Effects of Brief Mood-Improving Interventions on Immunity. A Systematic Review & Meta-Analysis

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Abbreviated running title: Brief Interventions that Induce Improvements in Mood: Effects on Immunity

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Abstract

Objectives

Positive mood has been associated with enhanced immune function. Interventions that improve mood could, therefore, provide a mechanism for optimising 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 25th July 2018. We identified 42 interventions suitable for inclusion, six of which were tested in multiple sub-populations. Random effects meta-analyses were performed for pre-post experimental group immune outcomes measured in at least 5 intervention studies.

Results

While interventions were heterogeneous, 81% resulted in a statistically significant change in at least one immune parameter following the positive mood intervention for one or more of the sub-populations 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 IL-6 production (g=0.12) and non-significant effects on NK cell activity (g=0.15).

Conclusions

The current literature provides modest evidence 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.

Keywords: Positive affect, immunity, intervention, positive mood, systematic review, meta-analysis

Abbreviations: s-IgA = Secretory immunoglobulin serotype A; MeSH = Medical subheadings; EPHPP = Effective Public Health Practice Project; IL-6 = Interleukin 6; NK = Natural killer cell; RCT = Randomised Controlled Trial

1. 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). While 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, joy) and dispositions can beneficially contribute to health outcomes including those which may have immunological aetiologies (2–7).

Multiple biological pathways between sub-cortical 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 (sIgA) 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 boosting positive affect could potentially act as an ‘immune enhancer’ in clinically meaningful ways.

While 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. While 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 healthcare providers.

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 prior to 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 healthcare settings where interactions are also, generally, brief.

In this paper we systematically review and meta-analyse the evidence that mood improvements resulting from brief, single session interventions are related to immunity. The primary aims of this review are to (1) identify the size and nature of the existing literature base relating to brief mood-enhancing interventions and immunity, (2) to assess the quality of this literature, and (3) examine the impact of mood enhancing interventions on immunological outcomes.

2. Method

2.1. Search Strategy

Systematic electronic searches were conducted of EMBASE, PsycINFO, PsycARTICLES, and MEDLINE from earliest records to 25th July 2018. A comprehensive overview of the search terms employed can be found in the supplementary appendix. In brief, the searches included synonym terms relating to (1) intervention/manipulation (e.g., *modulat*, induc*)* (2) mood (e.g., *emotion*, happ*),* and (3) immunity (e.g., *immun*, cytokine*).* Medical subheadings (MeSH) 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.

2.2. 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 pre- and post-intervention for a study to be included, with any later follow-ups also included. Studies which 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 following 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, distraction from prior stressor). Negative mood inductions and 'neutral' interventions acting as a control group (e.g., rest, reading) were not included. Studies focusing exclusively on endocrine outcomes (e.g., cortisol), animal studies, and conference proceedings were also excluded.

2.3. 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, as 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 randomised controlled trials (29).

2.4. 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, NJ; Internet: https://www.meta-analysis.com/). Due to 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 5 interventions [secretory IgA (s-IgA) concentration, natural killer cell activity (NK activity), and interlukin-6 (IL-6) production]. Population subgroups (e.g., carers, patients) were included separately in meta-analyses when presented as such in the published article. Where available, unadjusted pre/post-vaccination means, standard deviations, and pre-post correlations were preferentially used to calculate effect sizes. However, where these were not available: change scores, and paired *p* and t-test values (with no-covariates included) were also used. As pre-post correlations are rarely reported, where pre-post correlations were unknown we calculated effect sizes assuming a positive correlations of .25, .5, and .75 as described by Norris et al. (30). As these assumptions yielded very similar meta-analytic effect size estimates, the findings reported in this paper are based on a correlation of .5 (analyses assuming correlations of .25 and .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 Cochran's *Q* test with significant heterogeneity indicated by a *p*-value <.1, and the percentage of no-chance heterogeneity assessed using the I^2 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).

3. Results

3.1. Study Selection Process

The flow of studies through the review process is presented in Figure 1**Error! Reference source not found.**. 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 sub-populations (e.g., older vs younger adults). The most common reasons for exclusion from the 168 articles identified for full-text examination were the intervention lasting longer than a single session (n = 47) and not including an appropriate manipulation check (n = 30).

[INSERT FIGURE 1 HERE]

3.2. Studies Characteristics

The most common origin of studies was the USA (k=13), with a large number from Japan (k=12). The remaining studies were conducted in the UK (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 randomised order. Eleven studies were randomised controlled trials 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.

3.3. 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 odours (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). The majority of 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 mins, median= 40 mins).

3.4. Quality Assessments

A summary of quality assessment ratings for each of the EPHPP individual domain and global quality ratings are 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 selection bias was an issue for nearly all studies. In the selection bias domain, all but one study was classified as weak, indicating 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, eleven studies where classified as strong (indicating 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 regards to the data collection method, 10 studies were

categorised as strong - meaning that outcome measures (immune) had been demonstrated as both valid and reliable – with the remaining 21 studies classified as moderate due to 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 three as weak.

