

Psychosocial Interventions and Immune System Function

A Systematic Review and Meta-analysis of Randomized Clinical Trials

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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 2017⁷ 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 immunity¹⁸ 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

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.

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 post-operative 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

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) guidelines³⁴ 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 con-

tinuous 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 `robmeta` 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 sen-

sitive 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 asymmetry⁴² 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 sciences³⁸ 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 ($\tau^2 = 0.14$), 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.

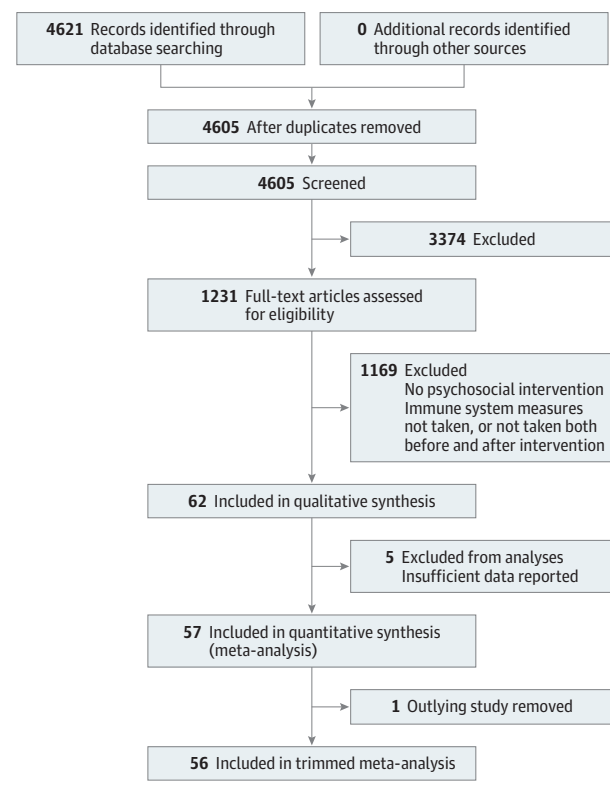
Intervention Type

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

Figure 1. PRISMA Flow Diagram Depicting Selection of Studies



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 ($F_{1, 55} = 3.70$; $P = .06$).

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 ($B = .001$, $\beta = .005$, $t_{4.4} = 0.10$; $P = .93$) (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

