Effects of Brief Mood-Improving Interventions on Immunity: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Positive mood has been associated with enhanced immune function. Interventions that improve mood could therefore provide a mechanism for optimizing immune-related health outcomes. Brief interventions that improve mood, also known as mood inductions, potentially offer a pragmatic approach to enhancing immune function for finite periods where this would be beneficial to health (e.g., in advance of vaccination or surgery). This review sought to systematically examine the evidence regarding the effects of brief, single-session positive mood interventions on immunity.

Methods: Systematic searches of electronic databases were performed from earliest records to July 25, 2018. We identified 42 interventions suitable for inclusion, 6 of which were tested in multiple subpopulations. Random-effects meta-analyses were performed for pre-post experimental group immune outcomes measured in at least five intervention studies.

Results: Although interventions were heterogeneous, 81% resulted in a statistically significant change in at least one immune parameter after the positive mood intervention for one or more of the subpopulations examined. However, studies were, in general, of low-to-moderate quality with small sample sizes (median n = 32) and did not examine the persistence or clinical relevance of the immune changes observed. Random-effects meta-analyses showed a significant medium-sized effect of interventions on increasing secretory IgA concentration (g = 0.65), a small but statistically significant effect for increased Interleukin-6 production (g = 0.12), and nonsignificant effects on natural killer cell activity (g = 0.15).

Conclusions: The current literature suggests that improvements in mood resulting from brief interventions can influence some immune parameters in ways indicative of enhanced immune function. However, there is a need for higher-quality research in this area that focuses on clinically relevant immune outcomes and mechanisms.

Key words: positive affect, immunity, intervention, positive mood, systematic review, meta-analysis.

INTRODUCTION

Research exploring links between psychological experiences, immunity, and health has historically been dominated by a focus on the effects of negative emotions such as stress, depression, and loneliness (1). Although an imbalance still exists, over the past two decades, growing interest in positive psychology has resulted in an accumulation of evidence that positive affective states (e.g., happiness and joy) and dispositions can beneficially contribute to health outcomes including those that may have immunological etiologies (2–7).

Multiple biological pathways between subcortical regions of the brain responsible for affective processing and the immune system have been described including endocrine and cytokine-mediated inflammatory routes (5) as well as the direct autonomic innervation of primary and secondary lymphatic organs extending from the central nervous system (8–10). Numerous observational and experimental studies provide strong evidence for a direct relationship between greater positive affect and enhanced immune function. For example, in a prospective longitudinal diary study, secretory immunoglobulin A (s-IgA) response to rabbit albumin was found to be enhanced on days where participants reported greater positive mood (11). Viral challenge studies have shown reduced susceptibility to infection in those with more positive affective styles (12,13), and higher levels of trait positive affect has been associated with enhanced hepatitis B vaccination responses (14). Together, these data suggest that boosting positive affect could potentially act as an “immune enhancer” in clinically meaningful ways.

Although long-term improvements in positive affect levels, and therefore as a result immune function, are self-evidently desirable, interventions that target prolonged mood change face considerable barriers in being widely adopted. Although there is some sparse evidence that positive affect intervention studies can achieve long-term mood benefits (15), to date, such interventions have required multiple interactive sessions with trained professionals, completed over a period of weeks and considerable participant dedication. This makes them expensive and somewhat burdensome for health care providers.

EPHPP = Effective Public Health Practice Project, IL-6 = interleukin-6, NK = natural killer cell, RCT = randomized controlled trial, s-IgA = secretory immunoglobulin serotype A

Supplemental Content

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An alternative and arguably more pragmatic approach to exploiting the relationship between mood and immune function involves targeting brief positive mood interventions (also known as positive mood inductions) at particularly salient time points where enhanced immune function for finite periods may be beneficial, for example, immediately before vaccination or in advance of surgery. Positive mood on the day of vaccination has been associated with enhanced antibody responses to some strains of influenza vaccination (16), and brief relaxation has been shown to improve clinical wound healing in surgical patients (17). There is also considerable body of evidence showing more negative emotional states to be associated with poorer immune function (18), wound healing (19), and surgical recovery (20). Brief interventions that induce positive mood (or reduce negative mood) could be expected to be relatively cheap to implement and could therefore potentially be incorporated into health care settings where interactions are also, generally, brief.

In this article, we systematically review and meta-analyze the evidence that mood improvements resulting from brief, single-session interventions are related to immunity. The primary aims of this review are to a) identify the size and nature of the existing literature base relating to brief mood-enhancing interventions and immunity, b) to assess the quality of this literature, and c) examine the impact of mood enhancing interventions on immunological outcomes.

METHODS

Search Strategy

Systematic electronic searches were conducted in EMBASE, PsycINFO, PsycARTICLES, and MEDLINE from earliest records to July 25, 2018. A comprehensive overview of the search terms used can be found in the Supplemental Digital Content, http://links.lww.com/PSYMED/A592. In brief, the searches included synonym terms relating to a) intervention/ manipulation (e.g., modular* and induc*), b) mood (e.g., emotion* and happ*), and c) immunity (e.g., immun* and cytokine*). Medical subheadings were used when possible. Reference lists of included articles and previous reviews of potential relevance (21–27) were hand-searched to identify additional articles not picked up by the electronic searches.

Inclusion and Exclusion Criteria

English language studies appearing in a peer-reviewed journal, presenting primary research, reporting a single-session intervention measuring changes in mood and some aspect of immunity were included. Immune outcomes needed to be assessed both immediately preintervention and postintervention for a study to be included, with any later follow-ups also included. Studies that did not include an appropriate mood manipulation check (i.e., measure whether participants mood changed as a result of the intervention), physical activity interventions, or studies that examined recovery from a stressor or negative mood inductions after intervention were excluded, as these were deemed to preclude clarity on whether any immunological changes were driven by the interventions proposed mediating mechanisms (mood enhancement) or other factors (e.g., physical exertion and distraction from prior stressor). Negative mood inductions and "neutral" interventions acting as a control group (e.g., rest and reading) were not included. Studies focusing exclusively on endocrine outcomes (e.g., cortisol), animal studies, and conference proceedings were also excluded.

