Evaluating the effectiveness of innovative psychological intervention tools in optimizing health outcomes: A multimethod approach

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Effectiveness of stress-reducing interventions on response to challenges to the immune system: A meta-analytic review

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Abstract

There is consistent evidence showing an interplay between psychological processes and immune function in health and disease processes. The present systematic review and meta-analysis aimed to provide a concise overview of the effectiveness of stress-reducing psychological interventions on the activation of immune responses in both healthy subjects and patients. Included are three types of challenges: *in vivo*, *in vitro*, and psychophysiological. Such challenges are designed to mimic naturally occurring immune-related threats. A systematic literature search was conducted using PubMed, EMBASE, and PsychInfo, resulting in 75 eligible studies. Risk of bias was assessed with the Cochrane risk of bias tool. Across all studies, a small to moderate effect size was found for the effects of psychological interventions on optimizing immune function (g = .33). While largest effects were found for *in vivo* immune-related challenges (especially on studies that incorporated skin tests and wound healing), studies incorporating psychophysiological challenges and *in vitro* immune-related stimulations similarly suggest more optimal immune responses among those receiving stress-reducing interventions. These findings showed substantial heterogeneity depending on type of challenge, study populations, and intervention types. These data demonstrate support for the effectiveness of stress-reducing psychological interventions in improving immunity in studies that tested immune function by means of incorporating an *in vivo, in vitro,* or psychophysiological challenge.

Introduction

Stressful events can influence functioning of the immune system (41, 167), whereby chronic stress has mostly been found to suppress protective immune responses and promote pathological immune responses (42-44). These immune alterations can be expressed as slower wound healing (43, 44), impaired responses to vaccines (42), and the progression of infectious and immune-mediated diseases (42, 46).

Various psychological interventions have been found to effectively reduce stress, including cognitive behavioral therapy (CBT) (3), mindfulness meditation (168), mindfulness-based stress reduction (MBSR) (142), and relaxation (168). Therefore, it has been argued that such stress-reducing interventions may help to counteract the adverse effects of stress on immune functioning. A previous meta-analysis, however, found little support for an immune-optimizing potential of psychological interventions (169). Some supporting evidence was provided by studies using conditioning and hypnosis interventions, although the results were heterogeneous. Due to substantial variation in immune outcomes, generalizability was uncertain (169). More specifically, the immune outcomes in these studies varied from counting white blood cell subsets, to evaluating cell function by activating the immune system by either *in vitro* methods (i.e., exposing isolated white blood cells to immune-activating stimulus), or *in vivo* (i.e., stimulating an immune response in the intact person, e.g., vaccination). Each of these methods provides a different window and type of information on the functioning of the immune system. Counting cells in resting state provides information on the number of immune cells in the circulation. However, the circulation represents only a small and selective proportion of the total cell population, is highly dynamic within individuals, and the normal range of adequate cell numbers is rather broad. Therefore, in somatically healthy participants cell counts are of uncertain clinical significance. On the other hand, the immune system's response to activating stimuli is considered a more representative estimate of a person's ability to mount an adequate immune response in the face of a natural challenge, and may be considered a more biologically valid marker of immunocompetence (170).

In the studies that are reviewed here, *in vitro* activations include natural killer cell activity, stimulated lymphocyte proliferation response, and stimulated pro-inflammatory and anti-inflammatory cytokine production (i.e., chemical challenges), whereas *in vivo* stimulations include hypersensitivity responses to skin tests, time of healing of a biopsy wound, or the extent to which a vaccine produces antibodies (i.e., physical challenges). In addition to the above-mentioned *in vitro* and *in vivo* activations of the immune system, psychosocial stress can also challenge the immune system (40, 41, 171, 172). Therefore, a number of studies have evoked psychosocial stress in their participants by exposing

them to psychophysiological challenges, i.e., challenges that have the potential to evoke a psychophysiological stress response, including exposure to a psychosocial stress task, to obtain additional information on how stress-reducing psychological interventions may optimize the extent to which the immune system responds to these challenges (173). A recent systematic review provided support for the effectiveness of psychological interventions in optimizing wound healing (174). There is, however, no recent examination of the effectiveness of stress-reducing interventions on a broader range of immune challenges, also taking psychophysiological challenges into account.

In the last few decades, studies have evaluated how the immune system responds to chemical, physical, and psychophysiological challenges after undergoing a stress-reducing psychological intervention. Since there has been no systematic review of this literature, no consensus exists on the effectiveness of stress-reducing psychological interventions on subsequent responses to challenges to the immune system. Therefore, the aim of the current systematic review and meta-analysis is to summarize the effectiveness of stress-reducing psychological interventions directed at optimizing immune function, focusing on studies incorporating various *in vivo* or *in vitro* immune-related and/or psychophysiological stimulations/challenges into the study design. We expected that after a stress-reducing psychological intervention, participants would show a more optimized immune response to challenges as compared to participants that did not receive a stress-reducing psychological intervention. More specifically, after the stress-reducing psychological intervention we expected higher natural killer cell activity, higher anti-inflammatory cytokine responses, lower pro-inflammatory cytokine responses, higher lymphocyte proliferation responses, higher antibody responses, higher delayed-type hypersensitivity responses, as well as faster wound healing. We analyzed the pooled effects of the three types of challenges together, as well as separately.

Methods

This systematic review and meta-analysis was performed according to the PRISMA criteria (175) and was registered in PROSPERO (registration number: CRD42017055722).

Inclusion and exclusion criteria

Studies were included when they met the following inclusion criteria: incorporation of a stress-reducing psychological intervention (which was defined as having cognitive behavior change techniques as the main component, i.e., duration more than 50% of the intervention time, such as psychotherapy, mindfulness or relaxation); inclusion of immune outcome measures assessed in blood or saliva (e.g., quantification of cytokines,

lymphocytes), incorporation of immune-related and/or psychophysiological challenges into the study design which were assessed after the start of the stress-reducing psychological intervention, and incorporation of at least one control group without a stress-reducing psychological intervention. Articles were excluded when they assessed immunological functioning not by objective measurements or parameters, but when they were, for example, solely based on self-report (e.g., self-reported infection), when they were based on case studies, or when they had insufficient methodological or statistical details about the immune or psychophysiological challenges or results (e.g., conference abstracts).

Literature search strategy

A systematic search was conducted using the databases PubMed, EMBASE, and PsychInfo until January 26, 2017. Search terms included Medical Subject Headings (MeSH) and words from title/abstract (tiab) as qualifiers, classified in three categories: stress-reducing psychological interventions, immune function, and immune-related as well as psychophysiological challenges (see Supplemental Table 1 for the search strategy per database). All retrieved references were loaded into Endnote and two independent reviewers (LS and PC) screened the titles, abstracts, and subsequently full texts when appropriate regarding study eligibility and relevance. The reference lists of the included studies were additionally searched for potential eligible studies.

Data extraction

A data extraction form was used to extract relevant data from the eligible studies. Extracted information for each study included: study population (e.g., healthy participants or patients), participant demographics, details of the intervention and control condition, study methodology, incorporated chemical, physical, and/or psychophysiological challenges, immune outcome parameters, relevant outcome data, statistical analyses, and relevant information concerning the methodological quality assessment. The information was extracted by the two reviewers (LS, PC) independently. Discrepancies were identified and resolved through discussion by involving one or more additional reviewer(s) (DV, JB, AE).

Methodological quality assessment in included studies

Two reviewers (LS, PC) furthermore independently assessed risk of bias (RoB) of the included studies using the Cochrane risk of bias tool (176). The biases that were assessed included selection bias (process of randomization and concealment of allocation), performance bias (blinding of participants and research personnel), detection bias (blinding of outcome assessment), reporting bias (handling of missing data), and attrition

bias (description of reasons for withdrawal in all conditions). Biases were classified as being low, high or unclear. Disagreements between the review authors regarding the RoB in particular studies were resolved by discussion, with involvement of a third review author (DV) if necessary.

Data analyses

Data were analyzed using Comprehensive Meta-Analysis software version 3.3.070 (Biostat, Englewood, CO). Hedges *g* was the effect size metric that was applied on the descriptive statistics of the study. The effect size was calculated by subtracting the pre- from the post-immune outcome parameters in the control group and subsequently subtract this difference score from the difference score in the intervention group, divided by the pooled standard deviation and weighted across the number of subjects in each group. Effect sizes of 0.2 can be considered as small, whereas 0.5 and 0.8 can be considered as moderate and large, respectively (177). For the included studies performing within-subjects comparisons, the correlation coefficient could not be derived and therefore a correlation coefficient of $r = .05$ was imputed. In case a study contained multiple conditions with eligible psychological interventions, these groups were combined into one single pairwise comparison, according to the recommendations of the Cochrane handbook (176). The pooled effects were analyzed using a random effects model, since substantial variation was present in research characteristics (e.g., various types of challenges and immune outcomes). Heterogeneity was assessed by evaluating the I^2 statistic and by visual inspection of the forest plot. Values of $I^2 = 25\%$, 50%, and 75% can be interpreted as low, moderate, and high heterogeneity, respectively. In case the results of a study were based on post-intervention scores only (e.g., in case of wound healing studies), the effect size was based on the post-intervention scores. When the descriptive statistics were not available, authors were requested to provide those data and when the data were not provided, alternative methods were used to calculate the effect size (e.g., using reported statistics, reported mean change scores, etc.). When studies reported that the results were not significant, without further specifications of the outcomes, effect sizes were computed assuming no differences between the groups ($r = .00$). Because this is a rather conservative strategy that had to be applied to a substantial proportion of the data (i.e., imputation was used in 23.8% of the cases), meta-analyses were performed with and without those studies in order to evaluate potential bias of this method. All immune outcomes were scaled in the direction of positive Hedges *g* representing an optimized immune function.

The pooled effects of all three different types of challenges (i.e., *in vitro* immune-related stimulations, *in vivo* immune-related challenges, and psychophysiological challenges)

were analyzed together and separately. The *in vitro* immune-related stimulations were subsequently subcategorized into natural killer cell activity (NKCA), stimulated lymphocyte proliferation response (LPR), and stimulated cytokine production. *In vivo* immune-related challenges were subdivided into wound healing, vaccine responses, and hypersensitivity responses after skin tests. *In vivo* psychophysiological challenges were further subdivided into acute and more protracted stress challenges, separately for plasma numbers of lymphocytes (i.e., enumeration of CD4, CD8, and CD56 numbers) and cytokines (i.e., quantification of IL-1ß, IL-6, IL-8, and TNF-α). When the outcomes of *in vitro* stimulations were assessed on multiple concentrations of the stimulus (e.g., multiple effector-to-target ratios to evaluate NKCA or various dilutions to evaluate LPR), the effect size was derived from the concentration that most optimally differentiated conditions (i.e., the stimulus concentrations that showed the largest differences). Planned subset analyses evaluated the effects of different types of challenges within a specific category.

Data of at least three studies had to be available in order to conduct a meta-analysis. Sensitivity analyses were performed concerning the reliability of the results. In order to assess the stability of the overall effect size, it was investigated whether the effects were similar when studies with a substantial risk of bias (i.e., studies containing at least one classification of high risk of bias) were excluded from the analyses. In addition, publication bias was assessed by inspection of the funnel plot and applying the trim and fill method (178).

Results

Search results

Figure 1 shows the flow-chart of the systematic search and study selection. A total of 19,780 studies (including duplicates) were found by searching PubMed, EMBASE, and PsychInfo. After removing duplicates and screening the studies on title and abstract, 138 articles were examined in full text by the two independent reviewers. Of these, 65 articles fulfilled the inclusion criteria. Screening of the reference lists of the included articles yielded 9 additional eligible studies, which were not identified in the primary search as most of these studies did not specify immune outcome measures in the title and/or abstract. In total, 75 studies reported in 74 articles were included.

RoB assessment

Supplemental Figure 2 presents the RoB graph and Supplemental Figure 3 the RoB summary. Of the 75 studies, 68 (90.7%) did not provide sufficient details on the methods used to randomize participants and 71 articles (94.7%) did not sufficiently specify the

methods of allocation concealment (unclear RoB). RoB on performance was low for 2 articles (2.7%), due to adequate blinding procedures. In 9 articles (12.0%), participants and/or personnel were aware of group allocation, which could have led to performance bias (high RoB). For 26 articles (34.7%), the RoB concerning lack of blinding of participants and personnel was low. In 35 articles (46.7%), the drop-out rates and reasons for drop-out were sufficiently described and unrelated to the study outcomes, which resulted in a low RoB evaluation regarding incomplete outcome data. No study protocol was available for 73 articles (96.1%), resulting in an unclear RoB regarding selective reporting.