3.5. 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 vs younger adults). Of these, a statistically significant improvement from pre- to post-intervention 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 back rub (35)] 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 odour (36)] showed a decrease in positive affect following 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 secretory IgA (s-IgA) concentration/flow rate (i=17), natural killer (NK) cell count or activity (i=12) and Interleukin-6 (IL-6) production (i=10). Secretory IgA is a class of antibody, most typically measured in saliva, which

acts as a first line of defence against pathogens on mucosal surfaces. Natural killer 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. Interleukin-6 (IL-6) is a pro-inflammatory 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 summarises 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 which showed non-significant 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 Canadia testing compared to controls, indicating a more blunted immune response.

Of the 17 interventions in which s-IgA was measured, fourteen resulted in a significant increase in s-IgA concentration or flow rates in all sub-populations examined (33,37–44), two reported no effects (37,45), and one demonstrated an increase in s-IgA concentration but did not assess the significance of the change (45). 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 some aspect of NK cell count or activity was measured, findings were less consistent: with six interventions demonstrating increased NK cell counts or activity following the intervention (46–50), five finding no effect (32,51–54), and one 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 (55). When comparing interventions which 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 sub-population showed significant increases in IL-6 following the intervention (32 - older adults), with the remainder showing no significant changes (32 - younger adults,36,56–60).

3.6. Meta-Analyses of Immunological Outcomes

Broadly speaking, meta-analyses mirrored the findings of the above narrative synthesis. For s-IgA concentration outcomes, 12 pre- to post-intervention comparisons (including general population and cancer patient sub-populations from Noto et al. 2010) had sufficient data for inclusion in a meta-analysis (see Figure 2). Pooling these

in a random effects meta-analysis produced an overall significant medium positive effect size of 0.65 (95%CI: 0.50, 0.80) indicating greater s-IgA concentrations post-intervention. Examination of Cochran's Q and the I^2 Statistic indicated low but non-significant heterogeneity [$Q(11) = 12.37$, $p = .337$; $I^2 = 11.04\%$].

[INSERT FIGURE 2 HERE]

For NK cell activity, effect sizes could be calculated for seven pre- to post-intervention comparisons (including younger and older adult sub-populations from Koyama et al. 2009). Pooling these in a random effects meta-analysis produced a small but non-significant positive effect size of 0.15 (95%CI: -.05, .34) indicating greater, but not significantly greater NK cell activity post-intervention (see Figure 3). Examination of Cochran's Q and the I^2 Statistic indicated low but non-significant heterogeneity [$Q(6) = 8.03$, $p = .24$; $I^2 = 25.3\%$].

[INSERT FIGURE 3 HERE]

For IL-6 production, 11 pre- to post-intervention comparisons (including carer, patient and bereaved carer sub-populations from Fancourt et al. 2016, primed and unprimed sub-populations from Kiecolt-Glaser et al. 2008, and younger and older adult sub-populations from Koyama et al. 2009) had sufficient data for inclusion in a meta-analysis (see Figure 4). Pooling these in a random effects meta-analysis produced a small but significant positive effect size of 0.12 (95%CI: .02-.23) indicating greater IL-

6 production post-intervention. Examination of Cochran's Q and the I^2 Statistic indicated moderate, but not significant heterogeneity [$Q(10) = 17.03$, $p = .074$; $I^2 = 41.29\%$]. Examination of the forest plot suggested a comparatively high effect size for the only older adult sub-population included in the analysis (Koyama et al. 2009) 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 .01-.17) with no notable heterogeneity [$Q(9) = 7.70$, $p = .57$; $I^2 = 0\%$].

[INSERT FIGURE 4 HERE]

3.7. 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 outcomes above found to significantly change from pre- to post-intervention 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 supplementary appendix. In brief, meta-regression analyses showed that for s-IgA concentration, when one outlying study (61) 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 following interventions which 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.

4. 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 below, with areas in need of further research highlighted.

4.1. 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 eleven studies were RCTs. In contrast, the majority adopted crossover or cohort designs, which are generally considered less rigorous tests of an intervention than RCTs (62). Sample sizes were, in general, relatively small – indicating the need for larger RCTs in the future. Nearly all studies only examined immune changes immediately post-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, 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 following stress exposure (63). However, whether similar persistence of immune effects accompany the induction of positive mood remains unclear.

4.2. 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., odour generation) or skilled facilitators (e.g., massage, 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 programme, mental recall of positive memories, and listening to music may have greater implementation potential due to their comparative ease of administration.

The vast majority of studies included in this review focused on healthy young adults, with only one study explicitly recruiting older adults (32) and one including children (33). Further, only a handful of studies focused on those with significant medical

illnesses, primarily cancer. Given the relative immunological naivety of children compared to young adults, the wide-ranging decline in immunological competence known to occur in later life (64,65) and immune alterations observed in some chronic illnesses (66), it is unclear whether any immune enhancing effects of brief mood improving interventions shown in younger adults are generalisable to these populations. Indeed, in the one study that compared older and younger adult cohorts (32), only the older adults saw immunological benefits following 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.

