19; P = .86). Even at 6 months posttreatment, CBT was significantly associated with enhanced immunity (ppc g = 0.32, 95% CI, 0.14-0.51; $t_{9.5}$ = 3.88; P = .003).

Finally, to examine the potential utility of group CBT for improving physical health conditions that CBT is not specifically designed to benefit (eg, autoimmune disorders), the model-estimated effect size associating CBT with a group component and markers of proinflammatory activity was moderate in magnitude in patients with autoimmune disorders (ppc g = 0.41, 95% CI, 0.07-0.76; $t_{7.4}$ = 2.80; P = .02) when there was no delay between treatment cessation and immune marker assessment.

Discussion

One of the most important recent discoveries in the health sciences involves the realization that the immune system is involved in the pathophysiology of not just a few disorders but several major health problems that cause substantial disease burden and mortality.[1,2] Given growing evidence showing that psychosocial factors play a role in shaping immunity,[3-6,8,12-20,100,101] we conducted what we believe is the first systematic review and meta-analysis of RCTs examining how 8 different psychosocial interventions affect 7 common immune outcomes that have broad clinical relevance. This comprehensive review of 56 RCTs revealed that psychosocial interventions were significantly associated with enhanced immune system function, as indexed most consistently by intervention-related decreases in levels of proinflammatory cytokines or markers (eg, interleukin-6, C-reactive protein) and, secondarily, by increases in immune cell counts (eg, CD56, CD4) over time. These associations were most consistent for CBT and for interventions incorporating multiple psychotherapies. Moreover, they did not differ by participants' age, sex, or intervention duration. Finally, we found that these associations persisted for at least 6 months following treatment cessation. Considered together, these results suggest that psychosocial interventions in general—and especially CBT and multiple or combined psychotherapeutic interventions—enhance immune system function and may thus represent a viable strategy for improving immune-related health outcomes.

Converted to percentages, these data reveal that, relative to the control group, psychosocial interventions were associated with an 18.0% (95% CI, 7.2%-28.8%) reduction in harmful immune system function as indexed, for example, by proinflammatory cytokine activity. In comparison, an RCT[102] found that, relative to a control group, treatment with a 40-mg dose of darapladib for reducing cardiovascular disease risk decreased interleukin-6 levels by 7.8% and C-reactive protein levels by 6.0%, whereas a 160-mg dose of darapladib decreased interleukin-6 levels by 12.3% and C-reactive protein levels by 13.0%. Psychosocial interventions thus appear to reduce systemic inflammatory activity in a manner that is similar to using darapladib for treating atherosclerosis.

In addition to being effective, psychosocial interventions may represent a relatively affordable strategy for improving immune-related health. For example, the mean CBT trial length in this meta-analysis was 10.4 weeks. Assuming that these CBT sessions took place once a week and that a therapist would normally charge $150 per session, the cost of using CBT to induce a persistent (eg, 6-month posttreatment) improvement in immune system function would be $1560 per patient. By comparison, the cost of using infliximab to reduce inflammation in persons with an autoimmune disorder is approximately $25 000 per patient per year.[103] Moreover, the functional improvement in immunity associated with CBT is approximately the same as the improvement achieved by adding a 10-mg/kg dose of infliximab every 4 weeks (ie, the maximum dose and frequency) to a methotrexate treatment regimen in individuals with rheumatoid arthritis (ie, estimated effect of CBT on proinflammatory markers: ppc g = 0.41; estimated effect of infliximab on C-reactive protein: ppc g = 0.46).[104] Finally, whereas the present meta-analysis revealed that the association between CBT and immune system function was significant for at least 6 months following therapy cessation, the effects of infliximab are shorter lasting and decay more quickly in patients who take the medication for inflammation-related health problems.[105] Cognitive behavior therapy may thus represent an affordable and relatively longer-lasting adjunctive treatment option for reducing inflammation-related disease risk.

Strengths and Limitations

The main strengths of this meta-analysis include its focus on RCTs with both preintervention and postintervention immunologic assessments, examination of most major psychosocial interventions and many different immune outcomes, and examination of several potential immunologic, demographic, and clinical moderating factors. However, several limitations should also be noted. First, the shortest intervention considered was 1 week, and all but 3 of the interventions examined were at least 4 weeks in duration. Therefore, our ability to detect differences in short-duration treatments was

limited. Relatedly, because studies do not regularly report session frequency, we were not able to consider differences in session frequency as a potential moderator. Second, sensitivity analyses indicated that the psychosocial interventions examined were associated with improvements in immune system function that persisted for at least 6 months following treatment, but there were too few studies with follow-up periods longer than 6 months to obtain reliable estimates from those studies. Third, as with any meta-analysis, it is possible that unpublished studies could have influenced the results.

Fourth, the control groups in the studies examined varied considerably, and it can be difficult to blind participants to their condition assignment in a psychotherapy RCT. Therefore, placebo and expectancy effects are possible. Fifth, although random assignment should equate intervention and control group participants on factors such as comedication and cotreatment, some study groups could have differed in the extent to which participants took some forms of medication or received other forms of treatment. Sixth, some effect sizes estimated in the moderator analyses may have been nonsignificant because of low statistical power. This is especially true for the analyses involving intervention type and disease state or reason for seeking treatment. Finally, although these data indicate that psychosocial interventions are associated with enhanced immune system function, they do not elucidate the mechanisms underlying these associations. It has been suggested that reductions in stress-related neural or psychological processes may help explain such associations,[3-6,106] but psychosocial interventions can have wide-ranging effects on human cognition and behavior, and additional research is needed to identify exactly how such interventions influence immune system activity and health.

Conclusions

In conclusion, recent research has shown that the immune system plays an integral role in many serious disease conditions and that psychosocial factors can modulate immune system function.[3-6,8,107-113] The present meta-analysis extends this work by identifying for the first time the types of psychosocial interventions that have the most robust associations with immune system function, the immune system outcomes that are most consistently associated with these interventions, and the various factors that moderate these associations. Specifically, we found that psychosocial interventions were associated with improvements in immune system function over time—in particular, with decreased proinflammatory cytokines or markers and increased immune cell counts—and that these associations were most consistent for interventions that incorporate CBT or multiple interventions. Given the effectiveness and relative affordability of psychosocial interventions for treating chronic disease, we suggest that psychosocial interventions may represent a viable strategy for reducing disease burden and improving human health. Looking forward, additional research is needed to elucidate the mechanisms through which psychosocial interventions exert relatively long-lasting, beneficial effects on the immune system and health.

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