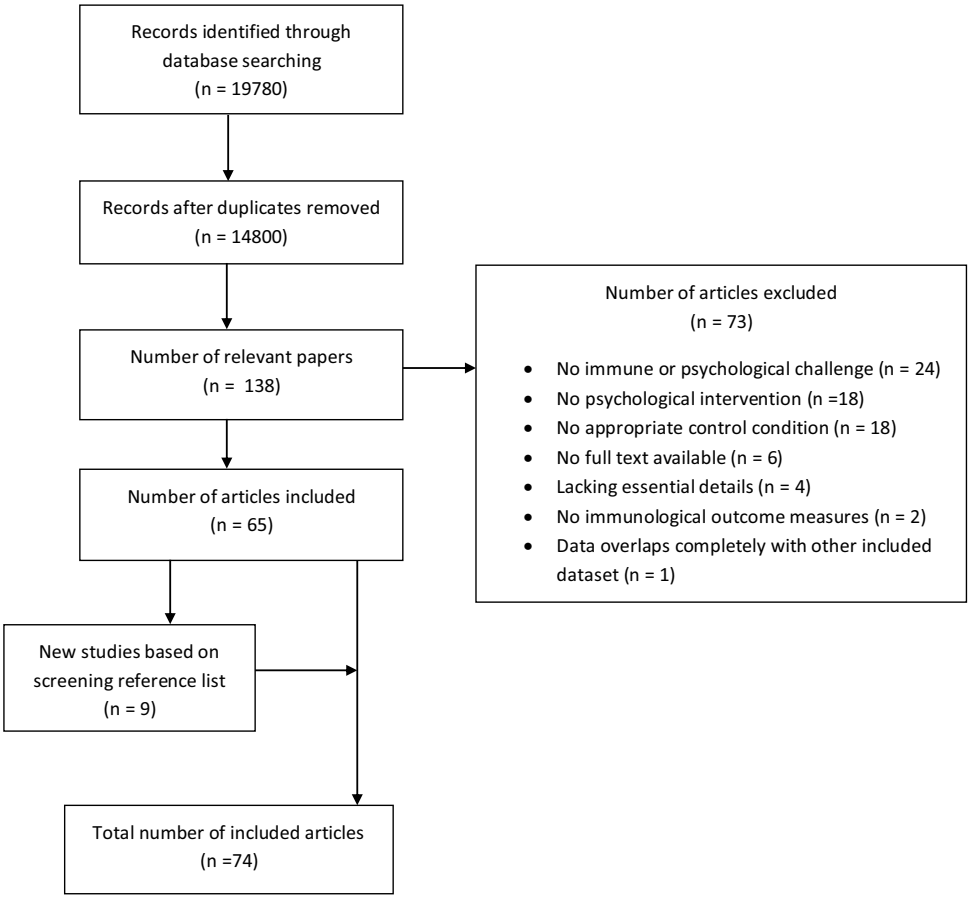

Figure 1. Flowchart of the study design showing the selection process, including reasons for exclusion.

Study selection was done by two independent reviewers.

Study characteristics

A total of 4,141 participants took part in the 75 studies. Detailed information concerning the study characteristics and incorporated psychological interventions are described in Supplemental Table 2. The total individual study sample size varied between N = 12 (179) and N = 252 (180) (*M* = 57, *SD* = 48). In 29 studies (38.7%), healthy volunteers were included as the study population (179, 181-207). Other samples included patients or vulnerable adults, for example with various types of cancer (208-227), patients with HIV infection (180, 228-232), patients with rheumatoid arthritis (173, 233-235), older adults (236-239), patients with asthma/allergies (240-242), widows/ women who lost a close relative to cancer (243, 244), patients with ulcerative colitis (245, 246), women with depression after bypass surgery (247), patients with late life insomnia (248), women suffering from infertility (249), veterans (250), and patients that underwent surgery (251). The mean age of participants varied between 18.5 and 78.8 years. Details on age were not provided in 7 studies (9.3%). Twenty-four studies (32.0%) only included female participants, whereas 9 studies (12.0%) only included male participants. In 36 studies (48.0%), both males and females were included. Details on gender were not reported for 6 studies (8.0%).

Type of stress-reducing psychological interventions

In total, 82 stress-reducing psychological interventions were evaluated in the 75 studies. Most interventions (28 interventions; 34.1%), were based on relaxation or stress management. Multicomponent cognitive-behavioral interventions were also common and assessed in 18 cases (22.0%), including psycho-education and various cognitive and behavioral techniques. Other interventions were based on mindfulness and/or meditation (13 interventions; 15.9%), hypnosis (12 interventions; 14.6%), emotional disclosure (7 interventions; 8.5%), and counseling (4 interventions; 4.9%). The interventions varied in their total duration from 1 single session to multiple sessions over a period of 12 months. Regarding the guidance of the interventions, all interventions included face-to-face or telephone appointments, except for 2 interventions that relied on self-practice. Of the guided interventions, 48 (58.5%) also encouraged self-practice.

Overall immune effects

Detailed information concerning the immune-related challenges and outcomes for each study is presented in Supplemental Table 3.

When performing an overall random-effects meta-analysis on the data, i.e., irrespective of the incorporated challenge, an overall small to moderate effect size was found (k = 84, g = .33 [95% CI .22; .43]) with moderate heterogeneity across the studies (I^2 = 59.41%).

When excluding the studies that were set at r = .00, a slightly higher overall small to moderate effect size was found (k = 64, g = .43 [95% CI .30; .55, I^2 = 67.69%]).

In vitro immune-related stimulations

Of the 75 studies, 52 studies (68.4%) incorporated at least one *in vitro* immune stimulation test, including NKCA (32 studies), LPR (28 studies), cytokine production (10 studies), and monocyte chemotaxis (1 study).

Figure 4 presents the forest plot on the random-effects meta-analysis for *in vitro* immune-related stimulations. Overall, a small effect size was found (k = 52, g = .28 [95% CI .15; .42]), with moderate heterogeneity across the studies (I^2 = 61.43%). After excluding the studies that were set at r = .00, a small to moderate effect size was found (k = 39, g = .39 [95% CI .22; .56], I^2 = 70.75%). When looking at specific subgroups of *in vitro* immune stimulation tests, we found a small effect size for NKCA (k = 31, g = .21 [95% CI .06; .35], I^2 = 40.22%), a small to moderate effect size for LPR (k = 28, g = .35 [95% CI .13; .57], I^2 = 73.07%), and a small to moderate effect size for cytokine production (k = 9, g = .32 [95% CI .14; .51], I^2 < .01%).

In vivo immune-related challenges

In vivo immune-related challenges were incorporated in the study designs of 17 studies (22.4%), including skin testing (8 studies), vaccination (5 studies), and wound healing (4 studies).

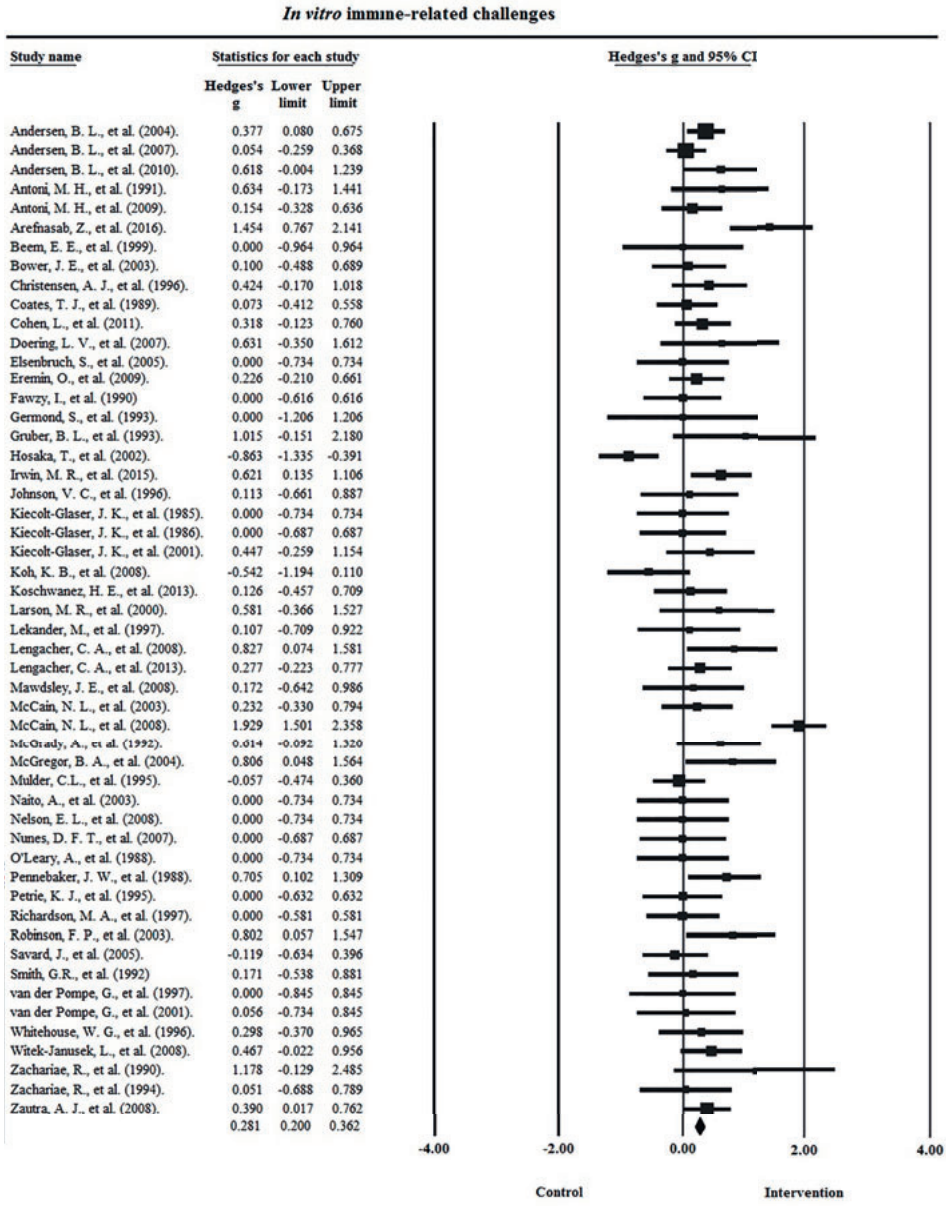

Figure 4. Forest plot of the random-effects meta-analysis on the studies incorporating in vitro immune-related stimulations.

Positive values for g indicate more optimal immune responses in the intervention condition than in the control condition.

Figure 5 presents the results of the random-effects meta-analysis on the pooled effects of *in vivo* immune-related challenges. A moderate effect size was found (k = 17, g = .61 [95% CI .34; .88]), with high heterogeneity across the studies (I^2 = 74.59%). After excluding the studies that were set at r = .00, a similar moderate effect size was found (k = 15, g = .64, [95% CI .35; .92], I^2 = 76.73%). When looking at specific subgroups within the *in vivo* immune-related challenges, a large effect size was found for studies using skin tests (k = 8, g = .80 [95% CI .30; 1.30], I^2 = 80.72%), whereas a small to moderate effect size was found for vaccine studies (k = 5, g = .37 [95% CI -.17; .90], I^2 = 77.69), and a moderate to large effect size for wound healing studies (k = 4, g = .75 [95% CI .45; 1.05], I^2 < 0.01%).

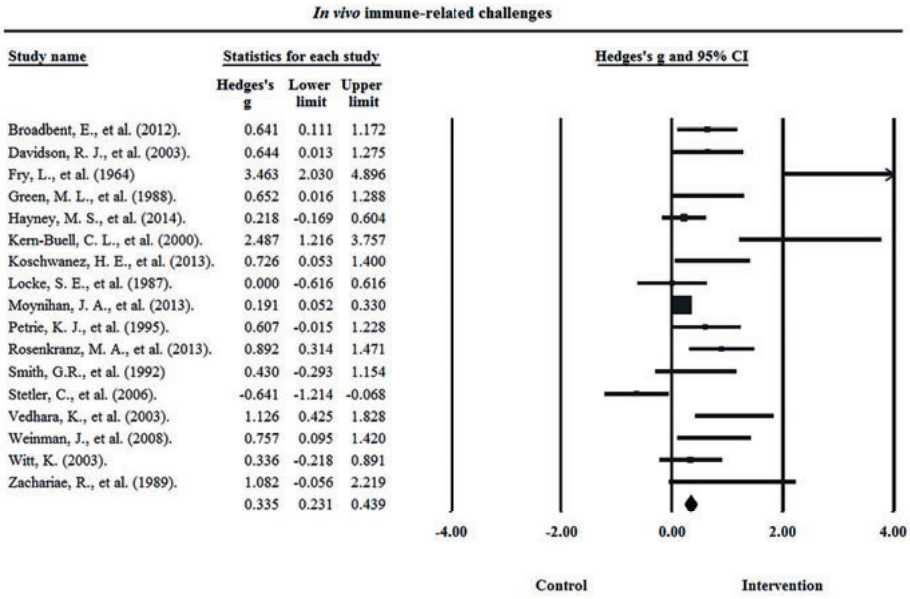

Figure 5. Forest plot of the random-effects meta-analysis on the studies incorporating in vivo immune-related challenges.

Positive values for g indicate more optimal immune responses in the intervention condition than in the control condition.