Quality Assessment

Study quality was assessed using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies (28). The EPHPP is designed to assess quality for any quantitative study design and assesses six primary domains: selection bias, study design, confounders, blinding, data collection method, and withdrawals/dropouts. Each of these domains is graded individually as strong, moderate, or weak, which are then combined into an overall global rating. A study receives a global rating of "strong" if none of the six individual domains are graded as weak, "moderate" if only one is coded as weak, and "weak" if two or more domains are assessed as weak. The EPHPP also includes items relating to intervention integrity and analyses; however, because these are not used to assessing the global rating of study quality, they were not assessed in the present review. The tool is recommended by the Cochrane Collaboration as an alternative to their own risk of bias tool that is primarily designed for randomized controlled trials (RCTs) (29).

Statistical Analysis

Calculation of effect sizes (Hedges g) for pre-post experimental group outcomes and random-effects meta-analyses were conducted using comprehensive meta-analysis version 3 (Biostat, Englewood, New Jersey; Internet: https://www.meta-analysis.com/). Because of concerns regarding the accuracy of effect size estimation in meta-analyses containing very few low- to moderate-quality studies, meta-analyses were only performed on immune outcomes measured in at least five interventions (s-IgA concentration, natural killer cell activity [NK activity], and interleukin-6 [IL-6] production). Population subgroups (e.g., carers and patients) were included separately in meta-analyses when presented as such in the published article. Where available, unadjusted pre/postvaccination means, SDs, and pre-post correlations were preferentially used to calculate effect sizes. However, where these were not available, change scores and paired t and t test values (with no covariates included) were also used. Because pre-post correlations are rarely reported, where pre-post correlations were unknown, we calculated effect sizes assuming a positive correlations of 0.25, 0.5, and 0.75 as described by Norris et al. (30) Because these assumptions yielded very similar meta-analytic effect size estimates, the findings reported in this article are based on a correlation of 0.5 (analyses assuming correlations of 0.25 and 0.75 are available upon request). Where insufficient information to calculate effect sizes was available, attempts were made to contact authors to provide additional information. In total, attempts were made to contact the authors of 18 articles for some form of additional information with a further 2 contacted for reasons of clarification. Of these, authors from 4 articles were able to provide the requested information, 6 responded but were unable to provide the data required, and 10 did not respond. Where immune outcomes were assessed at multiple dilutions, these were combined into a mean composite effect size for that outcome. Variation between effect sizes was assessed using the Cochran Q test with significant heterogeneity indicated by a p value < .1, and the percentage of no-chance heterogeneity assessed using the I² statistic (31). To examine whether the magnitude of the interventions effect on mood outcomes was associated with the magnitude of immune effects, post hoc exploratory meta-regressions were performed. Where multiple measures of mood were reported, these were combined into a mean composite mood effect size (this included measures shown to not be significantly different post-intervention).

RESULTS

Study Selection Process

The flow of studies through the review process is presented in Figure 1. Ultimately, 31 articles (hereafter designated “k”), reporting 42 interventions (hereafter designated “i”) were identified as suitable for inclusion in the review. Six of the interventions were examined and compared in two or more distinct subpopulations (e.g., older versus younger adults). The most common reasons for exclusion from the 168 articles identified for full-text examination were

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the intervention lasting longer than a single session (n = 47) and not including an appropriate manipulation check (n = 30).

Studies Characteristics
The most common origin of studies was the United States (k = 13), with a large number from Japan (k = 12). The remaining studies were conducted in the United Kingdom (k = 2), Canada, Australia, South Korea, and Israel (all, k = 1). Most commonly studies adopted a crossover design (k = 15; 48.4%), with participants receiving more than one intervention (with a gap between) in a randomized order. Eleven studies were RCTs, and five adopted a cohort design. Sample sizes were generally small, ranging from 5 to 193 with a median of 32 (mean = 39.7). Participants were most frequently adults self-selected from the general population (k = 17; 54.8%), although a substantial proportion recruited from exclusively student samples (k = 5; 16.1%). Only one study explicitly recruited older adults (32), with one study conducted in children (33). The remaining studies recruited from more specific populations including singers, method actors, couples, or patient groups with an existing health condition.

Intervention Characteristics
Interventions were varied, although the most common was a comedy film or audiotape (i = 7; 16.6%). Massage (i = 6), listening to (i = 4), or making music in the form of group drumming (i = 4) or singing (i = 1) were also popular intervention forms. The remaining interventions included pleasant or memory retrieving odors (i = 6), relaxation with or without immune suggestions (i = 4), acting out an imagined positive experience (i = 3), Qi therapy + rest (i = 2), mental recall of positive autobiographical events, watching film clips of attractive celebrities, hugging and kissing a romantic partner, receiving a footbath, and writing about self-congruencies (all, i = 1). Most interventions were administered on an individual basis (i = 26; 61.9%), with the remaining delivered in group settings (i = 12) or in couples (i = 1). No information was reported as to the nature of intervention administration in three cases. Interventions ranged from 90 seconds to 120 minutes in duration (mean = 48 minutes, median = 40 minutes).

Quality Assessments
A summary of quality assessment ratings for each of the EPHPP individual domain and global quality ratings is shown for each
study in Table 1. In terms of global quality ratings, 1 study was classified as strong, 20 as moderate, and 10 as weak. This is suggestive of weak-to-moderate overall quality for this literature. Further examination of the individual quality domains shows that selection bias was an issue for nearly all studies. In the selection bias domain, all but one study was classified as weak, indicating that participants were either self-selecting or that the sample selection processes were not adequately reported, with one classified as strong. In the study design domain, 11 studies were classified as strong (indicating that they classified as RCTs or clinical controlled trials), 20 as moderate, and none as weak. Confounders were often controlled for by the crossover nature of many study designs, resulting in 23 studies being classified as strong in this domain, none as moderate, and 8 identified as weak. All studies received a moderate rating for the blinding domain, in most cases because assessor and participant blinding was not mentioned. However, it is worth noting that changes made to the EPHPP tool coding instructions after initial quality assessments were made would require studies with insufficient reporting of blinding to be coded as weak. With regard to the data collection method, 10 studies were categorized as strong—meaning that outcome measures (immune) had been demonstrated as both valid and reliable—with the remaining 21 studies classified as moderate because of not reporting reliability statistics for the outcome measures or failing to refer to previous reports of the measure’s reliability. Most studies reported minimal or no attrition during the studies, meaning that for the withdrawals and dropouts domain, 28 studies were classified as strong, none as moderate, and only 3 as weak.