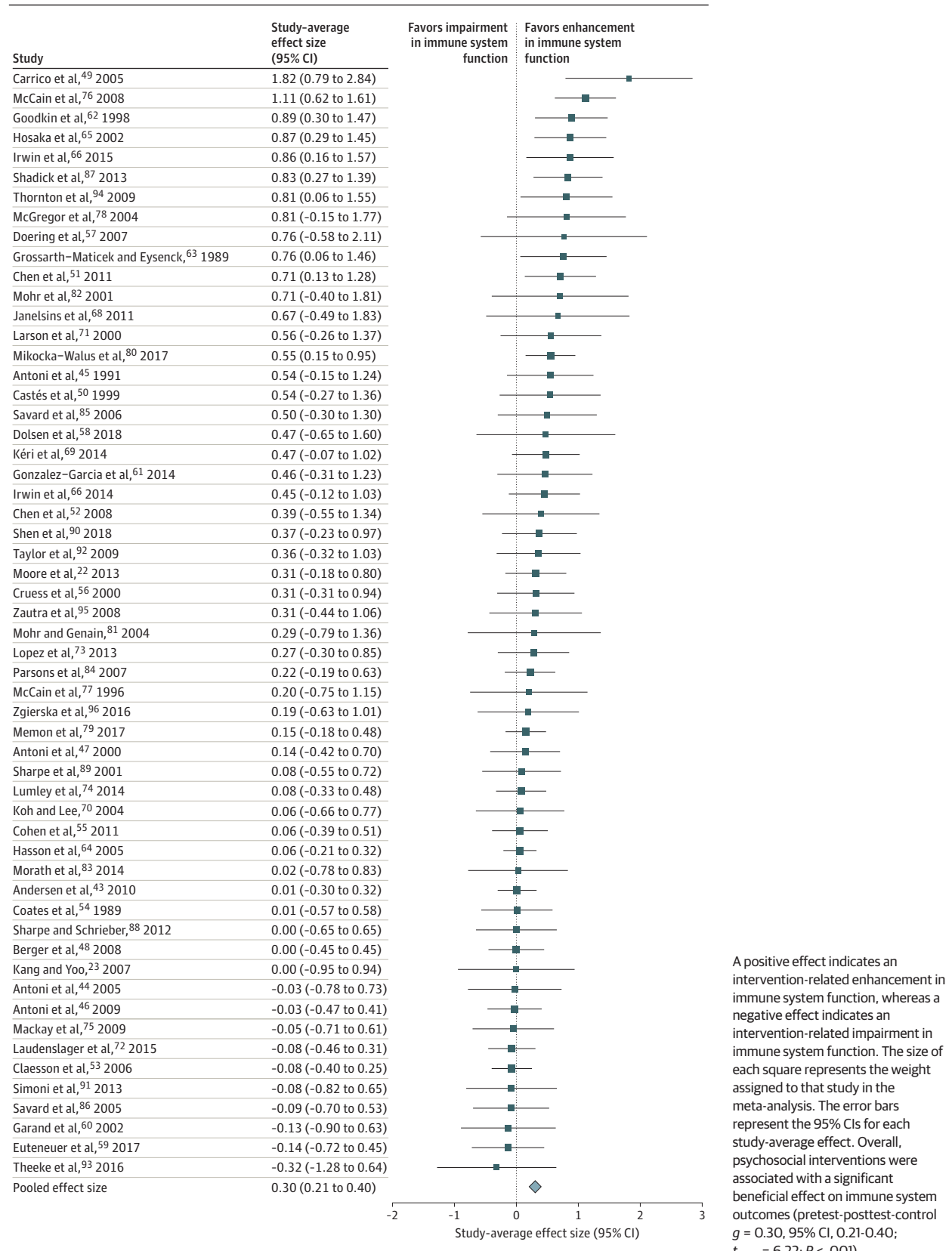


Table 1. Categorical Moderators of the Association Between All Psychosocial Interventions and Immune System Function

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

Moderator	All psychosocial interventions					CBT only				
	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 ($B = .002$, $\beta = .006$, $t_{3,7} = 0.19$; $P = .86$) (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 psychotherapies⁹⁹ 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 ($\tau^2 = 0.21$). 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 RCT¹⁰² 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 addi-

tional 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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REFERENCES

- Couzin-Frankel J. Inflammation bares a dark side. *Science*. 2010;330(6011):1621. doi:10.1126/science.330.6011.1621
- Slavich GM. Understanding inflammation, its regulation, and relevance for health: a top scientific and public priority. *Brain Behav Immun*. 2015;45:13-14. doi:10.1016/j.bbi.2014.10.012
- Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. *Psychol Bull*. 2011;137(6):959-997. doi:10.1037/a0024768
- O'Donovan A, Neylan TC. Associations of trauma and posttraumatic stress disorder with inflammation and endothelial function: on timing, specificity, and mechanisms. *Biol Psychiatry*. 2017;82(12):861-863. doi:10.1016/j.biopsych.2017.10.002
- Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull*. 2014;140(3):774-815. doi:10.1037/a0035302
- Slavich GM, Auerbach RP. Stress and its sequelae: depression, suicide, inflammation, and physical illness. In: Butcher JN, Hooley JM, eds. *APA Handbook of Psychopathology: Psychopathology: Understanding, Assessing, and Treating Adult Mental Disorders*. Vol 1. American Psychological Association; 2018:375-402. doi:10.1037/0000064-016
- GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7
- Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25(12):1822-1832. doi:10.1038/s41591-019-0675-0
- World Health Organization and International Initiative for Impact Evaluation. *An evidence map of social, behavioural and community engagement interventions for reproductive, maternal, newborn and child health*. World Health Organization; 2017.
- Institute of Medicine. *Psychosocial Interventions for Mental and Substance Use Disorders: A Framework for Establishing Evidence-Based Standards*. National Academies Press; 2015.
- National Institute of Mental Health. *National Institute of Mental Health Strategic Plan for Research*. National Institute of Mental Health; 2015.
- Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat Rev Immunol*. 2006;6(4):318-328. doi:10.1038/nri1810