Psychophysiological challenges

In 16 studies (19.7%), a psychophysiological challenge was incorporated, whereby acute challenges included a speech task, exams, cold pressor test, and treadmill exercise test (10 studies), and challenges of a more protracted character, including academic stress and HIV serostatus notification (6 studies).

In Figure 6, the results of the random-effects meta-analysis on the pooled effects of psychophysiological challenges is shown. One study was not included in the meta-analysis as the outcomes were only based on in vitro LPR stimulation, instead of plasma measurements T-cell enumeration or cytokine quantification. Overall, no effect was found (k = 15, g = .18 [95% CI .01; .35], I^2 < .01), whereas a small effect size was found when excluding the studies that were set at r = .00 (k = 10, g = .28 [95% CI .07; .49], I^2 < .01). When assessing studies that incorporated enumeration of lymphocyte subsets after a psychophysiological challenge (i.e., CD4, CD8, CD56), a small to moderate effect size was found for studies incorporating a more protracted stress challenge (k = 4, g = .33 [95% CI = -0.06; .72], I^2 = 1.68%). For acute stress challenges, there were not enough studies available that had incorporated those markers in order to evaluate the effects after an acute stress challenge (k = 2). For studies that incorporated plasma cytokine measurements (i.e., IL-1ß, IL-6, IL-8, TNF-α) after a psychophysiological challenge, a small effect size was described in studies incorporating an acute challenge (k = 4, g = .22 [95% CI -.04; .49], I^2 < .01%), whereas no studies incorporated those markers to evaluate the effects after a more protracted stress challenge.

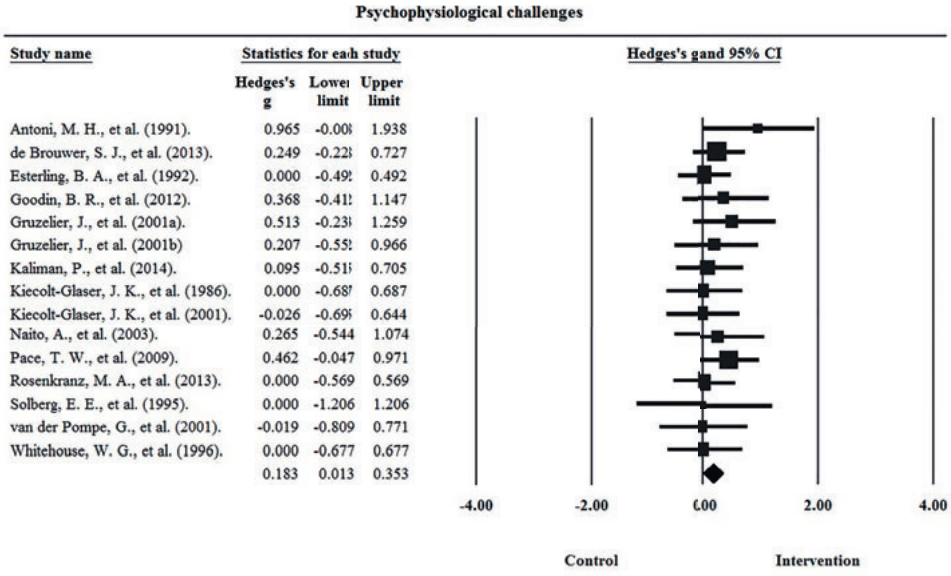

Figure 6. Forest plot of the random-effects meta-analysis on the studies incorporating psychophysiological challenges.

Positive values for g indicate more optimal immune responses in the intervention condition than in the control condition.

Sensitivity analyses

Risk of bias within studies

When studies with a presumed high risk of bias were excluded from the analyses, 23 of 84 outcomes were excluded. However, the overall effect size was not substantially altered (*k* = 61, *g* = .34 [95% CI .20; .48]).

Publication bias

The funnel plot is displayed in Figure 7 and suggests presence of publication bias. The trim and fill method indicates that 12 studies were expected to be missing with below-average effects, as indicated by the black dots. When imputing those studies, the effect size decreased to *g* = .21 [95% CI .09; .32]).

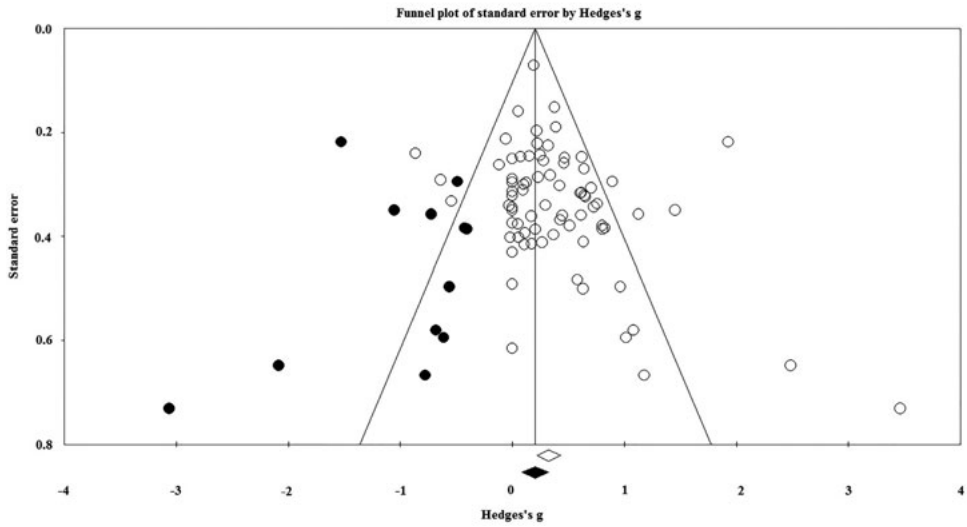

Figure 7. Funnel plot of standardized differences in mean by Hedges g.

Discussion

Over the last few decades, studies have evaluated the effectiveness of stress-reducing psychological interventions on immune function by incorporating chemical, physical, and psychophysiological challenges into the study design. These challenges are thought to present a biologically more valid reflection on the effectiveness of stress-reducing psychological interventions in optimizing immune function as compared to counting cells (170, 252, 253). The present systematic review and meta-analysis, for the first time, summarized immune-related outcomes after a chemical, physical, or psychophysiological

challenge following a stress-reducing psychological intervention in both healthy subjects and patients.

Overall, the findings demonstrated a small to moderate (heterogeneous) positive effect size for optimizing immune function. As a conservative method was applied to handle studies that reported no significant results without further specifying the actual group differences, the overall effect size possibly represents a slightly underestimated effect size. While the largest effects were found for *in vivo* immune-related challenges (especially on studies that incorporated skin tests and wound healing), studies incorporating psychophysiological challenges and *in vitro* immune-related stimulations similarly suggest more optimal immune responses among those receiving stress-reducing interventions.

When focusing on *in vitro* immune-related stimulations, small effect sizes were found. Studies were highly diverse regarding source of material and technical details of the stimulation. For example, studies varied in the target of stimulation (e.g., stimulation of T-cells, NK cells), the types of outcomes (e.g., proliferation, cytokine production, killing monocytes) and the types of concentrations and duration of stimuli. Likewise, a subset of studies stimulated whole blood, hereby performing tests in a biologically normal blood-plasma context, whereas others stimulated peripheral blood mononuclear cells (PBMCs), whereby tests are performed in artificial buffer solutions. Therefore, whole blood stimulations comprise a rather diverse range of cell populations (for example neutrophils, eosinophil's, etc.), whereas the cell populations in PBMCs are more well-defined, resulting in different environments of stimulation. In addition, important details were often lacking from the methods section, such as concentrations used or which type of immune cells were stimulated, while such aspects may substantially influence the results. Future studies are therefore encouraged to report more carefully on the methodological details. This could, for example, be acquired by applying a standard format for reporting the methodology, such as the Minimum Information About a Microarray Experiment (MIAME) guidelines (254) or the Minimal Information About T cell Assays (MIATA) standard (255). In addition, since *in vitro* stimulations are applied outside the body, those challenges may comprise a less biologically relevant valid representation of real-life immune threats as compared to *in vivo* challenges, although *in vitro* immune-related stimulations are easier to implement into the study design.

When focusing on *in vivo* immune-related challenges, studies on skin tests and wound healing found largest effect sizes and were mostly based on evaluating wound size alteration, instead of quantitative immune outcome measures. These outcome

parameters contain a rather unidirectional and straightforward representation of immune function (i.e., faster wound healing represents a more optimal immune response). Thus, of all immune-related challenges examined, most convincing evidence is found for stress-reducing psychological interventions optimizing immune performance in case of wound healing and skin-based tests. Even though these immune-related challenges probably represent a general stimulation of immune performance, this could imply that stress-reducing interventions could be particularly clinically relevant for patients with immune-related skin conditions, such as patients that recover from inflammation-sensitive surgical wounds. Contrary to these findings, only a small to moderate effect size was found for vaccines. Due to the small number of studies that incorporated a vaccine (5 studies), and variation in the type of incorporated vaccines and included time points (influenza vaccines, but also one study with a Hepatitis B vaccine incorporating various measurement points), the present meta-analysis could not provide a conclusive view on this subcategory of *in vivo* immune-related challenges. As few studies incorporated a vaccine, future research would be helpful to further elucidate the effects of psychological interventions on *in vivo* immune-related challenges, particularly in the area of vaccination and related immune outcomes.

For studies incorporating psychophysiological challenges, small effect sizes on immune measures were found when incorporating acute challenges (e.g., exam stress), and small to moderate effect sizes were found when incorporating chronic stressors (e.g., academic stress). Although the data did not seem to display high statistical heterogeneity, the incorporated challenges and immune outcome parameters were highly diverse across studies. More specifically, studies included acute challenges such as exams, speech tasks (some accompanied with or without a mental arithmetic task), a treadmill exercise test, and a cold pressor task, as well as more protracted stress challenges such as serostatus notification for individuals undergoing HIV testing and academic stress experienced by students during an examination period. Since the findings of the present study were based on a small number of studies with mostly limited ecological validity of the stressors, i.e., only some included challenges represented chronic stress as experienced by people in daily life, future work should focus on incorporating stressors with high external validity (e.g., social-evaluative stressors for socially anxious subjects or more daily-life chronic stress such as rumination) in order to evaluate the effects of psychological interventions on immune function (40).

Most the studies that incorporated psychophysiological challenges involved healthy participants (14 out of 17 studies). As healthy participants are supposed to have a well-functioning immune system, they are expected to show responses within the normal range

to standard immune system challenges, also in absence of a stress-reducing psychological intervention (167). The challenging situation to which these healthy participants are exposed therefore must be powerful enough to detect any relevant alterations in immune function in response to a psychological intervention. It is possible that combining a psychophysiological challenge with an *in vivo* immune-related challenge can boost the effects of the separate challenges and possibly provide healthy participants with a more robust immune system challenge. Only one study in the present systematic review and meta-analysis combined an *in vivo* immune-related challenge, i.e., suction blisters on the volar forearm, with a psychophysiological challenge, i.e., a Trier Social Stress Test (TSST), to evaluate the effects of a stress-reducing psychological intervention (200). In this study, participants who received a stress-reducing mindfulness intervention showed a lower post-stress (i.e., post-TSST) inflammatory response to the *in vivo* immune-related and psychophysiological challenges compared to a control group that received a control health enhancement program. The incorporation of both an *in vivo* immune-related challenge and a psychophysiological challenge provides a more elaborate view on the underlying processes of immune function after a psychological intervention, i.e., evaluating immune function after activating the immune system through different challenges that can boost each other's effectiveness. Future studies may consider incorporating multiple challenges in their design when examining immune function in healthy participants in order to hypothetically provide them with a rather robust challenge (256). Due to the heterogeneity that was observed in the included studies, we were not able to analyze the healthy participant studies and somatic patient studies separately. Future studies should systematically incorporate challenges to evaluate the effectiveness of a psychological intervention on immune function and adequately match the incorporated challenge(s) with the included study population, in order to gather a more homogeneous view on this topic.

Regarding the effective components of stress-reducing psychological interventions, no strong conclusions can be drawn at this point due to the substantial heterogeneity in the incorporated intervention elements across studies, including duration and number of sessions, intervention target, and ways of guidance (e.g., self-practice, structured guided sessions, etc.). An exploratory evaluation of the data, however, showed that multiple studies explored the role of self-practice during the intervention (e.g., completing homework assignments) for immune outcomes (181, 183, 186, 191, 192, 197, 200, 204, 213, 220, 223, 251). Most of these studies found a positive association between frequency of self-practice and optimized immune outcomes (181, 191, 192, 197, 200, 213, 223). Although we could not formally test this observation in our meta-analysis due to substantial heterogeneity in study designs (e.g., selection of immune outcomes and

differences in level of details concerning the specification of self-practice frequency), these findings possibly point to the importance of engaging participants with components of the psychological intervention. However, it is important to note that the studies included in the present systematic review and meta-analysis varied widely in the way engagement and the actual effectiveness of the stress-reducing psychological intervention was evaluated. In addition, a substantial number of studies did not report on whether the intervention was actually effective in reducing stress, making it hard to take this factor into account in our analyses. For the same reason, it was not possible to control for confounding factors, including body mass index, recent illness, female menstruation cycle, and so on. As failures to improve immunity can be due to the fact that the stress-reducing psychological interventions were actually not effective in reducing stress, future studies should also carefully evaluate to what extent participants were engaged with the stress-reducing psychological intervention, and whether these interventions were effective in reducing stress. In addition, the present findings were based on the assumption that higher levels of immune activation were associated with a more optimized immune response. However, enhanced immune responses are not necessary beneficial, e.g., in the case of inflammatory and autoimmune disorders (257). In certain cases, optimization is not based on larger immune responses, but on normalization of immune outcomes. Future studies should therefore take the health consequences of the immune response into account when evaluating the effectiveness of a psychological intervention on immune function. Note that as the aim of a stress-reducing psychological intervention is to optimize health outcomes by stress reduction, it would be most relevant to recruit individuals that experience chronic stress with a substantial impact on immune function to evaluate the effectiveness of stress-reducing psychological interventions (169). In addition, future studies should focus on unraveling the effective intervention components in optimizing immune responses by evaluating the effectiveness of intervention components separately, but also in combination with each other.