4.3. 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 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, due to 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 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 (67–69) appear to have had little impact in this area thus far.

Looking beyond the included studies, it is noteworthy that a 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 (70).

4.4. Impact of Brief Interventions on Immunity

Despite the weaknesses in this literature, the substantial majority (34 of 42; 81.0%) of interventions included in this review were associated with at least one significant immunological change in one or more of the sub-populations assessed. Two interventions that actually resulted in a reduction in positive affect, correspondingly also resulted in blunted immune responses compared to controls. This consistency, regardless of the specific intervention employed, 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 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 following 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 (71) considered non-specific markers of immunity. While some of the immune parameters measured form part of the cascade of innate and adaptive immunological processes that follow antigenic challenge (e.g., cytokines, NK cells), due to the redundancy and complexity inherent in the immune system, it is hard to determine the importance of changes to individual components measured in isolation, to real-world clinical outcomes. While increases in non-specific aspects of immunity may be indicative of enhanced in-vivo immune responses to challenge (72,73), there is a clear need for future research to move away from a reliance on non-specific indices of immunity.

4.5. Strengths and Limitations

The present review did not exclude studies on the basis of design-type to maximise the identification of relevant research evidence and the quality of included studies were assessed using an established standardised tool. However, this review did not seek to retrieve and include relevant unpublished articles (the so-called grey 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. Yet, 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 positive mood improvements, as well as immune function changes (see 74). However, in this review we excluded such interventions to minimise the potential confounding effects of the physiological exertion on the relationship between positive mood changes and immunity. Yet, while most interventions were fairly passive (e.g., watching a comedy film) some included interventions involving some degree of physical effort (e.g., choir singing, 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, increased bodily movement).

5. Concluding Remarks

Brief interventions that improve mood can influence some immune parameters in ways which 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. As the literature reviewed was rated as low-to-moderate quality and somewhat heterogeneous, the degree of confidence in the pooled findings are 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.

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Figure Captions

Figure 1: PRISMA flow diagram of study selection process

Figure 2: Forest Plot of Meta-analysis for Pre-Post Effect Sizes on S-IgA

Figure 3: Forest Plot of Meta-analysis for Pre-Post Effect Sizes on NK Cell Activity

Figure 4: Forest Plot of Meta-analysis for Pre-Post Effect Sizes on IL-6 Production