13. Slavich GM, Cole SW. The emerging field of human social genomics. *Clin Psychol Sci*. 2013;1(3):331-348. doi:10.1177/2167702613478594
14. Irwin MR. Human psychoneuroimmunology: 20 years of discovery. *Brain Behav Immun*. 2008;22(2):129-139. doi:10.1016/j.bbi.2007.07.013
15. Fagundes CP, Way B. Early-life stress and adult inflammation. *Curr Dir Psychol Sci*. 2014;23:277-283. doi:10.1177/0963721414535603
16. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annu Rev Psychol*. 2002;53:83-107. doi:10.1146/annurev.psych.53.100901.135217
17. Rohleder N. Stress and inflammation: the need to address the gap in the transition between acute and chronic stress effects. *Psychoneuroendocrinology*. 2019;105:164-171. doi:10.1016/j.psneuen.2019.02.021
18. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull*. 2004;130(4):601-630. doi:10.1037/0033-2909.130.4.601
19. Uchino BN, Trettenvik R, Kent de Grey RG, Cronan S, Hogan J, Baucom BRW. Social support, social integration, and inflammatory cytokines: a meta-analysis. *Health Psychol*. 2018;37(5):462-471. doi:10.1037/hea0000594
20. Kiecolt-Glaser JK, Wilson SJ. Lovesick: how couples' relationships influence health. *Annu Rev Clin Psychol*. 2017;13:421-443. doi:10.1146/annurev-clinpsy-032816-045111
21. Miller GE, Brody GH, Yu T, Chen E. A family-oriented intervention reduces inflammation in low-SES African American youth. *Proc Natl Acad Sci U S A*. 2014;111(31):11287-11292. doi:10.1073/pnas.1406578111
22. Moore RC, Chattillion EA, Ceglowski J, et al. A randomized clinical trial of behavioral activation (BA) therapy for improving psychological and physical health in dementia caregivers: results of the Pleasant Events Program (PEP). *Behav Res Ther*. 2013;51(10):623-632. doi:10.1016/j.brat.2013.07.005
23. Kang HY, Yoo YS. Effects of a bereavement intervention program in middle-aged widows in Korea. *Arch Psychiatr Nurs*. 2007;21(3):132-140. doi:10.1016/j.apnu.2006.12.007
24. Crepez N, Passin WF, Herbst JH, et al; HIV/AIDS Prevention Research Synthesis Team. Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning. *Health Psychol*. 2008;27(1):4-14. doi:10.1037/0278-6133.27.1.4
25. Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. *Ann N Y Acad Sci*. 2016;1373(1):13-24. doi:10.1111/nyas.12998
26. Pascoe MC, Thompson DR, Jenkins ZM, Ski CF. Mindfulness mediates the physiological markers of stress: systematic review and meta-analysis. *J Psychiatr Res*. 2017;95:156-178. doi:10.1016/j.jpsychores.2017.08.004
27. Bower JE, Irwin MR. Mind-body therapies and control of inflammatory biology: a descriptive review. *Brain Behav Immun*. 2016;51:1-11. doi:10.1016/j.bbi.2015.06.012
28. Deng W, Cheung ST, Tsao SW, Wang XM, Tiwari AF. Telomerase activity and its association with psychological stress, mental disorders, lifestyle factors and interventions: a systematic review. *Psychoneuroendocrinology*. 2016;64:150-163. doi:10.1016/j.psneuen.2015.11.017
29. Morgan N, Irwin MR, Chung M, Wang C. The effects of mind-body therapies on the immune system: meta-analysis. *PLoS One*. 2014;9(7):e100903. doi:10.1371/journal.pone.0100903
30. Scott-Sheldon LA, Kalichman SC, Carey MP, Fielder RL. Stress management interventions for HIV+ adults: a meta-analysis of randomized controlled trials, 1989 to 2006. *Health Psychol*. 2008;27(2):129-139. doi:10.1037/0278-6133.27.2.129
31. O'Toole MS, Bovbjerg DH, Renna ME, Lekander M, Mennin DS, Zachariae R. Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: a systematic review and meta-analysis. *Brain Behav Immun*. 2018;74:68-78. doi:10.1016/j.bbi.2018.04.005
32. Cristea IA, Karyotaki E, Hollon SD, Cuijpers P, Gentili C. Biological markers evaluated in randomized trials of psychological treatments for depression: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2019;101:32-44. doi:10.1016/j.neubiorev.2019.03.022
33. Qi L, Wang J, Zhang HL. Meta-analysis of psychological interventions on breast cancer patients' immune function. In: *Proceedings of the 2nd International Conference on Sustainable Development; December 2-4, Xi'an, China*. Atlantic Press; 2017. doi:10.2991/icdsd-16.2017.93
34. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008
35. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull*. 2004;130(3):355-391. doi:10.1037/0033-2909.130.3.355
36. Morris SB. Estimating effect sizes from pretest-posttest-control group designs. *Organ Res Methods*. 2008;11:364-386. doi:10.1177/1094428106291059
37. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-analysis*. John Wiley & Sons, Ltd; 2009. doi:10.1002/9780470743386
38. Scammacca N, Roberts G, Stuebing KK. Meta-analysis with complex research designs: dealing with dependence from multiple measures and multiple group comparisons. *Rev Educ Res*. 2014;84(3):328-364. doi:10.3102/0034654313500826
39. Hedges LV, Tipton E, Johnson MC. Robust variance estimation in meta-regression with dependent effect size estimates. *Res Synth Methods*. 2010;1(1):39-65. doi:10.1002/jrsm.5
40. Tanner-Smith EE, Tipton E. Robust variance estimation with dependent effect sizes: practical considerations including a software tutorial in STATA and SPSS. *Res Synth Methods*. 2014;5(1):13-30. doi:10.1002/jrsm.1091
41. Tipton E. Small sample adjustments for robust variance estimation with meta-regression. *Psychol Methods*. 2015;20(3):375-393. doi:10.1037/met0000011
42. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
43. Andersen BL, Thornton LM, Shapiro CL, et al. Biobehavioral, immune, and health benefits following recurrence for psychological intervention participants. *Clin Cancer Res*. 2010;16(12):3270-3278. doi:10.1158/1078-0432.CCR-10-0278
44. Antoni MH, Cruess DG, Klimas N, et al. Increases in a marker of immune system reconstitution are predated by decreases in 24-h urinary cortisol output and depressed mood during a 10-week stress management intervention in symptomatic HIV-infected men. *J Psychosom Res*. 2005;58(1):3-13. doi:10.1016/j.jpsychores.2004.05.010
45. Antoni MH, Baggett L, Ironson G, et al. Cognitive-behavioral stress management intervention buffers distress responses and immunologic changes following notification of HIV-1 seropositivity. *J Consult Clin Psychol*. 1991;59(6):906-915. doi:10.1037/0022-006X.59.6.906
46. Antoni MH, Lechner S, Diaz A, et al. Cognitive behavioral stress management effects on psychosocial and physiological adaptation in women undergoing treatment for breast cancer. *Brain Behav Immun*. 2009;23(5):580-591. doi:10.1016/j.bbi.2008.09.005
47. Antoni MH, Cruess DG, Cruess S, et al. Cognitive-behavioral stress management intervention effects on anxiety, 24-hr urinary norepinephrine output, and T-cytotoxic/suppressor cells over time among symptomatic HIV-infected gay men. *J Consult Clin Psychol*. 2000;68(1):31-45. doi:10.1037/0022-006X.68.1.31
48. Berger S, Schad T, von Wyl V, et al. Effects of cognitive behavioral stress management on HIV-1 RNA, CD4 cell counts and psychosocial parameters of HIV-infected persons. *AIDS*. 2008;22(6):767-775. doi:10.1097/QAD.0b013e3282f511dc
49. Carrico AW, Antoni MH, Pereira DB, et al. Cognitive behavioral stress management effects on mood, social support, and a marker of antiviral immunity are maintained up to 1 year in HIV-infected gay men. *Int J Behav Med*. 2005;12(4):218-226. doi:10.1207/s15327558ijbm1204_2
50. Castés M, Hageg I, Palenque M, Canelones P, Corao A, Lynch NR. Immunological changes associated with clinical improvement of asthmatic children subjected to psychosocial intervention. *Brain Behav Immun*. 1999;13(1):1-13. doi:10.1006/brbi.1999.0551
51. Chen HY, Cheng IC, Pan YJ, et al. Cognitive-behavioral therapy for sleep disturbance decreases inflammatory cytokines and oxidative stress in hemodialysis patients. *Kidney Int*. 2011;80(4):415-422. doi:10.1038/ki.2011.151
52. Chen HY, Chiang CK, Wang HH, et al. Cognitive-behavioral therapy for sleep disturbance in patients undergoing peritoneal dialysis: a pilot randomized controlled trial. *Am J Kidney Dis*. 2008;52(2):314-323. doi:10.1053/j.ajkd.2008.03.012
53. Claesson M, Birgander LS, Jansson JH, et al. Cognitive-behavioural stress management does not improve biological cardiovascular risk indicators in women with ischaemic heart disease: a randomized-controlled trial. *J Intern Med*. 2006;260(4):320-331. doi:10.1111/j.1365-2796.2006.01691.x