**Narrative Synthesis**

In total, the 42 interventions were examined across a total of 50 groups (e.g., those with and without a specific health condition; older versus younger adults). Of these, a statistically significant improvement from preintervention to postintervention in at least one mood outcome was observed in 46 (92.0%) of the groups examined. Of those not showing a significant mood improvement, two interventions (listening to music for 15 minutes (34) and a

| Authors (Year of Publication) | Selection Bias | Study Design | Confounders | Blinding | Data Collection Method | Withdrawals and Dropouts | Global Rating |
|------------------------------|----------------|--------------|-------------|----------|------------------------|--------------------------|--------------|
| Bartlett et al. (1993) (34) | Weak           | Strong       | Weak        | Moderate | Moderate               | Strong                    | Weak         |
| Bennet et al. (2003) (35)   | Weak           | Strong       | Weak        | Moderate | Strong                 | Strong                    | Weak         |
| Bittman et al. (2001) (36)  | Weak           | Strong       | Weak        | Moderate | Moderate               | Moderate                 | Weak         |
| Burns et al. (2001) (37)    | Weak           | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Moderate     |
| Donoyama et al. (2010) (38) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Moderate     |
| Donoyama and Shihasaki (2010) (39) | Weak       | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Moderate     |
| Fancourt et al. (2016) (40) | Strong         | Moderate     | Strong      | Moderate | Strong                 | Strong                    | Strong       |
| Futterman et al. (1992) (41) | Weak           | Moderate     | Strong      | Moderate | Moderate               | Strong                    | Moderate     |
| Futterman et al. (1994) (42) | Weak           | Moderate     | Weak        | Moderate | Moderate               | Strong                    | Weak         |
| Groër et al. (1994) (43)    | Weak           | Strong       | Weak        | Moderate | Moderate               | Weak                     | Weak         |
| Hall et al. (1992) (44)     | Weak           | Moderate     | Strong      | Moderate | Moderate               | Strong                    | Moderate     |
| Hewson-Bower and Drummond (1996) (33) | Weak   | Strong       | Strong      | Moderate | Strong                 | Strong                    | Moderate     |
| Jung et al. (2006) (45)     | Weak           | Strong       | Weak        | Moderate | Moderate               | Strong                    | Weak         |
| Kiecott-Glaser et al. (2008) (46) | Weak       | Moderate     | Strong      | Moderate | Moderate               | Weak                     | Weak         |
| Kimata (2004) (47)          | Weak           | Moderate     | Strong      | Strong   | Strong                 | Strong                    | Moderate     |
| Knapp et al. (1992) (48)    | Weak           | Moderate     | Weak        | Moderate | Moderate               | Strong                    | Weak         |
| Koyama et al. (2009) (32)   | Weak           | Moderate     | Weak        | Moderate | Moderate               | Strong                    | Weak         |
| Labott et al. (2010) (49)   | Weak           | Strong       | Strong      | Moderate | Strong                 | Moderate                 | Moderate     |
| Lefcourt et al. (1990) (50) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Strong       |
| Matsunaga et al. (2008) (51) | Weak           | Moderate     | Strong      | Moderate | Moderate               | Strong                    | Moderate     |
| Matsunaga et al. (2011) (52) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Strong       |
| Matsunaga et al. (2011) (53) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Strong                    | Moderate     |
| Matsunaga et al. (2013) (54) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Strong                    | Moderate     |
| Mittwoch-Jaffe et al. (1995) (55) | Weak    | Strong       | Strong      | Moderate | Moderate               | Strong                    | Moderate     |
| Noto et al. (2010) (56)     | Weak           | Moderate     | Strong      | Moderate | Strong                 | Weak                     | Weak         |
| Pawlow and Jones (2005) (57) | Weak           | Strong       | Strong      | Moderate | Moderate               | Strong                    | Moderate     |
| Rider et al. (1990) (58)    | Weak           | Strong       | Strong      | Moderate | Strong                 | Strong                    | Moderate     |
| Strauman et al. (2004) (59) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Strong       |
| Takahashi et al. (2001) (60) | Weak           | Moderate     | Strong      | Moderate | Strong                 | Strong                    | Moderate     |
| Wachi et al. (2007) (61)    | Weak           | Moderate     | Strong      | Moderate | Strong                 | Moderate                 | Moderate     |
| Yamamoto and Nagata (2011) (62) | Weak    | Strong       | Strong      | Moderate | Strong                 | Strong                    | Moderate     |
back rub (43) showed a reduction in state anxiety in the predicted direction, but this was not statistically significant. The remaining two (primed and unprimed exposure to a lavender odor (46)) showed a decrease in positive affect after the interventions.

Most studies measured multiple immune outcomes (k = 21; 67.7%), with none of these identifying a primary immune outcome. The number of immune outcomes ranged across studies from 1 to 19, with a mean of 5 per study (median = 3). The most common immune outcome measures related to s-IgA concentration/flow rate (i = 17), NK cell count or activity (i = 12), and interleukin-6 (IL-6) production (i = 10). s-IgA is a class of antibody, most typically measured in saliva, that acts as a first line of defense against pathogens on mucosal surfaces. NK cells are critical components of the innate immune system with multiple functions including providing rapid, cytotoxic responses to kill viral-infected cells. NK cells were measured both enumeratively and in relation to their activity/function in response to stimulation ex vivo. IL-6 is a proinflammatory cytokine (chemical messenger) that can be produced by and influence the function of multiple immune cells including antibody secreting B cells. Other immune outcomes were only measured in a few or single studies.

Table 2 summarizes the findings of studies included in the review. Most interventions resulted in at least one observed significant immunological change in at least one tested population (i = 34; 81.0%). Considering the four groups in whom interventions did not induce a statistically significant improvement in mood outcomes, two that showed nonsignificant improvements in state anxiety reported increased s-IgA concentration and IL-1, respectively, with the two showing decreases in positive affect also showing reduced wheal sizes in the delayed hypersensitivity to Candida testing compared with controls, indicating a more blunted immune response.