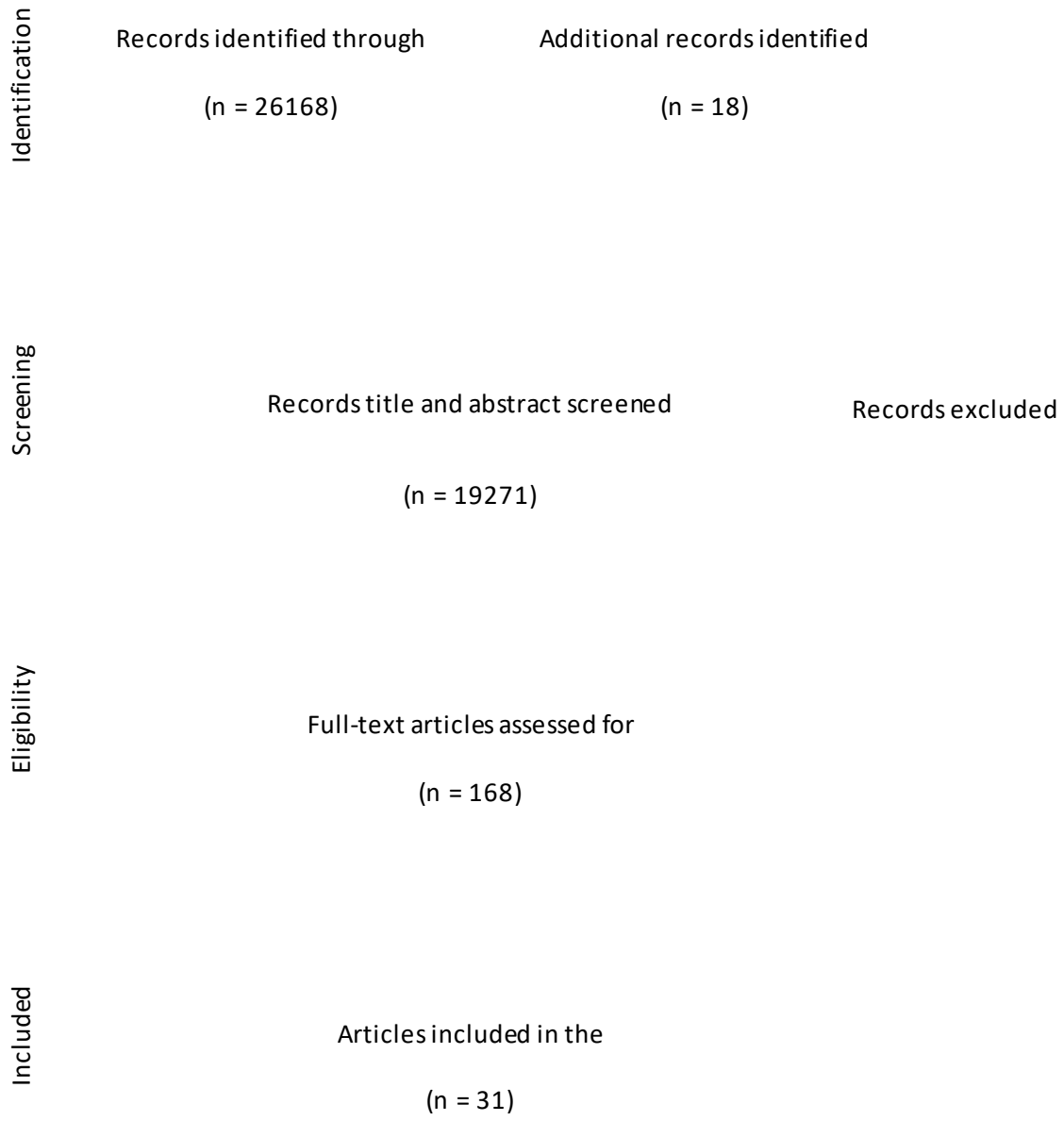

Figure 1: PRISMA flow diagram of study selection process

Studyname	Intervention	Outcome	Statistics for each study			
			Hedges's g	Lower limit	Upper limit	Standard error
Burns et al. 2001	Music - Listening	S-IgA	0.942	0.172	1.712	0.393
Donoyama & Shibasaki 2010	Massage - Freshman	S-IgA	1.012	0.221	1.803	0.403
Donoyama & Shibasaki 2010	Massage - Instructor	S-IgA	0.460	-0.196	1.115	0.335
Donoyama & Shibasaki 2010	Massage - Sophomores	S-IgA	1.153	0.317	1.989	0.426
Donoyama et al. 2010	Massage	S-IgA	1.072	0.459	1.685	0.313
Noto et al. 2010 - Cancer Patients	Massage	S-IgA	0.422	0.052	0.793	0.189
Noto et al. 2010 - General	Massage	S-IgA	1.106	0.485	1.727	0.317
Pawlow & Jones 2005	Relaxation Training	S-IgA	0.667	0.334	1.000	0.170
Rider et al. 1990	Music + Immune Imagery	S-IgA	0.365	0.068	0.663	0.152
Rider et al. 1990	Music + Unguided Imagery	S-IgA	0.564	0.190	0.939	0.191
Yamamoto & Nagata 2011	Footbath	S-IgA	0.830	0.126	1.534	0.359
Groer et al. 1994	Back Rub	S-IgA	0.711	0.212	1.210	0.254
			0.646	0.497	0.796	0.076