54. Coates TJ, McKusick L, Kuno R, Stites DP. Stress reduction training changed number of sexual partners but not immune function in men with HIV. *Am J Public Health*. 1989;79(7):885-887. doi:10.2105/AJPH.79.7.885
55. Cohen L, Parker PA, Vence L, et al. Presurgical stress management improves postoperative immune function in men with prostate cancer undergoing radical prostatectomy. *Psychosom Med*. 2011;73(3):218-225. doi:10.1097/PSY.0b013e31820a1c26
56. Cruess S, Antoni M, Cruess D, et al. Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in HIV-positive men. *Psychosom Med*. 2000;62(6):828-837. doi:10.1097/00006842-200011000-00013
57. Doering LV, Cross R, Vredevoe D, Martinez-Maza O, Cowan MJ. Infection, depression, and immunity in women after coronary artery bypass: a pilot study of cognitive behavioral therapy. *Altern Ther Health Med*. 2007;13(3):18-21.
58. Dolsen MR, Soehner AM, Harvey AG. Pro-inflammatory cytokines, mood, and sleep in interepisode bipolar disorder and insomnia. *Psychosom Med*. 2018;80:87-94. doi:10.1097/PSY.0000000000000529
59. Euteneuer F, Dannehl K, Del Rey A, Engler H, Schedlowski M, Rief W. Immunological effects of behavioral activation with exercise in major depression: an exploratory randomized controlled trial. *Transl Psychiatry*. 2017;7(5):e1132. doi:10.1038/tp.2017.76
60. Garand L, Buckwalter KC, Lubaroff D, Tripp-Reimer T, Frantz RA, Ansley TN. A pilot study of immune and mood outcomes of a community-based intervention for dementia caregivers: the PLST intervention. *Arch Psychiatr Nurs*. 2002;16(4):156-167. doi:10.1053/apnu.2002.34392
61. Gonzalez-Garcia M, Ferrer MJ, Borrás X, et al. Effectiveness of mindfulness-based cognitive therapy on the quality of life, emotional status, and CD4 cell count of patients aging with HIV infection. *AIDS Behav*. 2014;18(4):676-685. doi:10.1007/s10461-013-0612-z
62. Goodkin K, Feaster DJ, Asthana D, et al. A bereavement support group intervention is longitudinally associated with salutary effects on the CD4 cell count and number of physician visits. *Clin Diagn Lab Immunol*. 1998;5(3):382-391. doi:10.1128/CDLI.5.3.382-391.1998
63. Grossarth-Maticek R, Eysenck HJ. Length of survival and lymphocyte percentage in women with mammary cancer as a function of psychotherapy. *Psychol Rep*. 1989;65(1):315-321. doi:10.2466/pr0.1989.65.1.315
64. Hasson D, Anderberg UM, Theorell T, Arnetz BB. Psychophysiological effects of a web-based stress management system: a prospective, randomized controlled intervention study of IT and media workers [ISRCTN54254861]. *BMC Public Health*. 2005;5:78. doi:10.1186/1471-2458-5-78
65. Hosaka T, Matsubayashi H, Sugiyama Y, Izumi S, Makino T. Effect of psychiatric group intervention on natural-killer cell activity and pregnancy rate. *Gen Hosp Psychiatry*. 2002;24(5):353-356. doi:10.1016/S0163-8343(02)00194-9
66. Irwin MR, Olmstead R, Carrillo C, et al. Cognitive behavioral therapy vs tai chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. *Sleep*. 2014;37(9):1543-1552. doi:10.5665/sleep.4008
67. Irwin MR, Olmstead R, Breen EC, et al. Cognitive behavioral therapy and tai chi reverse cellular and genomic markers of inflammation in late-life insomnia: a randomized controlled trial. *Biol Psychiatry*. 2015;78(10):721-729. doi:10.1016/j.biopsych.2015.01.010
68. Janelins MC, Davis PG, Wideman L, et al. Effects of tai chi chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. *Clin Breast Cancer*. 2011;11(3):161-170. doi:10.1016/j.clbc.2011.03.013
69. Kéri S, Szabó C, Kelemen O. Expression of toll-like receptors in peripheral blood mononuclear cells and response to cognitive-behavioral therapy in major depressive disorder. *Brain Behav Immun*. 2014;40:235-243. doi:10.1016/j.bbi.2014.03.020
70. Koh KB, Lee Y. Reduced anxiety level by therapeutic interventions and cell-mediated immunity in panic disorder patients. *Psychother Psychosom*. 2004;73(5):286-292. doi:10.1159/000078845
71. Larson MR, Duberstein PR, Talbot NL, Caldwell C, Moynihan JA. A presurgical psychosocial intervention for breast cancer patients: psychological distress and the immune response. *J Psychosom Res*. 2000;48(2):187-194. doi:10.1016/S0022-3999(99)00110-5