Of the 17 interventions in which s-IgA was measured, 14 resulted in a significant increase in s-IgA concentration or flow rates in all subpopulations examined (33, 37–39, 48, 54, 56, 60, 62), 2 reported no effects (37, 63), and 1 demonstrated an increase in s-IgA concentration but did not assess the significance of the change (63). Of the two interventions that resulted in no significant change, one was a 90-minute music improvisation group in cancer patients and the other was among students who were encouraged to express their emotions while watching a comedy film. Both of these interventions had very small samples (number of participants receiving the intervention: nine and eight, respectively).

Of the 12 interventions in which NK cell count or activity was measured, findings were less consistent, with 6 interventions demonstrating increased NK cell counts or activity after the intervention (42, 45, 51, 59, 60), 5 finding no effect (32, 35, 41, 49, 61), and 1 finding no significant changes in NK cell activity from before to immediately after the intervention, but significantly greater increases when compared with the control group (36). When comparing interventions that showed an increase in NK cell count or activity to those which did not, no clear differences were evident in terms of intervention type, length, or study size.

Of the 10 interventions in which IL-6 production was measured, only one study subpopulation showed significant increases in IL-6 after the intervention (Ref. 32 for older adults), with the remainder showing no significant changes (Ref. 32 for younger adults) (40, 46, 52–55).

Meta-analyses of Immunological Outcomes

Broadly speaking, meta-analyses mirrored the findings of the aforementioned narrative synthesis. For s-IgA concentration outcomes, 12 preintervention to postintervention comparisons (including general population and cancer patient subpopulations from Noto et al. (56)) had sufficient data for inclusion in a meta-analysis (Figure 2). Pooling these in a random-effects meta-analysis produced an overall significant medium positive effect size of 0.65 (95% confidence interval [CI] = 0.50–0.80) indicating greater s-IgA concentrations after intervention. Examination of the Cochran Q and the I² statistic indicated low but nonsignificant heterogeneity (Q(11) = 12.37, p = .337; I² = 11.04%).

For NK cell activity, effect sizes could be calculated for seven preintervention to postintervention comparisons (including younger and older adult subpopulations from Koyama et al. (32)). Pooling these in a random-effects meta-analysis produced a small but nonsignificant positive effect size of 0.15 (95% CI = −0.05 to 0.34) indicating greater but not significantly greater NK cell activity after intervention (Figure 3). Examination of the Cochran Q and the I² statistic indicated low but nonsignificant heterogeneity (Q(6) = 8.03, p = .24; I² = 25.3%).

For IL-6 production, 11 preintervention to postintervention comparisons (including carer, patient, and bereaved carer subpopulations from Fancourt et al. (40), primed and unprimed subpopulations from Kiecolt-Glaser et al. (46), and younger and older adult subpopulations from Koyama et al. (32)) had sufficient data for inclusion in a meta-analysis (Figure 4). Pooling these in a random-effects meta-analysis produced a small but significant positive effect size of 0.12 (95% CI = 0.02–0.23) indicating greater IL-6 production after intervention. Examination of the Cochran Q and the I² statistic indicated moderate but not significant heterogeneity (Q(10) = 17.03, p = .074; I² = 41.29%). Examination of the forest plot suggested that a comparatively high effect size for the only older adult subpopulation included in the analysis (Koyama et al. (32)) may account for much of the heterogeneity observed. When this subpopulation was excluded from the meta-analysis, the pooled effect size reduced but remained significant at 0.10 (95% CI = 0.01–0.17) with no notable heterogeneity (Q(9) = 7.70, p = .57; I² = 0%).

Post Hoc Exploratory Meta-Regressions With Mood as Moderating Variable

Meta-regression analyses were conducted to examine whether the magnitude of the interventions effect on mood outcomes was associated with the magnitude of immune effects for those aforementioned outcomes found to significantly change from preintervention to postintervention in pooled meta-analyses (s-IgA and IL-6 production). A detailed description of these results and limitations of this approach are presented in the Supplemental Digital Content, http://links.lww.com/PSYMED/A592. In brief, meta-regression analyses showed that for s-IgA concentration, when one outlying study (55) with an exceptionally high reported mood effect size (Hedges g = 7.65; all others studies, Hedges g < 1.8) was excluded from the analysis, s-IgA effect sizes were significantly associated with mood effect sizes (Q(1) = 4.68, p = .031). This relationship was such that larger increases in s-IgA concentration were seen after interventions that induced larger improvements in mood. For IL-6 production, the results suggested no significant relationship between...
mood and IL-6 effect sizes ($Q(1) = 0.31, p = .581$). Given the few studies amenable for inclusion in these analyses, the subsequent low power, and the heterogeneity of the included interventions, these analyses should be considered with due caution.

**DISCUSSION**

The present review was conducted to identify and assess the existing literature relating to the effects on immunity of brief interventions that enhance mood. Specifically, the review aimed to identify the size and nature of the existing literature base, assess the quality of this literature, and examine the impact of mood-enhancing interventions on immunological outcomes. Findings relating to each of these aims are discussed in turn hereinafter, with areas in need of further research highlighted.

**Size and Nature of the Literature**

The review identified a moderate-sized literature of 31 articles presenting one or more brief mood-improving interventions and measuring an aspect of immunity. Only 11 studies were RCTs. In contrast, the majority adopted crossover or cohort designs, which are generally considered less rigorous tests of an intervention than RCTs (65). Sample sizes were, in general, relatively small, indicating the need for larger RCTs in the future. Nearly all studies only examined immune changes immediately after intervention, with only two studies measuring aspects of immunity in a later follow-up. As such, there is very little evidence regarding the extent to which brief mood-enhancing interventions have persistent effects on immunity. Such evidence is needed to determine how close to an immune challenge (e.g., vaccination and surgery) an intervention would need to be delivered to be effective, and whether this differs according to the intensity or duration of positive affect induced. Evidence from a recent meta-analysis on induced stress has shown that brief laboratory stressor exposures can result in changes to cytokine profiles that persist up to 120 minutes after stress exposure (66). However, whether similar persistence of immune effects accompanies the induction of positive mood remains unclear.

**Intervention Characteristics**

A heterogeneous selection of interventions was identified. Many of the interventions lasted 60 minutes or longer, making them poor candidates for some health care settings where encounters may be brief (e.g., primary care). However, interventions less than 5 minutes in duration showed some evidence of immune effects and may be more suitable for such contexts. Further research is needed relating to the minimum required length of a positive mood intervention to induce immune changes. Several interventions relied on specialist equipment (e.g., odor generation) or skilled facilitators (e.g., massage and group drumming) that would likely make such interventions relatively costly to implement, giving them limited potential for widespread implementation. In contrast, some non-specialist intervention forms including watching or listening to a comedy program, mental recall of positive memories, and listening to music may have greater implementation potential owing to their comparative ease of administration.