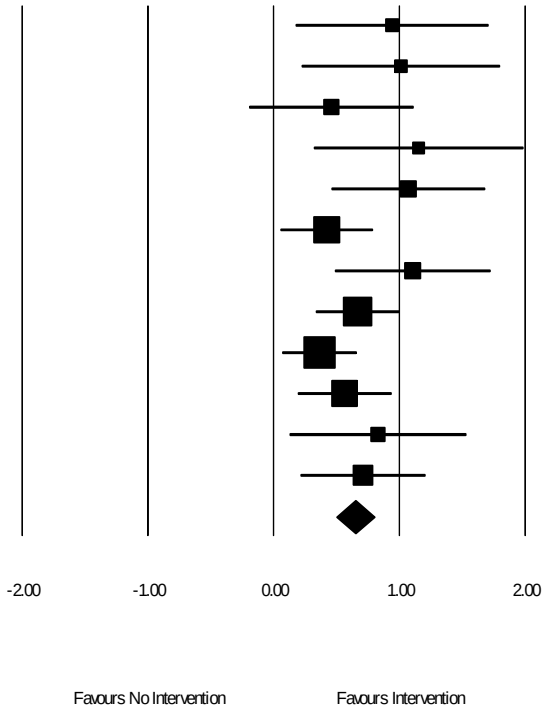

Figure 2: Forest Plot of Meta-analysis for Pre-Post Effect Sizes on S-IgA

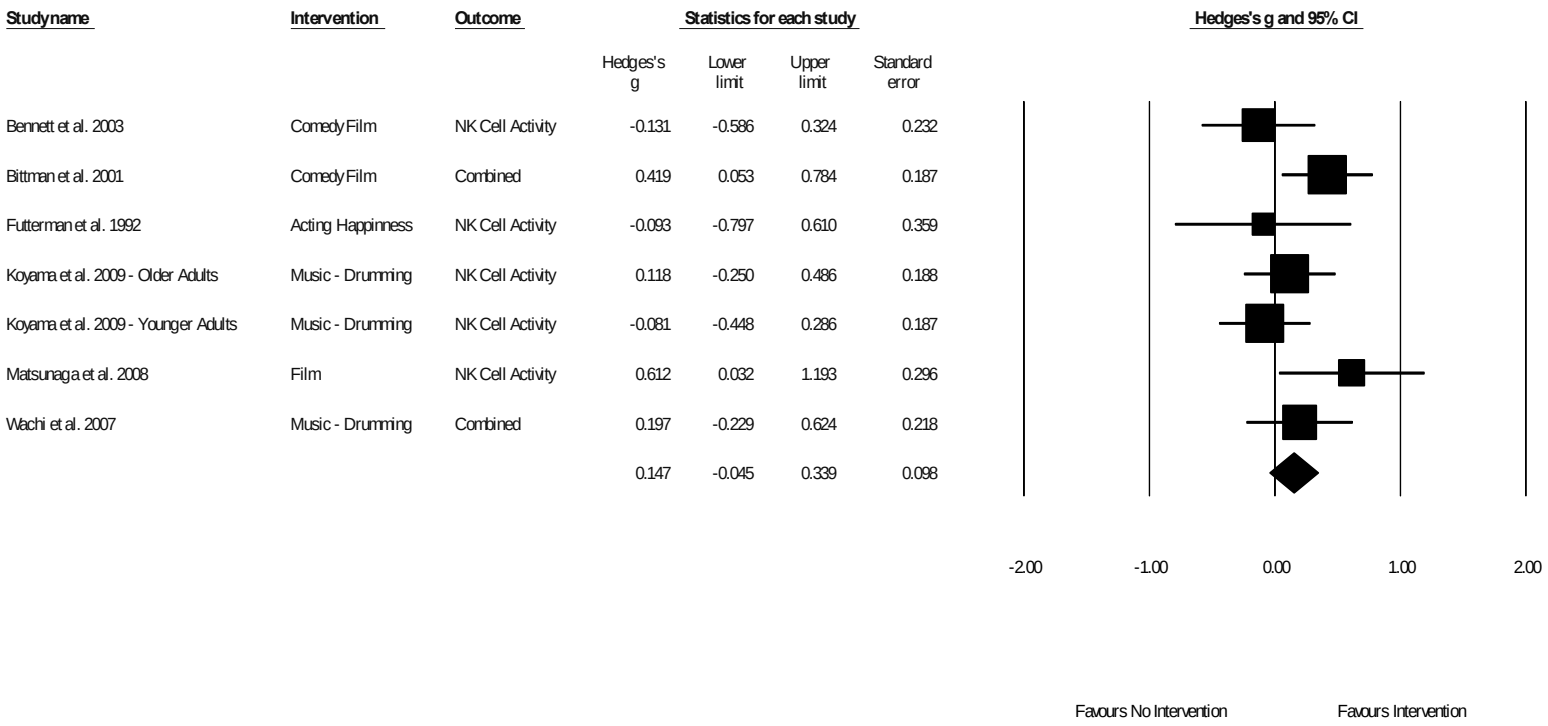

Figure 3: Forest Plot of Meta-analysis for Pre-Post Effect Sizes on NK Cell Activity

Study name	Intervention	Outcome	Hedges's g	Lower limit	Upper limit	Standard error
Fancourt et al. 2016 - Bereaved Carers	Singing	IL-6	0.186	-0.055	0.426	0.123
Fancourt et al. 2016 - Cancer Patients	Singing	IL-6	0.044	-0.217	0.305	0.133
Fancourt et al. 2016 - Carers	Singing	IL-6	0.020	-0.208	0.249	0.117
Kiecolt-Glaser et al. 2008 - Primed Participants	Odour - Lavender	IL-6	0.159	-0.026	0.344	0.095
Kiecolt-Glaser et al. 2008 - Primed Participants	Odour - Lemon	IL-6	0.170	-0.085	0.424	0.130
Kiecolt-Glaser et al. 2008 - Unprimed Participants	Odour - Lavender	IL-6	0.200	-0.019	0.418	0.112
Kiecolt-Glaser et al. 2008 - Unprimed Participants	Odour - Lemon	IL-6	-0.031	-0.241	0.180	0.108
Koyama et al. 2009 - Older Adults	Music - Drumming	IL-6	0.773	0.345	1.201	0.218
Koyama et al. 2009 - Younger Adults	Music - Drumming	IL-6	-0.197	-0.581	0.186	0.196
Matsunaga et al. 2011a	Odour	IL-6	0.309	-0.096	0.713	0.206
Mittwoch-Jaffe et al. 1995	Comedy Film	IL-6	0.032	-0.214	0.278	0.125
			0.124	0.022	0.226	0.052