In conclusion, the present systematic review and meta-analysis provided evidence for the effects of stress-reducing interventions in optimizing immune function when immune outcomes were evaluated by utilizing tests that apply challenges to the immune system. While consistent evidence came from studies that evaluated immune function through an *in vivo* immune-related challenge, specifically studies incorporating skin tests and studies on wound healing, similar but smaller effect sizes were found for *in vitro* immune-related stimulations and immune responses to psychophysiological challenges. Due to the large heterogeneity in study designs, there is a need for future research that incorporates immune- and psychophysiological challenges, as these have a high external validity and are suited for possible clinical applications in immune-related diseases. Studies in healthy

participants have to make sure that the immune challenge is robust enough, for example by combining separate challenges. Finally, future studies should carefully report on the methodological details according to standardized guidelines, including the actual stress-reducing effectiveness of the psychological interventions, and appropriate interpretation of the immune outcomes. This can result in further insights on the immune outcomes that are responsive for change as well as a thorough view on the effective intervention components to optimize immune responses in the short and longer term.

Acknowledgements

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Supplemental material

Supplemental Table 1. Search terms for Pubmed, EMBASE and PsychInfo.

Pubmed

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EMBASE

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A”.ti,ab OR “SAA”.ti,ab OR complement factor*.ti,ab OR “complement activation”.ti,ab OR “immune challenge”.ti,ab OR “L-selectin”.ti,ab OR “E-selectin”.ti,ab OR “sCD62L”.ti,ab OR “sCD62E”.ti,ab OR “Psychological Stress”.ti,ab OR “Trier Social Stress Test”.ti,ab OR “TSST”.ti,ab OR “perceived stress”.ti,ab OR “examination stress”.ti,ab OR “arithmetic task”.ti,ab OR “arithmetic test”.ti,ab OR “mental arithmetic”.ti,ab OR “cold pressor”.ti,ab OR “mirror tracing”.ti,ab OR “mock job interview”.ti,ab OR “PASAT”.ti,ab OR “anger recall task”.ti,ab OR “anger recall test”.ti,ab OR “public speaking”.ti,ab OR “oral presentation”.ti,ab OR “Auditory serial addition task”.ti,ab OR “Auditory serial addition test”.ti,ab OR “stroop task”.ti,ab OR “stroop test”.ti,ab OR laboratory stress*.ti,ab OR laboratory challenge*.ti,ab OR acute stress*.ti,ab OR “speech task”.ti,ab OR “speech test”.ti,ab OR “public speech task”.ti,ab OR “public speech test”.ti,ab OR speech stress*.ti,ab OR cognitive stress*.ti,ab OR “cognitive challenge”.ti,ab OR mental stress*.ti,ab OR “stress induced”.ti,ab OR *”physiological stress”/ OR *”Mental Stress”/ OR *”acute stress”/ OR “behavioral stress”/ OR “stress-evoked cortisol response”.ti,ab OR “combat training”.ti,ab OR bungee jump*.ti,ab OR parachute jump*.ti,ab) AND (“Hypnosis”.ti,ab OR *”Hypnosis”/ OR “Self Disclosure”/ OR Psychotherap*.ti,ab OR exp *”psychotherapy”/ OR “Writing”.ti,ab OR “Relaxation Therapy”.ti,ab OR *”Meditation”/ OR “Conditioning”.ti,ab OR exp *”Conditioning”/ OR “stress management”.ti,ab OR “disclosure”.ti,ab OR “mindfulness practice”.ti,ab OR “Expressive writing”.ti,ab OR “Cognitive behavioral therapy”.ti,ab OR “cognitive-behaviour therapy”.ti,ab OR “cognitive-behavior therapy”.ti,ab OR “cognitive-behavioural therapy”.ti,ab OR “cognitive-behavioral therapy”.ti,ab OR “relaxation”.ti,ab OR “Guided imagery”.ti,ab OR “CBT”.ti,ab OR exp *”Behavior Therapy”/ OR “psychoeducational”.ti,ab OR “psychoeducation”.ti,ab OR “psycho-educational”.ti,ab OR “psycho-education”.ti,ab OR ((exp *”Counseling”/ OR “counselling”.ti,ab OR “counseling”.ti,ab) NOT (“genetic counseling”/ OR “genetic counselling”.ti,ab OR “genetic counseling”.ti,ab)) OR (((“therapy”.ti,ab OR “therapies”.ti,ab OR treatment*.ti,ab) ADJ3 (“cognitive”.ti,ab OR “behavior”.ti,ab OR “behavioral”.ti,ab OR “behaviour”.ti,ab OR “behavioural”.ti,ab OR “conditioning”.ti,ab OR “cognition”.ti,ab)) OR “behavior modification”.ti,ab OR “behaviour modification”.ti,ab OR conditioning therap*.ti,ab OR “conditioning treatment”.ti,ab OR cognition therap*.ti,ab OR “cognitive treatment”.ti,ab)) AND (english OR dutch).la AND exp “Humans”/ NOT (conference review OR conference abstract).pt

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Supplemental Table 2. Study characteristics and details concerning the intervention

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Andersen, et al. (2004).	Women surgically treated for regional breast cancer	*N* = 227 *M* age = 50.8, *SD* = 10.8	Multicomponent cognitive behavioral intervention (Control = AO)	4 months	Appointments: 18 group sessions of 1.5 hrs	Psychologist
Andersen, et al. (2007).	See Andersen, B. L., et al. (2004)	See Andersen, B. L., et al. (2004)	Multicomponent cognitive behavioral intervention (Control = AO)	12 months	Appointments: 26 group sessions of 1.5 hrs	Psychologist
Andersen, et al. (2010).	Women with recurrent breast cancer	*N* = 62 *M* age = 53.7, *SD* = 11.3	See Andersen, B. L., et al. (2007	See Andersen, B. L., et al. (2007)	See Andersen, B. L., et al. (2007)	See Andersen, B. L., et al. (2007)
Antoni, et al. (1991).	Healthy gay men	*N* = 47 *M* age = 30.5	Stress management (Control = AO)	2.5 months	Appointments: biweekly group sessions (weekly 1 session of 45 min and 1 session of 1.5 hrs) Self-practice: daily relaxation exercises	Psychologist
Antoni, et al. (2009).	Women who underwent breast cancer treatment	*N* = 128 *M* age = 49.7, *SD* = 7.9	Stress management (Control = Condensed educational version of the intervention during a seminar lasting 5-6 hrs at the midpoint of the 10-week period)	2.5 months	Appointments: weekly group sessions Self-practice: daily relaxation exercises	Guided by intervention facilitators who were supervised by psychologists
Arefnasab, et al. (2016).	Male veterans with pulmonary injury	*N* = 40 *M* age = 49.4, range = 42-59	Mindfulness (Control = WLC)	2 months	Appointments: weekly group sessions of 2 hrs Self-practice: daily home practice	Clinician specialist
Beem, et al. (1999).	Widows	*N* = 18 *M* age = 58.6, *SD* = 4.9	Counseling (Control = AO)	4 months	Appointments: 13 group sessions (2 sessions of 5 hrs and 11 sessions of 2.5 hrs)	Trained counselors who were supervised
Bower, et al. (2003).	Women who lost a close relative to breast cancer	*N* = 43 *M* age = 42.1, *SD* = 8.3	Emotional disclosure (Control = writing about various non-emotional topics)	1 month	Self-practice: weekly 20 min sessions	Unguided appointments; instructions were mailed by a research assistant
Broadbent, et al. (2012).	Patients who underwent surgery (Male: 25%; Female: 75%)	*N* = 60 *M* age = 51.3, *SD* = 16.8	Stress management (Control = CAU)	± 10 days	Appointments: 1 individual session of 45 min Self-practice: daily 20 min with a CD at least 3 days before surgery and 7 days after surgery	Psychologist

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
de Brouwer, et al. (2013).	Patients with RA (Male: 41.9%; Female: 58.1%)	*N* = 74 *M* age = 58.8, *SD* = 10.6	Stress management (Control = CAU)	2 weeks + 7 weeks relapse prevention	Appointments: biweekly individual sessions of 1 hr Self-practice: relapse prevention checklist for 9 weeks	Psychologist
Christensen, et al. (1996).	Male college undergraduates	*N* = 43 Age not specified	Emotional disclosure (Control = Reading about a hypothetical situation that described a student's experience with failing a course)	1 session	Appointment: 1 individual session of ± 35 min	Structured session; way of guidance not further specified
Coates, et al. (1989).	Men with HIV infection	*N* = 64 *M* age = 34.9	Stress management (Control = WLC)	2 months	Appointments: weekly group sessions of 2 hrs and one-day retreat after 1 month	Structured sessions; way of guidance not further specified
Cohen, et al. (2011).	Men with prostate cancer undergoing radical prostatectomy	*N* = 159 *M* age = 60.5, *SD* = 6.7	Stress management (Control = CAU)	2 sessions	Appointments: 2 individual sessions of 1-1.5 hrs and 2 brief booster sessions Self-practice: relaxation by audiotapes	Psychologist
			Counseling (Control = CAU)	2 sessions	Appointments: 2 individual sessions of 1-1.5 hrs and 2 brief booster sessions	Psychologist
Davidson, et al. (2003).	Healthy participants (Male: 29.3%; Female: 70.7%)	*N* = 41 *M* age = 36; Range = 23-56	Mindfulness/meditation (Control = WLC)	2 months	Appointments: weekly group sessions of 2.5-3 hrs and 1 silent retreat of 7 hrs at week 6 Self-practice: 1 hr daily during 6 days per week	Psychologist
Doering, et al. (2007).	Women with a clinical depression after CABG	*N* = 15 *M* age = 59.8, *SD* = 8.6	Multicomponent cognitive behavioral intervention (Control = CAU)	2 months	Appointments: weekly individual sessions of 1 hr Self-practice: homework assignments	Trained nurse therapist
Elsenbruch, et al. (2005).	Patients with UC (Male: 33.3%, Female: 66.7%)	*N* = 30 *M* age = 42.7, *SD* = 10	Multicomponent cognitive behavioral intervention (Control = WLC)	2.5 months	Appointments: weekly sessions of 6 hr	Structured sessions; way of guidance not further specified
Eremin, et al. (2009).	Women with locally advanced breast cancer undergoing multimodality therapy	*N* = 80 *M* age = 49.9, *SD* = 11.5	Relaxation (Control = CAU)	Not specified	Appointments: 5 individual sessions Self-practice: regular home practice through audiotapes	Structured sessions; way of guidance not further specified