Most studies included in this review focused on healthy young adults, with only one study explicitly recruiting older adults (32) and one including children (33). Furthermore, only a handful of studies focused on those with significant medical illnesses, primarily cancer. Given the relative immunological naivety of children compared with young adults, the wide-ranging decline in immunological competence known to occur in later life (67,68), and immune alterations observed in some chronic illnesses (69), it is unclear whether any immune enhancing effects of brief mood-improving interventions shown in younger adults are generalizable to these populations. Indeed, in the one study that compared older and younger adult cohorts (32), only the older adults saw immunological benefits after the intervention. Further research in children and older adults, both with and without significant medical illnesses, would be beneficial, in particular exploring whether mood-enhancing interventions have larger immunological effects in these populations.

**Quality of the Literature**

Overall study quality in the reviewed literature was weak to moderate, with nearly all studies at risk of selection bias. Future studies in this area would benefit from more directed recruitment strategies, to ensure that participants are representative of the target population. When considering the other domains assessed by the EPHPP study quality instrument, the reviewed studies were typically well designed to control for potential confounding factors and, because of their brief nature, showed little evidence of problematic attrition. Reporting standards were, however, generally poor, with few studies providing details about recruitment processes, study blinding, the reliability of immunological outcome measures, or providing sufficient details to allow for future inclusion in a meta-analysis. Attempts made to obtain further details from authors were not always successful, thus limiting the number of studies that could be included in the meta-analytic portion of this review. Calls made over recent decades, across research domains, to improve recording standards (70–72) seem to have had little impact in this area thus far.

Looking beyond the included studies, it is noteworthy that many potentially relevant articles were excluded from the present review because they had not measured mood before and after the intervention. The absence of appropriate manipulation checks limits the insight that can be gained from these studies, as it is not possible to ascertain whether any immunological changes resulting from the interventions are related to mood enhancement or some other factor. Future studies in this area should consider the inclusion of an appropriate manipulation check as essential (73).

**Impact of Brief Interventions on Immunity**

Despite the weaknesses in this literature, the substantial majority (34/42; 81.0%) of interventions included in this review were associated with at least one significant immunological change in one or more of the subpopulations assessed. Two interventions that actually resulted in a reduction in positive affect correspondingly also resulted in blunted immune responses compared with controls. This consistency, regardless of the specific intervention used, gives credibility to the hypothesis that brief positive mood–enhancing interventions could induce short-term immunological change in ways relevant to health. However, it is critical to note that most studies included measures of multiple immune parameters, did not specify a primary immune outcome, and did not adjust for
| Authors, Origin, Study Design | Sample Type, Sample Size*, Mean Age (SD), Range, Female% | Intervention Description, Duration, Mode of Delivery | Immune Outcome(s) Measured [n] | Main Findings |
|-------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------|---------------|
| Bartlett et al. (34), United States, RCT | General population, 20, NR (NR), NR, 50% | Listening to music, 15 min, individual | IL-1 [1] | Note: Control condition comprised reading magazines. This study also included a separate experimental and control group who only had outcomes assessed at 24 h after intervention. Significant increase in IL-1 in those listening to music. No significant change in IL-1 among those in the control group.

| Bennett et al. (35), United States, RCT | General population, 33, NR (NR), NR, 100% | Comedy film, NR, group | NK cell cytotoxicity [1] | Note: Control condition comprised viewing a neutral film. No significant differences in NK cell cytotoxicity change between participants who viewed the comedy film compared with the control.

| Bittman et al. (36), United States, RCT | General population, 60, NR (NR), NR, 48% | Drumming; 60 min; group | NK cell activity ×4 concentrations; lymphokine-activated killer activity with IL-2 × 2 concentrations; lymphokine-activated killer activity with IFN-γ ×2 concentrations; baseline for IFN-γ stimulated ×2 concentrations; IL-2; IFN-γ; leukocyte count [13] | Note: Control condition comprised reading quietly. Significant increases from before to immediately after intervention in baseline for IFN-γ stimulated (both concentrations); lymphokine-activated killer activity with IFN-γ (both concentrations). There were no significant changes in other immune outcomes. Compared with controls the intervention arm had significantly larger increases from before to immediately after the intervention in NK cell activity at effector to target ratio of 6:1; NK cell activity at effector to target ratio of 12:1; baseline for IFN-γ stimulated at both concentrations and lymphokine-activated killer activity with IFN-γ at both concentrations. There were no significant differences between groups in other immune outcomes. |
Burns et al. (37), United Kingdom, crossover

Cancer patients, 9, NR (NR), NR, 67%

a) Listening to live music, 60 min, group

S-IgA concentration; S-IgA secretion rate [2]

b) Music improvisation, 90 min, group

S-IgA concentration and secretion rates increased significantly after intervention a. No significant differences in immune outcome measures for intervention b.

Donoyama et al. (38), Japan, crossover

General population, (postmenopausal women), 17, 54.4 (2.1), NR, 100%

Massage, 40 min, individual

S-IgA concentration [1]

Note: Control group rested for matched time on massage table

S-IgA concentration increased significantly after both massage and rest. No significant differences between massage and rest on S-IgA concentration changes.

Donoyama and Shibasaki (39) Japan, crossover

General population, (postmenopausal women), 10, NR (NR), NR, 100%

a) Massage (by student with 6-mo training), 40 min, individual

S-IgA concentration [1]

Note: Study included a control group who rested for matched time on massage table

S-IgA concentration increased significantly after all interventions and control group. No significant differences between interventions on S-IgA concentration changes.

b) Massage (by student with 15-mo training), 40 min, individual

c) Massage (by instructor with >15-y experience), 40 min, individual

No significant changes in any of the immune outcomes from pre-to-post intervention.