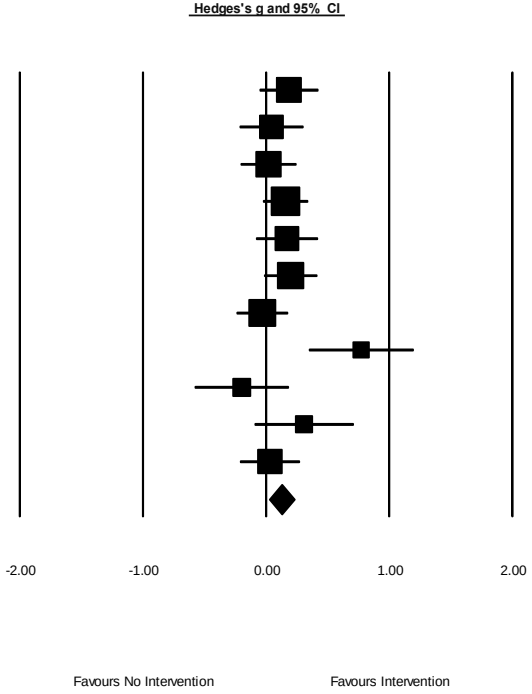

Figure 4: Forest Plot of Meta-analysis for Pre-Post Effect Sizes on IL-6 Production

Table 1: Summary of quality assessments

Authors (Year of publication)	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	Global Rating
Bartlett et al. (1993)	Weak	Strong	Weak	Moderate	Moderate	Strong	Weak
Bennet et al. (2003)	Weak	Strong	Weak	Moderate	Strong	Strong	Weak
Bittman et al. (2001)	Weak	Strong	Weak	Moderate	Moderate	Strong	Weak
Burns et al. (2001)	Weak	Moderate	Strong	Moderate	Strong	Strong	Moderate
Donoyama et al. (2010)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Donoyama & Shibasaki (2010)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Fancourt et al. (2016)	Strong	Moderate	Strong	Moderate	Strong	Strong	Strong
Futterman et al. (1992)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Futterman et al. (1994)	Weak	Moderate	Weak	Moderate	Moderate	Strong	Weak
Groër et al. (1994)	Weak	Strong	Weak	Moderate	Moderate	Weak	Weak
Hall et al. (1992)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Hewson-Bower & Drummond (1996)	Weak	Strong	Strong	Moderate	Strong	Strong	Moderate
Jung et al. (2006)	Weak	Strong	Weak	Moderate	Moderate	Strong	Weak
Kiecolt-Glaser et al. (2008)	Weak	Moderate	Strong	Moderate	Moderate	Weak	Weak
Kimiata (2004)	Weak	Moderate	Strong	Moderate	Strong	Strong	Moderate
Knapp et al. (1992)	Weak	Moderate	Weak	Moderate	Moderate	Strong	Weak

Authors (Year of publication)	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	Global Rating
Koyama et al. (2009)	Weak	Moderate	Weak	Moderate	Moderate	Strong	Weak
Labott et al. (2010)	Weak	Strong	Strong	Moderate	Strong	Strong	Moderate
Lefcourt et al. (1990)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Matsunaga et al. (2008)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Matsunaga et al. (2011a)	Weak	Moderate	Strong	Moderate	Strong	Strong	Moderate
Matsunaga et al. (2011b)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Matsunaga et al. (2013)	Weak	Moderate	Strong	Moderate	Strong	Strong	Moderate
Mittwoch-Jaffe et al. (1995)	Weak	Strong	Strong	Moderate	Moderate	Strong	Moderate
Noto et al. (2010	Weak	Moderate	Strong	Moderate	Strong	Weak	Weak
Pawlow & Jones (2005)	Weak	Strong	Strong	Moderate	Moderate	Strong	Moderate
Rider et al. (1990)	Weak	Strong	Strong	Moderate	Strong	Strong	Moderate
Strauman et al. (2004)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Takahashi et al. (2001)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Wachi et al. (2007)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Yamamoto & Nagata (2011)	Weak	Strong	Strong	Moderate	Moderate	Strong	Moderate

Table 2: Summary of Included Studies

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. (1993) USA RCT	General Population 20, NR (NR), NR, 50%	Listening to Music, 15 mins, 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 hours post-intervention. Significant increase in IL-1 in those listening to music. No significant change in IL-1 among those in control group.
Bennett et al. (2003) USA 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 to the control.
Bittman et al. (2001) USA RCT	General Population 60; NR (NR); NR, 48%	Drumming; 60 mins; Group	NK cell activity x4 concentrations; Lymphokine-activated Killer Activity with IL-2 x2 concentrations Lymphokine-activated Killer Activity with IFN-γ x2 concentrations;	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 to 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

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
			Baseline for IFN-γ stimulated x2 concentrations; IL-2; IFN-γ; Leukocyte count (13)	Lymphokine-activated Killer Activity with IFN-γ at both concentrations. There were no significant differences between groups in other immune outcomes.
Burns et al. (2001) UK Crossover	Cancer Patients, 9, NR (NR), NR, 67%	a) Listening to live music, 60 mins, Group b) Music improvisation, 90 mins, Group	S-IgA concentration; S-IgA secretion rate (2)	S-IgA concentration and secretion rates increased significantly after intervention (a). No significant differences in immune outcome measures for intervention (b).
Donoyama et al. (2010) Japan Crossover	General Population (Post-Menopausal Women), 17, 54.4 (2.1), NR, 100%	Massage, 40 mins, 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 & Shibasaki (2010) Japan Crossover	General Population (Post-Menopausal Women), 10, NR (NR), NR, 100%	a) Massage (by student with 6 months training), 40 mins, Individual b) Massage (by student with 15 months	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.