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Esterling, et al. (1992).	HIV-1-infected and at risk gay men	*N* = 65 *M* age = 30.5	Stress management (Control = AO)	2.5 months	Appointments: weekly 1 session of 1.5 hrs and 1 session of 45 min Self-practice: take-home imagery tape from week 8 to 10	Psychologist
Fawzy, et al. (1990).	Cancer patients (Male: 45.9%; Female: 54.1%)	*N* = 61 *M* age = 42, range = 19-70	Multicomponent cognitive behavioral intervention (Control = CAU)	1.5 months	Appointments: weekly group sessions of 1.5 hrs	Structured sessions; way of guidance not further specified
Fry, et al. (1964).	Persons with asthma or hay-fever (Gender not specified)	*N* = 47 Age not specified	Hypnosis (Control = AO)	2 weeks	Appointments: 3 group meetings	Structured sessions; way of guidance not further specified
Germond, et al. (1993).	Women with RA	*N* = 14 *M* age = 49, *SD* = 9.4	Multicomponent cognitive behavioral intervention (Control = AO)	2 months	Appointments: biweekly group sessions of 2 hrs	Structured sessions; way of guidance not further specified
Goodin, et al. (2012).	Healthy participants (Male: 50%; Female: 50%)	*N* = 24 *M* age = 19.8, *SD* = 3.0	Hypnosis (Control = AO)	2 weeks	Appointments: weekly sessions	Research assistants who were supervised by a psychologist
Green, et al. (1988).	Students and college employees (Gender not specified)	*N* = 40 Age not specified	Relaxation (Control = WLC)	3 weeks	Appointments: 2 group sessions of 20 min Self-practice: daily 20 min home sessions	Structured sessions; way of guidance not further specified
Gruber, et al. (1993).	Women with breast cancer	*N* = 13 *M* age = 44.6, range = 34-50	Multicomponent cognitive behavioral intervention (Control = WLC)	9 weeks	Appointments: 4 weekly group sessions followed by biweekly biofeedback sessions Self-practice: twice daily relaxation and guided imagery practices	Structured sessions; way of guidance not further specified
Gruzelier, et al. (2001a).	Students (Male: 60.7%; Female: 39.3%)	*N* = 28 *M* age = 20.1	Hypnosis (Control = AO)	3 weeks	Appointments: 1 group session Self-practice: 9 tape recorded hypnosis sessions	Structured sessions; way of guidance not further specified
Gruzelier, et al. (2001b).	Students (Male: 61.3%; Female: 38.7%)	*N* = 31 *M* age = 19.1	Hypnosis (Control = AO)	3 weeks	Appointments: weekly group sessions of 20 min Self-practice: home practice of hypnosis through audio cassettes with a minimum of 3 sessions a week	Researchers
			Relaxation (Control = AO)	3 weeks	Appointments: weekly group sessions of 20 min Self-practice: home practice of hypnosis through audio cassettes with a minimum of 3 sessions a week	Researchers
Hayney, et al. (2014).	Healthy individuals (Male: 18.6%; Female: 81.4%)	*N* = 102 *M* age = 59.4; *SD* = 6.7	Mindfulness/meditation (Control = WLC)	2 months	Appointments: weekly group sessions of 2.5 hrs Self-practice: daily 45 min	Senior exercise physiology staff

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Hosaka, et al. (2002).	Japanese infertile women	*N* = 74 *M* age = 34.8	Multicomponent cognitive behavioral intervention (Control = CAU)	5 weeks	Appointments: weekly group sessions of 1.5 hrs	Nurses / psychiatrists
Irwin, et al. (2015).	Patients with late life insomnia (Male: 24%; Female: 76%)	*N* = 75 *M* age = 65.1, *SD* = 6.6	Multicomponent cognitive behavioral intervention (Control = sleep seminar)	4 months	Appointments: weekly group sessions of 2 hrs	Structured sessions; way of guidance not further specified
Johnson, et al. (1996).	Healthy volunteers (Gender not specified)	*N* = 24 Age not specified	Stress management (Control = AO with hypnotic induction at baseline)	3 weeks	Appointments: 1 session at the start and at the end for 12.5 minutes Self-practice: daily home practice with audiotapes of relaxation	Structured sessions; way of guidance not further specified
Kaliman, et al. (2014).	Expert meditators (Male: 42.5%; Female: 57.5%)	*N* = 40 *M* age = 50.1, *SD* = 10.0	Mindfulness/meditation (Control = intentional activities such as reading, watching documentaries, etc., without unique components of mindfulness)	1 session	Appointments: 1 group session of 8 hrs	Structured session; way of guidance not further specified
Kern-Buell, et al. (2000).	Nonsmoking patients with asthma (Male: 37.5%; Female: 62.5%)	*N* = 16 *M* age = 20.5, *SD* = 5.9	Relaxation (Control = WLC)	2 months	Appointments: 8 sessions of unspecified duration Self-practice: twice a day for 15 min with audiotapes of autogenic relaxation	Structured sessions; way of guidance not further specified
Kiecolt-Glaser, et al. (1985).	Geriatric population (Male: 20%; Female: 80%)	*N* = 45 *M* age = 74, range = 60-88	Relaxation (Control = WLC)	1 month	Appointments: 3 weekly individual sessions of 45 min	Trained psychology students
Kiecolt-Glaser, et al. (1986).	Healthy participants (Male: 64.7%; Female: 35.3%)	*N* = 34 *M* age = 23.5	Stress management (Control = WLC)	2.5 weeks	Appointments: 5-10 possible group sessions in 2.5 week of 35-45 min in length Self-practice: encouraged to practice relaxation outside the group sessions	Psychologist
Kiecolt-Glaser, et al. (2001).	Medical and dental students (Male: 42.4%; Female: 57.6%)	*N* = 33 *M* age = 23.5, *SD* = 2.0	Hypnosis (Control = WLC)	8 days	Appointments: 5 group sessions of 25-40 min Self-practice: daily practice of relaxation-self-hypnosis	Psychologists
Koh, et al. (2008).	Medical students (Male: 66.7%; Female: 33.3%)	*N* = 36 *M* age = 23.7, *SD* = 1.9	Relaxation (Control = WLC)	1 month	Appointments: 2 sessions of 1 hr Self-practice: twice a day for 15 min	Psychiatrist

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Koschwanez, et al. (2013).	Older adults (Male: 42.9%; Female: 57.1%)	*N* = 49 *M* age = 78.8, *SD* = 7.2	Emotional disclosure (Control = writing about their daily activities)	3 days	Appointments: daily individual sessions of 20 min	Researchers
Larson, et al. (2000).	Women with breast cancer	*N* = 41 *M* age = 56, *SD* = 13	Multicomponent cognitive behavioral intervention (Control = CAU)	2 sessions	Appointments: 2 sessions of 1.5 hrs Self-practice: twice daily relaxation practice through audiotapes	Psychologist
Lekander, et al. (1997).	Women with ovarian cancer	*N* = 22 *M* age = 56.8, *SD* = 10.5	Relaxation (Control = CAU)	2 months	Appointments: 3 individual sessions of 20-45 min Self-practice: relaxation practice on a regular basis through audiotapes	Psychologist
Lengacher, et al. (2008).	Women with breast cancer	*N* = 28 *M* age = 52.6, range 25-75	Stress management (Control = CAU)	1 month	Appointments: 1 individual session of 0.5 hrs Self-practice: listening to guided imagery tapes for three times a week	Psychologist
Lengacher, et al. (2013).	Women with breast cancer	*N* = 82 *M* age = 58, *SD* = 9	Mindfulness/meditation (Control = CAU)	1.5 months	Appointments: weekly 2 hrs sessions Self-practice: daily meditation and yoga practice, and other homework assignments	Psychologist
Locke, et al. (1987).	Healthy volunteers (Male: 42.9%; Female: 57.1%)	*N* = 42 *M* age = 26, *SD* = 4	Hypnosis (Control = AO)	3 days	Appointments: 6 sessions of unspecified duration Self-practice: 5 audiotaped reinforcement practice sessions	Structured sessions; way of guidance not further specified
Mawdsley, et al. (2008).	Patients with active UC (Male: 60%; Female: 40%)	*N* = 25 *M* age = 41.0, range = 23-63	Hypnosis (Control = listening to relaxing music of their own choice for 50 min)	1 session	Appointments: 1 session of 50 min	Hypnotherapist
McCain, et al. (2003).	Persons with HIV infection (Male: 80%; Female: 20%)	*N* = 148 *M* age = 39.4, median = 39.0	Stress management (Control = WLC)	2 months	Appointments: weekly group sessions of 1.5 hrs Self-practice: daily practice of the learned skill for 1 week through audiotapes	Structured sessions; way of guidance not further specified Mental health nurse
			Counseling (Control = WLC)	2 months	Appointments: weekly group sessions of 1.5 hrs weekly	

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
McCain, et al. (2008).	Persons with HIV infection (Male: 60.3%; Female: 39.7%)	*N* = 252 *M* age = 42.2	Relaxation (Control = WLC)	2.5 months	Appointments: weekly group sessions of 1.5 hrs Self-practice: routinely practice with relaxation	Experienced and licensed investigator in stress management
McGrady, et al. (1992).	Healthy adults (Male: 56.3%; Female: 43.7%)	*N* = 32 *M* age = 24.9	Relaxation (Control = AO)	1 month	Appointments: weekly group sessions of 0.5 hrs and weekly individual sessions of 0.5 hrs Self-practice: by an autogenic relaxation tape twice a day	Structured sessions; way of guidance not further specified
McGregor, et al. (2004).	Women with early-stage breast cancer	*N* = 29 *M* age = 47.5, *SD* = 6.3	Stress management (Control = AO with 1-day stress management education seminar after 10 weeks)	2.5 months	Appointments: weekly group sessions of 2 hrs Self-practice: weekly homework assignments	Structured sessions; way of guidance not further specified
Moynihan, et al. (2013).	Older adults (Male: 38%; Female: 62%)	*N* = 200 *M* age = 73.5, *SD* = 6.7	Mindfulness/meditation (Control = WLC)	2 months	Appointments: weekly group sessions of 2 hrs and 1 session of 7 hrs	Licensed MBSR trainer
Mulder, et al. (1995).	Men with asymptomatic HIV-infection	*N* = 165 *M* age = 38.7, range = 21-61	Multicomponent cognitive behavioral intervention (Control = WLC)	15 weeks	Appointments: weekly sessions of 2.5 hrs	Structured sessions; way of guidance not further specified
Naito, et al. (2003).	Healthy students (Male: 45.8%; Female: 54.2%)	*N* = 48 Range age = 19-37	Hypnosis (Control = 8 mock neurofeedback sessions over 1 month)	1 month	Appointments: weekly sessions Self-practice: three times a day self-hypnosis for two weeks, thereafter once a day	Hypnotherapist
Nelson, et al. (2008).	Women who survived cervical cancer	*N* = 36 *M* age = 47.9, *SD* = 2.9	Counseling (Control = CAU)	± 3 months	Appointments: 5 weekly individual sessions of 45-50 min and a booster session	Psychologist
Nunes, et al. (2007).	Women with breast cancer undergoing radiotherapy	*N* = 34 *M* age = 52.5, *SD* = 1.8	Relaxation (Control = CAU)	3.5 weeks	Appointments: daily group sessions of 0.5 hrs Self-practice: twice daily at home	Psychologist
O'Leary, et al. (1988).	Women with RA	*N* = 30 *M* age = 49.3, range = 22-75	Multicomponent cognitive behavioral intervention (Control = reading a help book which was also provided to the intervention group)	5 weeks	Appointments: weekly group sessions of 2 hrs	Researchers

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Pace, et al. (2009).	Healthy adults (Male: 47.5%; Female: 52.5%)	*N* = 61 *M* age = 18.5, *SD* = 0.7	Mindfulness/meditation (Control = attending health discussion groups with a requirement of at least 12 hrs participation)	1.5 months	Appointments: biweekly group sessions of 50 min Self-practice: through audiotapes with meditation practice	Researchers
Pennebaker, et al. (1988).	Healthy undergraduates (Male: 28%; Female: 72%)	*N* = 50 Age not specified	Emotional disclosure (Control = writing on an assigned topic without discussing their own thoughts / feelings)	4 days	Appointments: daily individual writing sessions of 20 min	Researchers
Petrie, et al. (1995).	Medical students (Male: 52.5%; Female: 47.5%)	*N* = 40 *M* age = 21.5, *SD* = 2.4	Emotional disclosure (Control = writing on different aspects of their use of time objectively with minimum use of emotions)	4 days	Appointments: daily individual writing sessions	Structured sessions; way of guidance not further specified
van der Pompe, et al. (1997).	Women with breast cancer	*N* = 31 *M* age = 58.8, *SD* = 8.0	Multicomponent cognitive behavioral intervention (Control = WLC)	13 weeks	Appointments: weekly group sessions of 2.5 hrs	Psychologist
van der Pompe, et al. (2001).	See van der Pompe, G., et al. (1997)	See van der Pompe, G., et al. (1997)	See van der Pompe, G., et al. (1997)	See van der Pompe, G., et al. (1997)	See van der Pompe, G., et al. (1997)	See van der Pompe, G., et al. (1997)
Richardson, et al. (1997).	Women with breast cancer	*N* = 47 *M* age = 46, *SD* = 8.7	Counseling (Control = CAU)	1.5 months	Appointments: weekly group sessions	Social workers
			Hypnosis (Control = CAU)	1.5 months	Appointments: weekly group sessions Self-practice: twice daily 20 min relaxation and imagery practice	Hypnotherapist
Robinson, et al. (2003).	Individuals with HIV infection (Male: 94.1%; Female: 5.9%)	*N* = 34 *M* age = 41.0, *SD* = 6.6	Mindfulness/meditation (Control = AO)	2 months	Appointments: weekly group sessions of 2.5 hrs and 1 session of 8 hrs Self-practice: daily practice for at least 45 min	Psychologist
Rosenkranz, et al. (2013).	Healthy volunteers (Male: 20.4%; Female: 79.6%)	*N* = 49 *M* age = 45.9, *SD* = 10.9	Mindfulness/meditation (Control = health enhancement program without the unique components of mindfulness)	2 months	Appointments: weekly sessions of 2.5 hrs and 1 full day session Self-practice: daily at home practice for 45-60 min	Licensed MBSR trainer
Savard, et al. (2005).	Women with breast cancer and chronic insomnia	*N* = 57 *M* age = 54.1, *SD* = 7.4	Multicomponent cognitive behavioral intervention (Control = WLC)	2 months	Appointments: weekly group sessions of 1.5 hrs with 1 optional booster session 1 month after the treatment	Structured sessions; way of guidance not further specified