72. Laudenslager ML, Simoneau TL, Kilbourn K, et al. A randomized control trial of a psychosocial intervention for caregivers of allogeneic hematopoietic stem cell transplant patients: effects on distress. *Bone Marrow Transplant*. 2015;50(8):1110-1118. doi:10.1038/bmt.2015.104
73. Lopez CR, Antoni MH, Pereira D, et al. Stress management, depression and immune status in lower income racial/ethnic minority women co-infected with HIV and HPV. *J Appl Biobehav Res*. 2013;18(1):37-57. doi:10.1111/jabr.12003
74. Lumley MA, Keefe FJ, Mosley-Williams A, et al. The effects of written emotional disclosure and coping skills training in rheumatoid arthritis: a randomized clinical trial. *J Consult Clin Psychol*. 2014;82(4):644-658. doi:10.1037/a0036958
75. Mackay GM, Forrest CM, Christofides J, et al. Kynurenine metabolites and inflammation markers in depressed patients treated with fluoxetine or counselling. *Clin Exp Pharmacol Physiol*. 2009;36(4):425-435. doi:10.1111/j.1440-1681.2008.05077.x
76. McCain NL, Gray DP, Elswick RK, et al. A randomized clinical trial of alternative stress management interventions in persons with HIV infection. *J Consult Clin Psychol*. 2008;76(3):431-441. doi:10.1037/0022-006X.76.3.431
77. McCain NL, Zeller JM, Cella DF, Urbanski PA, Novak RM. The influence of stress management training in HIV disease. *Nurs Res*. 1996;45(4):246-253. doi:10.1097/0006199-199607000-00009
78. McGregor BA, Antoni MH, Boyers A, Alferi SM, Blomberg BB, Carver CS. Cognitive-behavioral stress management increases benefit finding and immune function among women with early-stage breast cancer. *J Psychosom Res*. 2004;56(1):1-8. doi:10.1016/S0022-3999(03)00036-9
79. Memon AA, Sundquist K, Ahmad A, Wang X, Hedelius A, Sundquist J. Role of IL-8, CRP and epidermal growth factor in depression and anxiety patients treated with mindfulness-based therapy or cognitive behavioral therapy in primary health care. *Psychiatry Res*. 2017;254:311-316. doi:10.1016/j.psychres.2017.05.012
80. Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy for inflammatory bowel disease: 24-month data from a randomised controlled trial. *Int J Behav Med*. 2017;24(1):127-135. doi:10.1007/s12529-016-9580-9
81. Mohr DC, Genain C. Social support as a buffer in the relationship between treatment for depression and T-cell production of interferon gamma in patients with multiple sclerosis. *J Psychosom Res*. 2004;57(2):155-158. doi:10.1016/S0022-3999(03)00601-9
82. Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of nonspecific and antigen-specific T_H1 responses in multiple sclerosis. *Arch Neurol*. 2001;58(7):1081-1086. doi:10.1001/archneur.58.7.1081
83. Morath J, Gola H, Sommershof A, et al. The effect of trauma-focused therapy on the altered T cell distribution in individuals with PTSD: evidence from a randomized controlled trial. *J Psychiatr Res*. 2014;54:1-10. doi:10.1016/j.jpsychires.2014.03.016
84. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2007;46(4):443-450. doi:10.1097/QAI.0b013e318158a461
85. Savard J, Simard S, Giguère I, et al. Randomized clinical trial on cognitive therapy for depression in women with metastatic breast cancer: psychological and immunological effects. *Palliat Support Care*. 2006;4(3):219-237. doi:10.1017/S1478951506060305
86. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: immunologic effects. *J Clin Oncol*. 2005;23(25):6097-6106. doi:10.1200/JCO.2005.12.513
87. Shadick NA, Sowell NF, Frits ML, et al. A randomized controlled trial of an internal family systems-based psychotherapeutic intervention on outcomes in rheumatoid arthritis: a proof-of-concept study. *J Rheumatol*. 2013;40(11):1831-1841. doi:10.3899/jrheum.121465
88. Sharpe L, Schrieber L. A blind randomized controlled trial of cognitive versus behavioral versus cognitive-behavioral therapy for patients with rheumatoid arthritis. *Psychother Psychosom*. 2012;81(3):145-152. doi:10.1159/000332334
89. Sharpe L, Sensky T, Timberlake N, Ryan B, Brewin CR, Allard S. A blind, randomized, controlled trial of cognitive-behavioural intervention for patients with recent onset rheumatoid arthritis: preventing psychological and physical morbidity. *Pain*. 2001;89(2-3):275-283. doi:10.1016/S0304-3959(00)00379-1
90. Shen X, Zhu X, Wu Y, et al. Effects of a psychological intervention programme on mental stress, coping style and immune function in percutaneous coronary intervention patients. *PLoS*