Fancourt et al. (40), United Kingdom, cohort

Cancer carers, bereaved carers, cancer patients

Cancer carers: 72, 56.9 (13.6), NR, 80.6%
Bereaved carers: 66, 59.7 (11.5), NR, 81.8
Cancer patients: 55, 60.8 (9.0), NR, 80%

Choir singing, 70 min, group

IL-2, IFN-γ, TNF-α, IL-4, IL-6, IL-17, MCP1, sIL2rα, sTNFR1, GM-CSF [10]

Across time, significant increases in GM-CSF, IL-2, IL-4, IL-17, TNF-α, sIL-2rα, and sTNFR1 after controlling for multiple comparisons. There were no significant differences across time for other immune outcomes.

Between-group comparisons showed sTNFR1 significantly increased in both carer groups but not patients. MCP1 significantly increased in bereaved carers but not in other groups. IL-17 significantly increased in bereaved carers and patients but not non-bereaved carers. No other significant between group differences for other immune outcomes.

Futterman et al. (41), United States, crossover

Method actors

5, 31.2 (NR), 25–38, 40%

Acting out a happiness scenario, <120 min, individual

NK cell activity; CD-3; CD-4; CD-8; CD-16; CD56; CD57 [7]

No significant changes in any of the immune outcomes from pre-to-post intervention.
TABLE 2. (Continued)

| Authors, Origin, Study Design | Sample Type, Sample Size, Mean Age (SD), Range, Female% | Intervention Description, Duration, Mode of Delivery | Immune Outcome(s) Measured [n] | Main Findings |
|------------------------------|----------------------------------------------------------|-----------------------------------------------------|--------------------------------|---------------|
| Futterman et al. (48), United States, crossover with the control group | Method actors (general population controls) Actors: 16, 35 (NR), 24–47, 0% Controls: 9, 29.4 (NR), 18–43, 11% | a) Acting out a euphoric happiness scenario; <120 min, individual b) Acting out a relaxed happiness scenario; <120 min, individual | NK cell cytotoxicity; lymphocyte response PHA × 2 concentration; CD-3%; CD-4%; CD-8%; CD-16%; CD-56%; CD57% [9] | Note: This study also included 2 negative mood induction conditions and a neutral condition. In all induced mood states (positive and negative combined), significant increases in CD-8%, CD-16%, CD-56%, CD-57%, and NK cell cytotoxicity from pre-to-post mood inductions. No significant effects on remaining immune parameters. Significant differential lymphocyte responses to high doses of PHA were observed between positive and negative mood inductions, with responses increased in both positive inductions but decreased in negative inductions. No differences in any other immune outcome. No immune outcomes changed in the control group |
| Groër et al. (43), United States, RCT | General population, middle-aged and older adults, 32, 65.8 (NR), 44–77, 68.8% | Back rub, 10 min, individual | S-IgA concentration; S-IgA secretion rate [2] | Note: Control condition comprised 10 min of bed rest. S-IgA concentration increased significantly more in those who received the back rub compared with controls. S-IgA secretion rate increased in both groups but did not significantly differ between groups. |
| Hall et al. (1992) (44) United States, cohort | General population, 19, 51 (NR), 22–81; 36.8% | Relaxation with immune-based imagery, 45 min, individual | Leukocyte count; lymphocytes; T cells; B-cells; lymphocyte response to PHA, Con-A, and Pokeweed [7] | Significant increases in leukocyte count and lymphocyte response to Pokeweed. No significant effects on other immune outcomes |
| Study | Country | Design | Population | Interventions | Outcomes |
|-------|---------|--------|------------|---------------|----------|
| Hewson-Bower and Drummond (33), Australia, RCT | Children with and without recurrent URTIs, 90 | a) Relaxation, 25 min, group | S-IgA concentration; S-IgA:albumin ratio [2] |
| | Children with URTIs: 9.4 (NR), 8–12, 44.4% | b) Relaxation with immune suggestions, 25 min, group | Note: Control condition comprised group conversation. S-IgA concentration increased significantly immediately after both relaxation conditions compared with controls. No effects on S-IgA:albumin Ratio in any condition. No differences between healthy children and those with recurrent URT infections. |
| | Healthy children: 9.7 (NR), 8–12, 44.6% | |
| Jung et al. (45), South Korea, RCT | General population, 24, Qi touch therapy + rest group: 25 (5), NR, 0% | a) Qi touch therapy + rest, 70 min, individual | Superoxide anions produced by neutrophils; NK cell cytotoxicity [2] |
| | Qi nontouch therapy + rest group: 26 (1), NR, 0% | b) Qi nontouch therapy + rest, 70 min, individual | At 10 min after both interventions, NK cytotoxicity was significantly increased from preintervention. At 1 h after intervention, this remained significant only in Qi nontouch therapy + rest condition. Superoxide anion production by neutrophils was increased in Qi nontouch therapy + rest condition at 10 min after intervention from preintervention but not at 1 h. No change in superoxide anion production at any time point in Qi-touch therapy + rest condition |
| Kiecolt-Glaser et al. (46), United States, crossover with additional randomization | General population, 56, 24.4 (6.1), 18–43, 62.5% | a) Primed exposure to lemon odor, 75 min, individual | Delayed hypersensitivity to Candida; lymphocyte response to Con A x3 concentrations; lymphocyte response to PHA x3 concentrations; in vitro IL-6 production; in vitro IL-10 production [9] |
| | b) Unprimed exposure to lemon odor, 75 min, individual | | Note: This study also included a distilled water control condition and exposure to a stressor postintervention. Smaller maximum and 72-h wheal size after delayed hypersensitivity to Candida test in those exposed to lavender odor. No significant changes to any of the other immune outcomes measured after the interventions |
| | c) Primed exposure to lavender odor, 75 min, individual | | |
| | d) Unprimed exposure to lavender odor, 75 min, individual | | |