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Smith, et al. (1992).	Healthy volunteers (Gender not specified)	*N* = 29 *M* age = 45, range = 28-60	Mindfulness/meditation (Control = AO)	1 week	Appointments: daily 2 sessions of 1hr Self-practice: 10 min 6 times daily using the learned techniques and listening to relaxation audiotapes 0.5 hrs upon arising and bedtime for the following week	Researchers
Solberg, et al. (1995).	Male runners	*N* = 12 Median age = 42.5, range = 27-49	Mindfulness/meditation (Control = AO)	7 weeks	Self-practice: regular 30 min sequences at home	Structured sessions; way of guidance not further specified
Stetler, et al. (2006).	Participants from University campus (Male: 10.4%; Female: 89.6%)	*N* = 47 *M* age = 27.5, *SD* = 10.3	Emotional disclosure (Control = writing about their schedule for the upcoming week)	11-15 days	Appointments: 3 individual sessions of 20 min	Researchers
Vedhara, et al. (2003).	Elderly (Male: 44.2%; Female: 55.8%)	*N* = 43 *M* age = 75, *SD* = 7	Stress management (Control = AO)	2 months	Appointments: weekly group sessions of 1 hr	Psychologist
Weinman, et al. (2008).	Male students and university staff	*N* = 36 *M* age = 22.2, *SD* = 4.1	Emotional disclosure (Control = writing about time management)	3 days	Appointments: daily individual writing sessions of 20 min	Structured sessions; way of guidance not further specified
Whitehouse, et al. (1996).	Students (Male: 40%; Female: 60%)	*N* = 35 *M* age = 24.8	Hypnosis (Control = WLC)	3.5 months	Appointments: weekly group sessions of 1.5 hrs Self-practice: daily diaries and 15 min self-hypnosis practice	Psychiatrist
Witek-Janusek, et al. (2008).	Women with breast cancer	*N* = 66 *M* age = 54.6, *SD* = 9.2	Mindfulness/meditation (Control = CAU)	2 months	Appointments: weekly group sessions of 2.5 hrs and 1 full day session Self-practice: homework assignments by a program workbook and audiotapes	Psychologist
Witt (2003).	Humans with birch pollen allergy (Gender not specified)	*N* = 72 *M* age = 42, range = 18-66	Multicomponent cognitive behavioral intervention (Control = AO)	1 month	Appointments: biweekly group sessions of 2.5 hrs	Structured sessions; way of guidance not further specified
Zachariae, et al. (1989).	Highly hypnotic susceptible subjects (Male: 72.2%; Female: 27.8%)	*N* = 18 Age not specified	Hypnosis (Control = AO)	4 days	Appointments: 1 session Self-practice: twice daily 20 min sessions using audiotapes of hypnosis and imagery during 3 days	Structured session; way of guidance not further specified

Study	Sample	Sample size (N) and age (M, SD)	Intervention type	Length	Intensity	Way of guidance
Zachariae, et al. (1990).	Healthy subjects (Gender not specified)	*N* = 14 Age not specified	Stress management (Control = AO)	10 days	Appointments: 1 individual session of 45 min and 1 individual session of 60 min	Structured sessions; way of guidance not further specified
Zachariae, et al. (1994).	Study 1: Healthy subjects (Male: 30%; Female: 70%)	Study 1: *N* = 30 *M* age = 30.5, *SD* = 8.9	Study 1: Stress management (Control = AO)	Study 1: 3 weeks	Study 1: Appointments: weekly individual sessions of 1 hr Self-practice: 5 times a week through an audio cassette tape	Study 1: Structured sessions; way of guidance not further specified
			Relaxation (Control = AO)	3 weeks	Appointments: weekly individual sessions of 1 hr Self-practice: 5 times a week through an audiocassette tape	Study 2: Structured sessions; way of guidance not further specified
	Study 2: Healthy subjects (Male: 30%; Female: 70%)	Study 2: *N* = 30 *M* age = 27.7, *SD* = 6.2	Study 2: Stress management (Control = AO)	Study 2: 3 weeks	Study 2: Appointments: weekly individual sessions of 1 hr Self-practice: 5 times a week through an audio cassette tape	Structured sessions; way of guidance not further specified
			Relaxation (Control = AO)	3 weeks	Appointments: weekly individual sessions of 1 hr Self-practice: 5 times a week through an audiocassette tape	
Zautra, et al. (2008).	Patients with RA (Male: 31.9%; Female: 68.1%)	*N* = 144 *M* age = 54.2, *SD* = 13.6	Mindfulness/meditation (Control = general education concerning RA and other health-related topics)	2 months	Appointments: weekly group sessions Self-practice: weekly homework practices	Psychologist
			Multicomponent cognitive behavioral intervention (Control = general education concerning RA and other health-related topics)	2 months	Appointments: weekly group sessions Self-practice: weekly homework practices	Psychologist

Note. AO = assessment-only; CABG = Coronary Artery Bypass Grafting; CAU = care as usual; CBSM = Cognitive Behavioral Stress Management; CBT = Cognitive Behavioral Therapy; HIV = Human Immunodeficiency Virus; hrs = hours; M = Mean; MBSR = Mindfulness Based Stress Reduction; min = minutes; N = Number; RA = Rheumatoid Arthritis; SD = Standard Deviation; UC = Ulcerative Colitis; WLC = waiting-list control.

Note 2. The reported *N* is based on the total study population for which age and gender were reported. This *N* could deviate from the study population for which the intervention outcomes were measured due to possible drop out during follow up measurements.

Supplemental Table 3. Challenges and outcomes

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
Andersen, et al. (2004).	-	In PBL: PHA → LPR Con A → LPR K562 → NKCC	-	Baseline and after intervention	CD3, CD4, CD8, CD56	↑ LPR to Con A**, ↑ LPR to PHA*	CD3, CD4, CD8, CD56, NKCC
Andersen, et al. (2007).	-	In PBL: PHA → LPR Con A → LPR K562 → NKCC	-	Before intervention, 8 months after intervention	-	↑ LPR to PHA*	LPR to Con A, NKCC
Andersen, et al. (2010).	-	In PBL: PHA → LPR Con A → LPR K562 → NKCC	-	Date of breast cancer recurrence, 4, 8 and 12 months later	-	From 4 to 12 months: ↑ NKCC* At 12 months: ↑ NKCC*, ↑ LPR to PHA*, ↑ LPR to Con A*	At 4 & 8 months: NKCC, LPR to Con A and PHA
Antoni, et al. (1991).	-	In whole blood: PHA → LPR PWM → LPR N/A → NKCC	Serostatus notification	3 days before serostatus notification (after intervention) and one week after serostatus notification	CD4, CD56	In seropositives: ↑ CD4**; ↑ LPR to PHA*; ↑ NKCC**, ↑ CD56*	LPR to PWM
Antoni, et al. (2009).	-	In PBMC: Anti-CD3 → IL-2, IL-4, and IFN- γ production	-	Before intervention, 3 months and 9 months after intervention	CD4, CD8, CD56, $CD56^+CD3^+$, CD19	3 months after intervention: ↑ IL-2 production*, ↑ IFN-γ production**, ↑ IL-2:IL-4 ratio*	At 9 months: IL-2, IFN- γ Overall: IL-4, CD4, CD8, CD56, $CD56^+CD3^+$, CD19
Arefnasab, et al. (2016).	-	In PBMC: PHA → LPR CON A → LPR	-	Before and after intervention	IL-17, $CD4^+$, $CD8^+$, CD56	↑ LPR to Con A**, ↑ LPR to PHA**, ↑ IL-17**	$CD4^+$, $CD8^+$, CD56
Beem, et al. (1999).	-	In PBMC: PHA → LPR anti-CD3 → LPR PWM → LPR K562 → NKCC	-	Before and after intervention	$CD19^+$, $CD20^+$, $CD3^+$, $CD4^+$, $CD8^+$, $CD5^+$, $CD16^+$, $CD56^+$, $CD3^-$		LPR to PHA / anti-CD3 / PWM, NKCC, $CD19^+$, $CD20^+$, $CD3^+$, $CD4^+$, $CD8^+$, $CD5^+$, $CD16^+$, $CD56^+$, $CD3^-$
Bower, et al. (2003).	-	In PBMC: K562 → NKCC	-	Before and after intervention	$CD3^-$, $CD16^+$, $CD56^+$		NKCC, $CD3^-$, $CD16^+$, $CD56^+$
Broadbent, et al. (2012).	Wound → hydroxyproline deposition	-	-	7 days after intervention	-	↑ Hydroxyproline deposition*	

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
de Brouwer, et al. (2013).	-	-	TSST	1 week after intervention before TSST, and 0, 20, 60 min after TSST and after 7-weeks relapse prevention before TSST, and 0, 20, 60 min after TSST	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IFN-γ, TNFα	After 7 weeks relapse prevention: ↓ stress-induced IL-8*	1 week after intervention: IL-8. Overall: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IFN-γ, TNFα
Christensen, et al. (1996).	-	In PBL: K562 → NKCC	-	Before and after intervention			Overall: NKCC
Coates, et al. (1989).	-	In N/A: N/A → NKCC Con A → LPR Candida antigen → LPR CMV → LPR	-	Before and after intervention	IgA, CD4, CD8		NKCC, LPR to Con A / candida antigen / CMV, IgA, CD4, CD8
Cohen, L., (2011).	-	In PBMC: K562 → NKCC	-	After intervention and 2 days after surgery	IL-1β, IL-12p70, IFN-γ, IL-6, IL-8, IL-10, TNF-α, CD3, CD19, CD16, CD56, CD4, $CD25^{high}/CD4^{+}$	Stress management group: ↑ NKCC*, ↑ IL-12p70*, ↑ IL-1ß*, ↑ TNF-α*	IL-6, IL-8, IL-10, IFN-γ, CD3, CD19, CD16, CD56, CD4, $CD25^{high}/CD4^{+}$
Davidson, et al. (2003).	Influenza vaccine → Influenza vaccine antibody titers	-	-	3-5 weeks after vaccination, 8-9 weeks after vaccination	-	↑ Antibody titers*	
Doering, et al. (2007).	-	In PBMC: K562 → NKCC	-	Baseline, 3 months and 6 months after surgery	IL-6, CRP		NKCC, IL-6, CRP
Elsenbruch, et al. (2005).	-	In whole blood: LPS → TNF-α production	-	Before and after intervention	CD3, $CD3^{+}CD4^{+}$, $CD3^{+}CD8^{+}$, $CD3^{-}CD16^{+}CD56^{+}$, $CD3^{-}CD20^{+,}$ $CD14^{+}$		TNF-α production, CD3, $CD3^{+}CD4^{+}$, $CD3^{+}CD8^{+}$, $CD3^{-}CD16^{+}CD56^{+}$, $CD3^{-}CD20^{+}$, $CD14^{+}$
Eremin, et al. (2009).	-	In PBMC: K562 → NKCC Daudi → LAK cell activity	-	3 days before start of chemotherapy, during chemotherapy before the 1st, 2nd, 4th and 6th cycle of chemotherapy, the day before surgery, 2 or 3 days after surgery, before radiotherapy, 4 and 12 weeks after radiotherapy	IL-1β, IL-2, IL-4, IL-6, TNF-α, $CD2^{+}$, $CD3^{+}$, $CD4^{+}$, $CD8^{+}$, $CD19^{+}$, $CD25^{+}$, $CD16^{+}$, $CD56^{+}$, $CD14^{+}$	After chemotherapy and 4 weeks after radiotherapy: ↑ $CD3^{+}$* 4 weeks after radiotherapy: ↑ $CD25^{+}$** 12 weeks after radiotherapy: ↑ LAK cell activity*	Other time points: CD3+, CD25+, LAK cell activity Overall: CD2+, CD4+, CD8+, CD19+, CD16+, CD56+, CD14+, IL-1β, IL-2, IL-4, IL-6, TNF-α, NKCC