- One. 2018;13(1):e0187745. doi:10.1371/journal.pone.0187745
91. Simoni JM, Wiebe JS, Saucedo JA, et al. A preliminary RCT of CBT-AD for adherence and depression among HIV-positive Latinos on the US-Mexico border: the Nuevo Día study. *AIDS Behav*. 2013;17(8):2816-2829. doi:10.1007/s10461-013-0538-5
92. Taylor CB, Conrad A, Wilhelm FH, et al. Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? *J Psychiatr Res*. 2009;43(16):1246-1252. doi:10.1016/j.jpsychires.2009.05.006
93. Theeke LA, Mallow JA, Moore J, McBurney A, Rellick S, VanGilder R. Effectiveness of LISTEN on loneliness, neuroimmunological stress response, psychosocial functioning, quality of life, and physical health measures of chronic illness. *Int J Nurs Sci*. 2016;3(3):242-251. doi:10.1016/j.ijnss.2016.08.004
94. Thornton LM, Andersen BL, Schuler TA, Carson WE III. A psychological intervention reduces inflammatory markers by alleviating depressive symptoms: secondary analysis of a randomized controlled trial. *Psychosom Med*. 2009;71(7):715-724. doi:10.1097/PSY.0b013e3181b0545c
95. Zautra AJ, Davis MC, Reich JW, et al. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *J Consult Clin Psychol*. 2008;76(3):408-421. doi:10.1037/0022-006X.76.3.408
96. Zgierska AE, Burzinski CA, Cox J, et al. Mindfulness meditation and cognitive behavioral therapy intervention reduces pain severity and sensitivity in opioid-treated chronic low back pain: pilot findings from a randomized controlled trial. *Pain Med*. 2016;17(10):1865-1881. doi:10.1093/pm/pnw006
97. Shields GS, Bonner JC, Moons WG. Does cortisol influence core executive functions? a meta-analysis of acute cortisol administration effects on working memory, inhibition, and set-shifting. *Psychoneuroendocrinology*. 2015;58:91-103. doi:10.1016/j.psyneuen.2015.04.017
98. Uttal DH, Meadow NG, Tipton E, et al. The malleability of spatial skills: a meta-analysis of training studies. *Psychol Bull*. 2013;139(2):352-402. doi:10.1037/a0028446
99. Roth A, Fonagy P. *What Works for Whom: A Critical Review of Psychotherapy Research*. 2nd ed. Guilford Press; 2005.
100. Herbert TB, Cohen S. Stress and immunity in humans: a meta-analytic review. *Psychosom Med*. 1993;55(4):364-379. doi:10.1097/00006842-199307000-00004
101. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun*. 2007;21(7):901-912. doi:10.1016/j.bbi.2007.03.011
102. Mohler ER III, Ballantyne CM, Davidson MH, et al; Darapladib Investigators. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 2008;51(17):1632-1641. doi:10.1016/j.jacc.2007.11.079
103. Bonafede MMK, Gandra SR, Watson C, Princic N, Fox KM. Cost per treated patient for etanercept, adalimumab, and infliximab across adult indications: a claims analysis. *Adv Ther*. 2012;29(3):234-248. doi:10.1007/s12325-012-0007-y
104. Lipsky PE, van der Heijde DM, St Clair EW, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis With Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med*. 2000;343(22):1594-1602. doi:10.1056/NEJM200011303432202
105. De Bie CI, Hummel TZ, Kindermann A, et al. The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited. *Aliment Pharmacol Ther*. 2011;33(2):243-250. doi:10.1111/j.1365-2036.2010.04507.x
106. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proc Natl Acad Sci U S A*. 2010;107(33):14817-14822. doi:10.1073/pnas.1009164107
107. Slavich GM, Giletta M, Helms SW, et al. Interpersonal life stress, inflammation, and depression in adolescence: testing social signal transduction theory of depression. *Depress Anxiety*. 2020;37(2):179-193. doi:10.1002/da.22987
108. Antoni MH. Psychosocial intervention effects on adaptation, disease course and biobehavioral processes in cancer. *Brain Behav Immun*. 2013;30(suppl):S88-S98. doi:10.1016/j.bbi.2012.05.009
109. Kiecolt-Glaser JK, Glaser R. Psychoneuroimmunology: can psychological interventions modulate immunity? *J Consult Clin Psychol*. 1992;60(4):569-575. doi:10.1037/0022-006X.60.4.569
110. Miller GE, Cohen S. Psychological interventions and the immune system: a meta-analytic review and critique. *Health Psychol*. 2001;20(1):47-63. doi:10.1037/0278-6133.20.1.47
111. Irwin MR, Slavich GM. Psychoneuroimmunology. In: Cacioppo JT, Tassinary LG, Berntson GG, eds. *Handbook of Psychophysiology*. 4th ed. Cambridge University Press; 2017:377-398. doi:10.1017/9781107415782.017
112. Slavich GM, Sacher J. Stress, sex hormones, inflammation, and major depressive disorder: extending social signal transduction theory of depression to account for sex differences in mood disorders. *Psychopharmacology*. 2019;236(10):3063-3079. doi:10.1007/s00213-019-05326-9
113. Slavich GM. Psychoneuroimmunology of stress and mental health. In: Harkness KL, Hayden EP, eds. *The Oxford Handbook of Stress and Mental Health*. Oxford University Press; 2020:519-546. doi:10.1093/oxfordhb/9780190681777.013.24