Continued on next page
TABLE 2. (Continued)

| Authors, Origin, Study Design | Sample Type, Sample Size, Mean Age (SD), Range, Female% | Intervention Description, Duration, Mode of Delivery | Immune Outcome(s) Measured [n] | Main Findings |
|------------------------------|-------------------------------------------------------|-----------------------------------------------------|--------------------------------|---------------|
| Kimata (47), Japan, crossover | Patients with atopic dermatitis having atopic keratoconjunctivitis and healthy general population, 48 Patients: 27 (NR), 22–43 General population: 26 (NR), 20–41, 50% | Comedy film, NR, group | Japanese cedar pollen-specific IgE; Japanese cedar pollen-specific IgG4; Japanese cedar pollen-specific IgA [3] | In general population, no significant effects of intervention as immune outcomes undetectable in tears. In patients with atopic dermatitis having atopic keratoconjunctivitis, there was a significant decrease in Japanese cedar pollen-specific IgE and IgG4 and significant increase in IgA immediately after and at 2 h after the intervention compared with baseline, but not at 4 h. |
| Knapp et al. (48), United States, cohort | General population, 20, NR (NR), NR, 50% | Mental recall and discussion of positive life interval with interviewer, NR, individual | Lymphocyte response to PHA ×2 concentration; lymphocyte response to Con-A; lymphocyte response to pokeweed; NK cell activity, leukocyte count, PMN cells, lymphocytes, monocytes, CD-3%; CD-4%; CD-8%; [12] | Significant increase in lymphocyte response to low-dose PHA immediately after intervention. No effects on other immune outcomes |
| Koyama et al. (32), Japan, cohort | General population, young and older adults Younger adults: 27, 27.9 (8.4), NR, 70.4% Older adults: 27, 70.3 (2.9), NR, 55.6% | Drumming, 60 min, group | NK cell activity; neutrophil count; lymphocyte count; T-cell count; B-cell count; CD-4 count; CD-8 count; CD-4/CD8 ratio; naive T-cell count; memory T-cell count; NK cell count; IFN-γ; IL-2; IL-4; IL-6; IL-10 [18] | In young adults, there were no significant changes to any of the immune outcomes from before to after the intervention. In older adults there were significant increases in lymphocyte count, T-cell count, CD-4 count, memory T-cell count, IFN-γ production, and IL-6 production. There were no significant changes in any other immune outcome. |
| Study | Location | Subjects | Intervention | Outcome Measure(s) | Notes |
|-------|----------|----------|--------------|--------------------|-------|
| Labott et al. (63) | United States | Students who considered themselves expressive, 39, 21.6 (NR), 18–40, 100% | a) Expressing emotions during a comedy film, 28 min, NR | S-IgA concentration [1] | Note: A negative mood induction condition (negative film) and control group (2 neutral films) were included in this study. Participants asked the inhibit emotions condition showed increases in S-IgA concentration from before to after the comedy film, however the significance of this change was not assessed. In the expressing emotion condition, there were no differences in S-IgA concentration from before to after the comedy film. |
| Lefcourt et al. (50) | Canada | Students, 41, NR (NR), NR, 48.7% | Comedy audiotape, 30 min, group | S-IgA concentration [1] | Significant increase in S-IgA concentration from before to immediately after intervention |
| Matsunaga et al. (51) | Japan | General population, 12, NR (NR), 20–29, 0% | Film containing actresses chosen by participants as attractive, 4 min, individual | NK cell activity [1] | Note: A neutral control film was included as a condition in this study. Significant increase in NK cell activity from before to immediately after intervention. No change from before to after control film |
| Matsunaga et al. (52) | Japan | General population, 23; NR (NR), 21–38, 78.3% | Odor selected by participant to invoke positive autobiographical memory, 90 s, individual | IL-2; IL-4; IL-6; IL-10; TNF-α [5] | Note: A neutral control odor condition was included as a condition in this study. No significant changes on any immune outcome from before to after odor intervention. IL-2 was significantly lower immediately after self-selected odor intervention compared with immediately after control odor. |
| Matsunaga et al. (53) | Japan | Romantic couples, 14, NR (NR), 21–38, 50% | Kissing and hugging partner, 60 min, couples | IL-6, TNF-α, IFN-γ [3] | Note: Control condition involved reading quietly separately. IFN-γ significantly decreased from before to immediately after intervention. No changes in IL-6 or TNF-α |
| Authors, Origin, Study Design | Sample Type, Sample Size, Mean Age (SD), Range, Female% | Intervention Description, Duration, Mode of Delivery | Immune Outcome(s) Measured [n] | Main Findings |
|-------------------------------|-------------------------------------------------------|-----------------------------------------------------|--------------------------------|---------------|
| Matsunaga et al. (54), Japan, crossover | General population, who self-report the ability to retrieve autobiographical odor memories, 10, NR (NR), 20–35, 70% | Odor selected by participant to invoke positive autobiographical memory, 3 × 60 s, individual | IL-2, IL-5, IL-6, IL-10, TNF-α, IFN-γ [6] | Note: A neutral control odor condition was included in this study. Significant decreases in TNF-α and IFN-γ immediately after self-selected odor compared with immediately after control odor. No differences in other immune outcomes. |
| Mittwoch-Jaffe et al. (55), Israel, RCT | General population, 123, NR (NR), NR, 52% | Comedy film, 45 min, group | IL-1b, IL-2, IL-3, IL-6, TNF-α [5] | Note: Comparison group watched a horror film for matched period of time. Significant increase in IL-2 and IL-3, and significant decrease in TNF-α from before to immediately after comedy film intervention. No changes on IL-1b and IL-6 |
| Noto et al. (56), Japan, crossover and cohort | a) General population, 15, 21.3 (1.1), NR, NR | Leg massage, 20 min, individual | S-IgA concentration [1] | Note: General population patients also took part in a rest control condition for a matched length of time. S-IgA concentration increased significantly after both the intervention and rest for general population participants, but no significant difference between these. S-IgA concentration also increased significantly after leg massage in cancer inpatients (this group did not receive the rest intervention). |
| Pawlow and Jones (57), United States, RCT | Students, 55, 24.0 (7.5), 19–57, 53% | Abbreviated progressive relaxation training, 25 min, individual | S-IgA concentration; S-IgA secretion rate [2] | Note: Control group sat quietly for a matched time period. Significant increase in S-IgA concentration and secretion rate, 5 min postintervention. |
| Study                          | Country        | Group Description                                      | Intervention Details                                                                 | Outcome Measures                                         | Notes                                                                                                                                 |
|-------------------------------|----------------|---------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Rider et al. (58), United States | RCT            | Students, 45, NR (NR), NR, 56%                          | a) Listening to music with immune imagery suggestions, 17 min, individual           | S-IgA concentration [1]                                  | Note: Control group sat quietly for a matched period. S-IgA concentration significantly increased in both interventions a and b above controls, but there was no significant difference between a and b. |
| Strauman et al. (59), United States | Crossover     | Students with high and low self-discrepancy, 32        | Writing about self-congruencies, 20 min, individual                                  | Leukocyte count; lymphocyte count; neutrophil count; CD-3 count; CD-4 count; CD-4%; CD-8 count; NK cell count; NK cell %; CD-19 count; CD-19%; NK cytotoxicity 3 x concentration; lysis per 1000 NK cells [19] | Note: A negative mood induction condition (writing about self-discrepancies) and control group (2 neutral films) were also part of this study. In both high- and low-discrepant students, there were significantly higher leukocyte, lymphocyte, CD-3, CD-4, CD-8, and NK cell counts immediately after self-congruency intervention compared with immediately after control condition. NK cell count increases were significantly higher in high discrepant compared with low discrepant students. In high discrepant students, lysis per 1000 NK cells was also significantly lower immediately after self-congruency intervention compared with immediately after control condition. |
| Takahashi et al. (60), Japan | Crossover      | General population, 21, NR (NR), 18–26, 0%             | Comedy film, 75 min, NR                                                             | NK cell activity 2 x concentration; CD-16%; CD-56%; CD-57%; leukocyte count [6] | Note: A neutral control film was included as a condition in this study. Significant increase in NK cell activity at effector to target ratio of 20:1 from before to immediately after comedy film intervention, but not after control film. No effects on other immune outcomes reported. |
| Authors, Origin, Study Design | Sample Type, Sample Size, Mean Age (SD), Range, Female% | Intervention Description, Duration, Mode of Delivery | Immune Outcome(s) Measured [n] | Main Findings |
|--------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------------------|---------------|
| Wachi et al. (61), Japan, crossover | Yamaha employees, 40, 38.4 (8.4), NR, 0% | Drumming, NR, group | NK cell activity 3× concentration; CD-56%, leukocyte count | Note: A control condition consisting of quite reading was included in this study. No significant changes in any of the immune outcomes assessed because of the intervention. |
| Yamamoto and Nagata (62), Japan, RCT | Cancer patients, 18 Experimental: 64.9 (5.8) Control (64.2 (8.9), NR, 33% | Footbath, 30 min, individual | S-IgA concentration | Note: Controls rested for a matched period. Significant increase in S-IgA concentration from preintervention to postintervention. No comparisons reported against controls. |