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
		training), 40 mins, Individual c) Massage (by instructor with >15 years experience), 40 Mins, Individual		
Fancourt et al. (2016) UK 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 mins, 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. (1992) USA Crossover	Method Actors 5, 31.2 (NR), 25-38, 40%	Acting out a happiness scenario, <120 mins, 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.

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. (1994) USA Crossover with 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 mins, Individual b) Acting out a relaxed happiness scenario; <120 mins, Individual	NK cell cytotoxicity; Lymphocyte response PHA x 2 concentration; CD-3%; CD-4%; CD-8%; CD-16%; CD-56%; CD57% (9)	Note: This study also included two 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.

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
Groër et al. (1994) USA RCT	General population middle-aged and older adults 32, 65.8 (NR), 44- 77, 68.8%	Back rub, 10 mins, Individual	S-IgA concentration; S-IgA secretion rate (2)	Note: Control condition comprised 10 mins of bed rest. S-IgA concentration increased significantly more in those who received the back rub compared to controls. S-IgA secretion rate increased in both groups but did not significantly differ between groups.
Hall et al. (1992) USA Cohort	General Population 19, 51 (NR), 22- 81; 36.8%	Relaxation with immune based imagery, 45 mins, 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.

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**
Hewson-Bower & Drummond (1996) Australia RCT	Children with and without recurrent URTIs 90, Children with URTIs: 9.4 (NR), 8-12, 44.4% Healthy Children: 9.7 (NR), 8-12, 44.6%	a) Relaxation, 25 mins, Group b) Relaxation with immune suggestions, 25 mins, Group	S-IgA concentration; S-IgA:albumin ratio (2)	Note: Control condition comprised group conversation. S-IgA concentration increased significantly immediately following both relaxation conditions compared to controls. No effects on S-IgA:Albumin Ratio in any condition. No differences between healthy children and those with recurrent URT infections.
Jung et al. (2006) South Korea RCT	General population 24, Qi touch therapy + rest group: 25 (5), NR, 0% Qi non-touch therapy + rest group: 26 (3), NR, 0%	a) Qi touch therapy + rest, 70 mins, Individual b) Qi non-touch therapy + rest, 70 mins, Individual	Superoxide anions produced by neutrophils; NK cell cytotoxicity (2)	At 10 mins following both interventions NK cytotoxicity was significantly increased from pre-intervention. At 1-hour post-intervention, this remained significant only in Qi non-touch therapy + rest condition. Superoxide anion production by neutrophils was increased in Qi non-touch therapy + rest condition at 10 minutes post-intervention from pre-intervention but not at 1 hour. No change in superoxide anion production at any time point in Qi-touch therapy + rest condition.

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
Kiecolt-Glaser et al. (2008) USA Crossover with additional randomization	General population 56, 24.4(6.1), 18-43, 62.5%	a) Primed exposure to lemon odour, 75 mins, Individual b) Unprimed exposure to lemon odour odour, 75 mins, individual c) Primed exposure to lavender odour , 75 mins, Individual d) Unprimed exposure to lavender odour , 75 mins, 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)	Note: this study also included a distilled water control condition and exposure to a stressor post-intervention. Smaller maximum and 72-hour wheal size following delayed hypersensitivity to Candida test in those exposed to lavender odour. No significant changes to any of the other immune outcomes measured following the interventions.

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 (2004) Japan Crossover	Patients with atopic dermatitis having atopic kertoconjuctivitis 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 kertoconjuctivitis, there was a significant decrease in Japanese cedar pollen-specific IgE and IgG4 and significant increase in IgA immediately following and at 2 hours following the intervention compared to baseline, but not at 4 hours.

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
Knapp et al. (1992) USA Cohort	General population 20, NR (NR), NR, 50%	Mental recall and discussion of positive life interval with interviewer, NR, Individual	Lymphocyte response to PHA x 2 concentration; Lymphocyte response to Con-A; Lymphocyte response to Pokeweed; NK cell activity, leukocyte count, PMN cells, lymphocytes, monocyes, CD-3%; CD-4%, CD-8% (12)	Significant increase in lymphocyte response to low dose PHA immediately following intervention. No effects on other immune outcomes.

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
Koyama et al. (2009) 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 mins, Group	NK cell activity; leukocyte count; 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.