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
Esterling, et al. (1992).	-	-	Serostatus notification	Before intervention, at week 5, 6 (after serostatus notification), 7, 8, 10 during the intervention	IgG Functional assays: EBV-VCA antibody titers, HHV-6 antibody titers, EBV-EA antibody titers	Week 6, 7, and 10 in HIV-infected participants: ↓ EBV-VCA antibody titers* Week 8 and 10 in HIV-infected participants: ↓ HHV-6 antibody titers**	Overall: IgG. Other time points: EBV-VCA and HHV-6
Fawzy, et al. (1990).	-	In PBL: IFN-augmented NKCC	-	1 week before intervention, immediately before the 5th or 6th intervention meeting, 6 months after intervention	CD4, CD8, CD16, CD56, CD57, CD38	At 6 weeks: ↑ CD57 LGL's*, ↑ CD8 T cell%*, ↑ CD57CD16** At 6 months: ↑ CD57 LGL's*, ↑ CD56**, ↑ CD57CD16*, ↑ CD16*, ↑ CD56**, ↓ CD4*, ↑ IFN-augmented NKCC*	At 6 weeks: CD4, CD56, CD38, IFN-augmented NKCC At 6 months: CD8, CD38
Fry, et al. (1964).	Skin prick test → wheal and flare size	-	-	Before and after hypnosis	-	↑ Decrease in wheal size**	Flare size
Germond, et al. (1993).	-	In N/A: PWM → LPR Con A → LPR PHA → LPR	-	Before intervention, during the 4th week and after the 8th week of intervention	-		LPR to PWM / Con A / PHA
Goodin, et al. (2012).	-	-	CPT	Before intervention, immediately following termination of CPT and at 15, 20, 25, 30, 40 min after CPT	sTNFαRII		sTNFαRII
Green, et al. (1988).	Candida injection → T_{DH} cell activity	-	-	Before and after intervention	sIgA, IgA, IgG and IgM	↓ T_{DH} cell activity*, ↑ sIgA**	IgA, IgG, IgM
Gruber, et al. (1993).	-	In N/A: Con A → LPR N/A → MLR N/A → NKCC	-	Three samples before intervention, weekly during intervention, three monthly after intervention until week 12.	IgG, IgA, IgM, total white cell counts, peripheral blood lymphocytes	Overall: ↓ White blood cell count*, ↑ LPR to Con A**, ↑ MLR**, ↑ peripheral blood lymphocytes**, IgG (direction not specified)**, ↑ NKCC*	IgA, IgM, IL-2 production

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
Gruzelier, et al. (2001a).	-	-	Exams (academic stress)	Before and after intervention	Total white blood count, CD3, CD4, CD8, CD19, CD56	↑ CD56**	Total white blood count, CD3, CD4, CD8, CD19.
Gruzelier, et al. (2001b).	-	-	Exams (academic stress)	Before intervention and after exams	CD3, CD4, CD8, CD19, CD56	↑ CD8*	CD3, CD4, CD19, CD56
Hayney, et al. (2014).	Influenza vaccine → influenza antibody concentrations	-	-	Before immunization, 3 weeks and 3 months after immunization	Nasal IgA Functional assays: IFN- γ, and IL-10 production in PBMC		Influenza antibody concentrations, nasal IgA, production of IFN-γ / IL-10
Hosaka, et al. (2002).	-	In PBMC: K562 → NKCC	-	Before and after intervention	-	After intervention: ↓ NKCC**	
Irwin, et al. (2015).	-	In PBMC: LPS → TNF, IL-6	-	CRP: before intervention, after intervention, 12 months after intervention TNF, IL-6 production: before intervention, 2 months after start of intervention, after intervention, 3 months after intervention, 12 months after intervention	CRP levels	Overall: ↓ CRP*. At 2 months after the start of the intervention: ↓ TNF production*	Overall: IL-6 production Directly after the intervention, at 3 and 12 months after completion of the intervention: TNF production
Johnson, et al. (1996).	-	In N/A: PHA → LPR K562 → NKCC	Doctor-patient role-play	Before intervention, after intervention (directly after the psychological stressor), 1 day or 2 days later	IL-1, IFN-γ, IgA		LPR to PHA, NKCC, IL-1, IFN- γ, IgA
Kaliman, et al. (2014).	-	-	TSST	Before and after intervention	RIPK2, COX2, CCR7, CXCR1, IL-6, TNF-α	↓ RIPK2**, ↓ COX-2*	CCR7, CXCR1, TNF-α, IL-6
Kern-Buell, et al. (2000).	DTH skin test → mumps induration size	-	-	Before and after intervention	White blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, CD4, CD8, CD56 Functional assays: candida and tetanus antigen response	↓ neutrophils*, ↑ basophils*, ↑ mumps induration size*	Candida and tetanus antigen response, white blood cell counts, lymphocytes, monocytes, eosinophils, CD4, CD8, CD56

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
Kiecolt-Glaser, et al. (1985).	-	In PBMC: PWM → LPR PHA → LPR K562 → NKCC	-	Before intervention, at the end of the intervention, 1 month after the intervention	Functional assays: HSV antibody titers	Overall: ↑ NKCC*, ↓ HSV antibody titers	LPR to PWM / PHA
Kiecolt-Glaser, et al. (1986).	-	In PBMC: K562 → NKCC	Exams (acute stress)	1 month after the first examination series, final day of 3-day examination series during examinations	CD4, CD8		NKCC, CD4, CD8
Kiecolt-Glaser, et al. (2001).	-	In PBL: PHA → LPR Con A → LPR LPS → IL-1ß K562 → NKCC	Exams (academic stress)	Before intervention, 3 days before academic examination	$CD3^+$, $CD4^+$, $CD8^+$, CD14, CD45	↑ LPR to PHA*, ↑ LPR to Con A*, ↑ $CD3^+$*, ↑ $CD4^+$*	IL-1ß production, NKCC, $CD8^+$, CD14, CD45
Koh, et al. (2008).	-	In PBMC: PHA → IL-6, IL-10, and TNF-α production	Exams (academic stress)	Before stress period and after stress period	-	After stress period: ↓ IL-6 production**, ↓ TNF-α production**, ↑ IL-10 production**	
Koschwanez, et al. (2013).	Wound → wound re-epithelialization	In whole blood: LPS → TNF-α, IL-1ß, and IL-6 production	-	Blood assays: Before intervention, immediately before the wound procedure (2 weeks after intervention) Wound assays: 7, 11, 14, 17 and 21 days after punch biopsy	-	At day 11 after punch biopsy: ↑ fully re-epithelialized wound*	At day 7, 14, 17 and 21: wound re-epithelialization Overall: TNF-α, IL-1ß, and IL-6 production
Larson, et al. (2000).	-	In PBMC: Anti-CD3 antibody → IFN-γ production K562 → NKCC	-	Before intervention, after intervention / pre-surgery, post-surgery	-	↑ IFN-γ production**	NKCC
Lekander, et al. (1997).	-	In PBMC: Con A → LPR K562 → NKCC	-	Before and after intervention	Lymphocytes, granulocytes, monocytes, white blood cell count	↑ Lymphocytes**	White blood cell count, monocytes, LPR to Con A, granulocytes, NKCC
Lengacher, et al. (2008).	-	In PBMC: IL-2 → LAK K562 → NKCC	-	Before and after intervention	-	↑ NKCC*, ↑ LAK*	
Lengacher, et al. (2013).	-	In whole blood: PHA → CD3+CD69+, IL-4, IFN- γ	-	Before intervention and after intervention	$CD4^+$, $CD8^+$, $CD19^+$, $CD16^+56^+$, $CD3^+CD69^+$	↑ $CD3^+CD69^+$ stimulation**, ↑ LPR to PHA for Th1/Th2 ratio*	IFN- γ and IL-4 stimulation, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+56^+$

	Challenges			Timing specifications	Other immune assays	Effects	
Study	*In vivo*	*In vitro* stimulus → target	Psycho-physiological	Measuring time points	Outcome parameters	Present	Absent
Locke, et al. (1987).	Skin testing with antigens → DTH response	-	-	After 24 hrs and after 48 hrs after intervention	-		DTH response
Mawdsley, et al. (2008).	-	In whole blood: LPS → IL-6 and TNF-α production	-	Before intervention, after intervention, 0.5 hrs after intervention	Serum IL-6, serum IL-13, CD16/CD56, platelet activation, leukocyte count, mucosal ROM production, rectal mucosal release of IL-13 and TNF-α	↓ Serum IL-6**, ↓ rectal mucosal fluid concentration of IL-13**, ↓ rectal mucosal blood flow**	Serum IL-13, TNF-α production, IL-6 production, CD16/CD56, platelet activation, leukocyte count, mucosal ROM production
McCain, et al. (2003).	-	In PBMC: K562 → NKCC PHA → cytokine production	-	Before intervention, after intervention, 6 months after intervention	$CD3^+/CD4^+$, $CD3^+/CD8^+/CD57^+$, $CD3^-/CD57^+$ lymphocytes, NKCC, IL-2, IFN-γ, IL-4, IL-10 Functional assay: Host viral load	Social support group immediately post intervention: ↓ IL-4*	Overall: $CD3^+/CD4^+$, $CD3^+/CD8^+$, $CD8^+/CD57^+$, $CD3^-/CD57^+$ lymphocytes, NKCC, IL-2, IFN-γ, IL-10, host viral load After 6 months: IL-4
McCain, et al. (2008).	-	In PBMC: PHA → LPR	-	Before intervention, after intervention, 6 months after intervention	-	Overall: ↑ LPR to PHA*	
McGrady, et al. (1992).	-	In PBMC: PHA → LPR Con A → LPR	-	Before and after intervention	Total white blood cell counts, differential counts	↑ LPR to PHA*, ↓ total white blood cell count*, ↓ neutrophil counts*	LPR to Con A
McGregor, et al. (2004).	-	In PBMC: anti-CD3 → LPR	-	Before intervention, 3 months after intervention	CD3, CD4, CD8, CD19, $CD3^-CD56^+$	↑ LPR to anti-CD3*	CD3, CD4, CD8, CD19, $CD3^-CD56^+$
Moynihan, et al. (2013).	Injection with KLH → anti-KLH antibody levels	-	-	Immediately after intervention (before injection), 3 weeks after intervention, 24 weeks after intervention	-	At 24 weeks follow up after antigen challenge: ↓ anti-KLH antibody levels*	At 3 weeks: anti-KLH antibody levels
Mulder, et al. (1995).	-	In whole blood: anti-CD3 → LPR	-	Before intervention, after every 3 months up to 24 months after intervention	CD4		LPR to anti-CD3, CD4
Naito, et al. (2003).	-	In PBMC: K562 → NKCC	Exams (acute stress)	Before intervention, during exams	CD4+%, CD8+%, CD56+%	↑ CD8+%*	CD56+%, CD4+%, NKCC

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
Nelson, et al. (2008).	-	In PBMC: Anti-CD3 / anti-CD28 → IFN-γ and IL-5	-	Before intervention and 2 weeks after intervention	IL-10, CD3, CD4, CD8, CD14, CD16, CD56		IL-10, IFN-γ production, IL-5 production, CD3, CD4, CD8, CD14, CD16, CD56
Nunes, et al. (2007).	-	In PBMC: PHA with dexamethasone and corticosterone → LPR	-	Before and after intervention	-		LPR to PHA
O'Leary, et al. (1988).	-	In PBMC: PHA → LPR Con A → LPR PWM → LPR	-	Before and after intervention	CD4, CD8		CD4, CD8, LPR to PHA / Con A / PWM
Pace, et al. (2009).	-	-	TSST	After intervention (before the TSST), and 30, 60, 75 and 90 min after TSST	IL-6		IL-6
Pennebaker, et al. (1988).	-	In PBMC: PHA → LPR Con A → LPR	-	LPR to PHA: Before intervention, after intervention, 6 weeks after intervention LPR to Con A: Before intervention, after intervention	-	Overall: ↑ LPR to PHA*	LPR to Con A
Petrie, et al. (1995).	Hepatitis B vaccine → anti-hepatitis B antibody levels	In PBMC: K562 → NKCC	-	After intervention (before the 1st vaccination), 1 month after intervention (before the 1st booster vaccination), 4 months after intervention (before the 2nd booster vaccination), at 6 months after the intervention	CD4, CD8, CD56, basophils	At 4 and 6 months after intervention: ↑ Hepatitis B antibody levels* Directly after intervention: ↓ CD4 counts*, ↓ basophils**	1 month after intervention: Hepatitis B antibody levels. At 4 months and 6 months after intervention: CD4, basophils. Overall: CD8, CD56, NKCC
van der Pompe, et al. (1997).	-	In whole blood: K562 → NKCC PWM → LPR PHA → LPR	-	Before and after intervention	CD4, CD8, CD3, CD16/56	Post treatment: ↓ CD8 cell percentages**, ↓ LPR to PWM**, ↓ CD4 cell percentages**, ↓ CD16/56 cell percentages**	CD3, NKCC, LPR to PHA