RCT = randomized controlled trial; NR = not reported; IL = interleukin; NK = natural killer; INF = interferon; S-IgA = secretory immunoglobulin isotype A; TNF = tumor necrosis factor; CD = cluster of differentiation; PHA = phytohemagglutinin; Con-A = concanavalin A; URTIs = upper respiratory tract infections; PMN = polymorphonuclear; MCP1 = monocyte chemoattractant protein 1; sIL-2Rα = soluble interleukin 2 receptor alpha; sTNF-R1 = soluble tumour necrosis factor receptor 1; GM-CSF = granulocyte macrophage colony stimulating factor.

a Total study sample size including comparator conditions, if applicable.
multiple comparisons. As such, the possibility of false-positive associations being found was high.

A causal relationship between positive mood improvements and immune function is partially supported by the exploratory meta-regression analysis on s-IgA outcomes, which suggested a dose-response relationship between positive mood and s-IgA changes. However, given the exploratory nature of this analysis and high heterogeneity of included studies, these findings (and the related null effects found for IL-6) should be interpreted with due caution.

Most of the immunological changes observed were broadly framed by authors as indicative of enhanced immune function after positive mood induction. However, a significant limitation is that the clinical relevance of these immunological changes was not effectively demonstrated in any of the included studies. For example, no studies included in this review investigated the effects of a mood-enhancing intervention on response to an administered in vivo immune challenge (e.g., vaccination) or related to a clinical outcome (e.g., recovery from surgery). Indeed, all but one study (47) considered nonspecific markers of immunity. Although some of the immune parameters measured form part of the cascade of innate and adaptive immunological processes that follow antigenic challenge (e.g., cytokines and NK cells), because of the redundancy and complexity inherent in the immune system, it is hard

![FIGURE 2. Forest plot of meta-analysis for pre-post effect sizes on s-IgA. s-IgA = secretory immunoglobulin serotype A; CI = confidence interval.](image)

![FIGURE 3. Forest plot of meta-analysis for pre-post effect sizes on NK cell activity. NK = natural killer; CI = confidence interval.](image)
to determine the importance of changes to individual components measured in isolation, to real-world clinical outcomes. Although increases in nonspecific aspects of immunity may be indicative of enhanced in vivo immune responses to challenge (74, 75), there is a clear need for future research to move away from a reliance on nonspecific indices of immunity.

Strengths and Limitations

The present review did not exclude studies on the basis of design type to maximize the identification of relevant research evidence, and the quality of included studies was assessed using an established standardized tool. However, this review did not seek to retrieve and include relevant unpublished articles (the so-called gray literature). The rationale behind this omission is that unpublished articles have not successfully gone through the peer-review process; thus, it is not possible to be certain of the articles’ quality and veracity. However, it is important to acknowledge that in excluding this literature the influence of any publication bias could be exacerbated, as interventions demonstrating no immune effects may have been less likely to be published.

It is noteworthy that short bouts of physical exertion (e.g., bicycling) can result in post-exercise mood improvements, as well as immune function changes (see Walsh et al. (76)). However, in this review, we excluded such interventions to minimize the potential confounding effects of the physiological exertion on the relationship between positive mood changes and immunity. However, although most interventions were fairly passive (e.g., watching a comedy film), some included interventions involving some degree of physical effort (e.g., choir singing and drumming); thus, it is not possible to completely disentangle whether any observed immunological changes in these studies result solely from the change in mood or the physical consequences of the interventions (e.g., changes in respiration and increased bodily movement).

CONCLUDING REMARKS

Brief interventions that improve mood can influence some immune parameters in ways that may be indicative of enhanced function. However, there is a need for higher-quality, more methodologically rigorous, and better-reported research in this area before firm conclusions can be drawn. Because the literature reviewed was rated as low- to moderate-quality and somewhat heterogeneous, the degree of confidence in the pooled findings is correspondingly modest. Currently, there is a paucity of evidence regarding the clinical importance of mood-induced immunological change, its persistence, or its relevance beyond young adult populations.

FIGURE 4. Forest plot of meta-analysis for pre-post effect sizes on IL-6 Production. IL-6 = interleukin-6; CI = confidence interval.

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