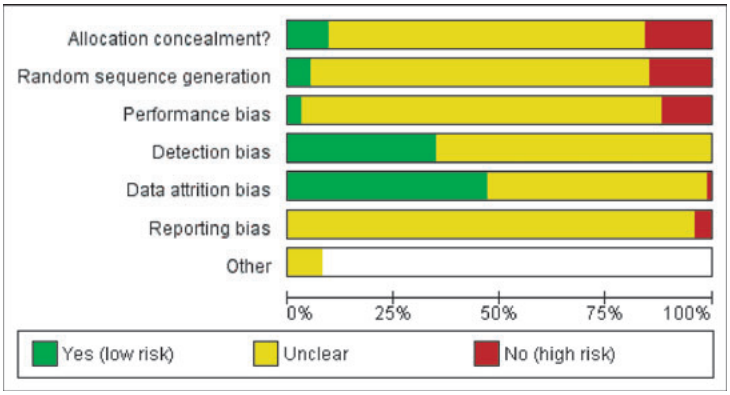
	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
van der Pompe, et al. (2001).	-	In whole blood: K562 → NKCC PWM → LPR PHA → LPR	Speech task	Before intervention (2 times before task onset, 5 min after task onset and 9 min and 37 min after task onset) and after intervention (2 times before task onset, 5 min after task onset and 9 min and 37 min after task onset)	CD3, CD4, CD8, CD16/56, CD19	After intervention (during stress induction): ↓ CD16/56*, ↓ NKCC*	LPR to PHA / PWM, CD3, CD4, CD8, CD19
Richardson, et al. (1997).	-	In PBMC: K562 → NKCC	-	Before and after intervention	IL-1α, IL-1ß, IL-2, IFN-γ, β-endorphins		NKCC, IL-1α, IL-1ß, IL-2, IFN-γ, β-endorphins
Robinson, et al. (2003).	-	In whole blood: K562 → NKCC	-	Before and after intervention	RANTES, SDF-1, CD16/CD56	After intervention: ↑ CD16/CD56**, ↑ NKCC*	SDF-1, RANTES
Rosenkranz, et al. (2013).	Suction blisters on the volar forearm → capsaicin-induced flare size	-	TSST	IL-8 and TNF-α in blister fluid: 4 weeks before intervention, within 4 weeks after the intervention, 4 months after the intervention Capsaicin-induced flare size: 4 weeks before intervention, within 4 weeks after the intervention	Functional assays: IL-8 and TNF-α in blister fluid	↓ capsaicin-induced flare size**	TNF-α and IL-8 in blister fluid
Savard, et al. (2005).	-	In PBL: K562 → NKCC In whole blood: LPS → IL-1ß, IFN- γ	-	Before intervention, after intervention, 3, 6 and 12 months after intervention	Whole blood cell count, $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+/CD56^+$, lymphocyte count	After intervention: ↑ IFN-γ production**, ↓ lymphocyte count*, ↑ IL-1β production* Follow-up: ↑ whole blood cell counts**, ↑ lymphocytes**, ↓↑ IFN-γ production**	Overall: NKCC, $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+/CD56^+$. After intervention: whole blood cell counts Follow-up: IL-1ß production
Smith, et al. (1992).	Varicella Zoster skin test → induration size, varicella zoster antigen response	In PBMC: PHA → LPR	-	Before intervention (before and after skin testing), after intervention at 24 hrs and 48 hrs	-	After 24-hrs: ↑ induration size*	Overall: LPR to PHA, varicella zoster antigen response After 48 hrs: induration size
Solberg, et al. (1995).	-	-	Treadmill exercise test	Before and after physical stress test	$CD2^+$, $CD4^+$, $CD8^+$ cell counts	↓ $CD8^+$ cell count*	$CD2^+$, $CD4^+$ cell counts

	Challenges			Timing specifications	Other immune assays	Effects	
Study	***In vivo***	***In vitro* stimulus → target**	**Psycho-physiological**	**Measuring time points**	**Outcome parameters**	**Present**	**Absent**
Stetler, et al. (2006).	Influenza vaccine → antibody response to vaccine	-	-	Before intervention, 1 and 3 months after vaccination	-	↓ Antibody response to vaccine*	
Vedhara, et al. (2003).	Influenza vaccine → Response to vaccine	-		Before vaccination, after vaccination	-	↑ Clinically appropriate response to vaccination**	
Weinman, et al. (2008).	Skin biopsy at the inner aspect of the upper non-dominant arm → wound diameter	-	-	7, 14, and 21 days after skin biopsy	-	14 and 21 days after skin biopsy: ↓ Wound diameter*	7 days after skin biopsy: wound diameter
Whitehouse, et al. (1996).	-	In PBMC: Con A → LPR PHA → LPR PWM → LPR K562 → NKCC	Exams (acute stress)	Before intervention, after intervention, 3 weeks after intervention (during final exams), 6 weeks after intervention (3 weeks after exams)	Activated T-cells, B-lymphocyte counts, white blood cells, granulocytes, NK cell count	After intervention: ↓ Activated T –cells**	Overall: B-lymphocyte counts, white blood cells, granulocytes, CD56, LPR to Con A / PHA / PWM, NKCC. At follow-up: activated T-cells
Witek-Janusek, et al. (2008).	-	In PBMC: PHA / PMA → IFN- γ, IL-4, IL-6 production K562 → NKCC	-	Before intervention, 1 month after the start of the intervention, after intervention, 1 month after intervention	CD3, CD16, CD19, CD56, CD4, CD8, CD16/CD56	Overall: ↑ NKCC*, ↑ IFN-γ production*, ↓ IL-4 production*, ↓ IL-6 production* After intervention and 1 month after intervention: ↓ IL-10 production*.	Overall: CD3, CD16, CD19, CD56, CD4, CD8, CD16/CD56 1 month after start of the intervention: IL-10 production
Witt (2003).	Histamine provocation, skin prick testing → wheal area	-	-	Before intervention (before start of birch pollen season), after intervention (at start of birch pollen season), 14 weeks after intervention (at end of birch pollen season)	-	Overall: ↓ Wheal area*	
Zachariae, et al. (1989).	Skin prick in the upper dermal layer on the ventral side of both forearms → wheal area, flare size, palpable induration	-	-	Before and after intervention	-	Type I reaction: ↓ flare size* Type IV reaction: ↓ palpable induration**, ↓ flare size*	Type I reaction: wheal area

	Challenges			Timing specifications	Other immune assays	Effects	
Study	*In vivo*	*In vitro* stimulus → target	Psycho-physiological	Measuring time points	Outcome parameters	Present	Absent
Zachariae, et al. (1990).	-	In whole blood: K562 → NKCC	-	Before intervention, 7 days after the 1st intervention session; 10 days after the 1st intervention session	Leukocyte differential count, leukocyte count	↑ NKCC*	Leukocyte differential count, leukocyte count
Zachariae, et al. (1994).	-	Study 1: In PBMC: PHA → LPR Con A → LPR PWM → LPR FMLP → Monocyte chemotaxis	-	Study 1: At the start and end of the 1st, 8th, and 15th day, and 36 days after the start of the intervention	Study 1: Monocyte chemo taxis, lymphocyte production	Study 1: Imagery group: ↑ monocyte chemo taxis at day 8*, ↑ LPR to PHA at day 8*, ↓ LPR to PWM at day 8 and 15** Relaxation group over time: ↑ monocyte chemotaxis at day 8*, ↓ LPR to PWM at day 8*	Study 1: Imagery group: LPR to Con A Relaxation group: LPR to PHA / Con A
	-	Study 2: In PBMC: K562 → NKCC	-		Study 2: -	Study 2: -	Study 2: NKCC
Zautra, et al. (2008).	-	In PBMC: LPS → IL-6	-	Before and after intervention	-	CBT group: ↓ IL-6 production*	Mindfulness meditation and emotion regulation group: IL-6 production

Note. PBL = Peripheral Blood Leukocytes; CBT = Cognitive Behavioral Therapy; CCR = C-C Chemokine Receptor; CD = Classification Determinant; CMV = Cytomegalovirus; Con A = Concanavalin A; COX = Cyclooxygenase; CPT = Cold Pressor Test; CRP = C-reactive Protein; CXCR = CXC Chemokine Receptor; DTH = Delayed Type Hypersensitivity; EBV-VCA = Epstein-Barr Virus Viral Capsid Antigen; EBV-EA = Epstein-Barr Virus Early Antigen; FMLP = Formyl-Methyl-Leucinc Peptide; HHV = Human Herpes Virus; HIV = Human Immunodeficiency Virus; hrs = hours; HSV = Herpes Simplex Virus; Ig = Immunoglobulin; IL = Interleukin; IFN = Interferon; KLH = Keyhole Limpet Hemocyanin; LAK = Lymphokine Activated Killer Cell; LGL = Large Granular Lymphocyte; LPR = Lymphocyte Proliferative Response; LPS = Lipopolysaccharide; min = minutes; MLR = Mixed Lymphocyte Responsiveness; N/A = Not Available; NKCC = Natural Killer Cell Cytotoxicity; PBMC = Peripheral Blood Mononuclear Cells; PHA = Phytohemagglutinin; PMA = Phorbol Myristate Acetate; PWM = Pokeweed Mitogen; RIPK = Receptor-interacting Protein Kinase; RANTES = regulated upon activation, normal T-cell expressed and presumably secreted; ROM = Reactive Oxygen Metabolite; SDF = stromal derived factor; T_{DH} cells = T Delayed Hypersensitivity cells; Th = T helper; TNF = Tumor Necrosis Factor; TSST = Trier Social Stress Test; * = $p \leq .05$; ** = $p \leq .01$.

Note 2. In the last two columns, an effect is specified as present when the intervention condition significantly differed from the control condition after the intervention. When more than two time points (i.e., before and after intervention) were taken into account, the time point on which an effect was found is specified. The direction of the effects is specified by using arrows and represent the outcomes for the intervention condition in perspective to the control condition. When no significant differences between the intervention and control condition were found, the outcome parameters are described in the column "absent".

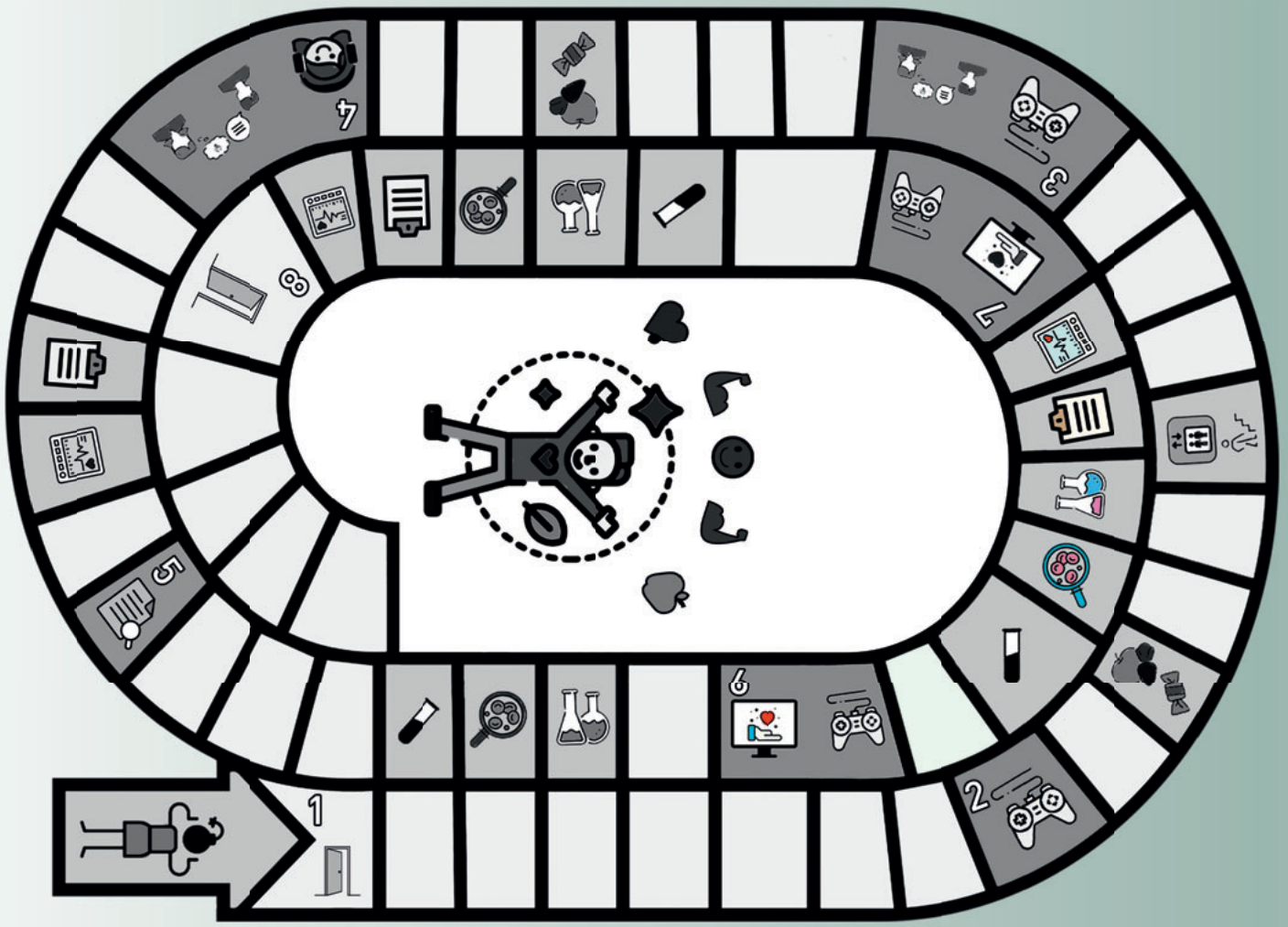


Supplemental Figure 2. Risk of bias graph.

Judgements of the independent review authors about the separate risk of bias items presented as percentages across all included studies.

Supplemental Figure 3. Risk of bias summary.

Judgments of the independent review authors about the separate risk of bias items for each of the included study presented as low, high or unclear.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