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
Labott et al. (1990) USA RCT with Crossover	Students who considered themselves expressive 39, 21.6 (NR), 18-40, 100%.	a) Expressing emotions during a Comedy Film, 28 mins, NR b) Inhibiting emotions during a comedy Film, 28 mins, NR	S-IgA concentration (1)	Note: A negative mood induction condition (negative film) and control group (two 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 emotions condition, there were no differences in S-IgA concentration from before to after the comedy film.
Lefcourt et al. (1990) Canada Cohort	Students 41, NR (NR), NR, 48.7%	Comedy Audiotape, 30 mins, Group	S-IgA Concentration (1)	Significant increase in S-IgA concentration from before to immediately following intervention.
Matsunaga et al. (2008) Japan Crossover	General population 12, NR (NR), 20-29, 0%	Film containing actresses chosen by participants as attractive, 4 mins, 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 post intervention. No change from before to after control film.

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. (2011a) Japan Crossover	General population 23; NR (NR), 21-38, 78.3%	Odour selected by participant to invoke positive autobiographical memory, 90 seconds, Individual	IL-2; IL-4; IL-6; IL-10; TNF-α (5)	Note: A neutral control odour condition was included as a condition in this study. No significant changes on any immune outcome from before to after odour intervention. IL-2 was significantly lower immediately following self-selected odour intervention compared to immediately following control odour.
Matsunaga et al. (2011b) Japan Crossover	Romantic Couples 14, NR (NR), 21-38, 50%	Kissing and hugging partner, 60 mins, 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.
Matsunaga et al. (2013) Japan Crossover	General population who self-report the ability to retrieve autobiographical odour memories 10, NR (NR), 20-35, 70%	Odour selected by participant to invoke positive autobiographical memory, 3 x 60 seconds, Individual	IL-2, IL-5, IL-6, IL-10, TNF-α, IFN-γ (6)	Note: A neutral control odour condition was included in this study. Significant decreases in TNF-α and IFN-γ immediately following self-selected odour compared to immediately following control odour. No differences in other immune outcomes.

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**
Mittwoch-Jaffe et al. (1995) Israel RCT	General Population 123, NR (NR), NR, 52%	Comedy film, 45 mins, 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, IL-3, and significant decrease in TNF-α from before to immediately following comedy film intervention. No changes on IL-1b and IL-6.
Noto et al. (2010) Japan Crossover & Cohort	a) General Population, 15, 21.3 (1.1), NR, NR b) Cancer Inpatients receiving chemotherapy, 29, 64.6 (12.8), NR. 38%	Leg massage, 20 mins, 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 & Jones (2005) USA RCT	Students, 55, 24.0 (7.5), 19-57, 53%	Abbreviated progressive relaxation training, 25 mins, 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 mins post-intervention.

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**
Rider et al. (1990) USA RCT	Students, 45, NR (NR), NR, 56%	a) Listening to music with immune imagery suggestions, 17 mins, Individual b) Listening to music with unguided imagery suggestions, 17 mins, Individual	S-IgA concentration (1)	Note: Control group sat quietly for a matched time period. S-IgA concentration significantly increased in both intervention (a) and (b) above controls, but there was no significant difference between (a) and (b).

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**
Strauman et al. (2004) USA Crossover	Students with high and low self-discrepancy 32, Low-discrepant: 19.51(1.58), NR, 100% High-discrepant-19.87 (1.41), NR, 100%	Writing about self-congruencies, 20 mins, Individual	Leukocyte count; lymphocyte count; lymphocyte %; neutrophil count; neutrophil %; CD-3 count; CD-3 %; CD-4 count; CD-4 %; CD-8 count; CD-8%; NK cell count; NK cell %; CD-19 count; CD-19%; NK cytotoxicity 3x concentration; lysis per 1000 NK cells (19)	Note: A negative mood induction condition (writing about self-discrepancies) and control group (two 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 following self-congruency intervention compared to immediately following control condition. NK cell count increases were significantly higher in high discrepant compared to low discrepant students. In high discrepant students, lysis per 1000 NK cells was also significantly lower immediately following self-congruency intervention compared to immediately following control condition.

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
Takahashi et al. (2001) Japan Crossover	General Population 21, NR (NR), 18-26, 0%	Comedy film, 75 mins, NR	NK cell activity 2x 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 following control film. No effects on other immune outcomes reported.
Wachi et al. (2007) Japan Crossover	Yamaha Employees 40, 38.4 (8.4), NR, 0%	Drumming, NR, Group	NK cell activity 3x concentration; CD-56%, Leukocyte count (5)	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 & Nagata (2011) Japan RCT	Cancer Patients, 18, Experimental: 64.9 (5.8) Control (64.2 (8.9), NR, 33%	Footbath, 30 mins, Individual	S-IgA concentration (1)	Note: Controls rested for a matched time period. Significant increase in S-IgA concentration from pre- to post-intervention. No comparisons reported against controls.

Note: SD= Standard Deviation; Mins= Minutes; NR= Not Reported; S-IgA = Secretory Immunoglobulin Isotype A; NK= Natural Killer; RCT= Randomised Controlled Trial; IL= Interleukin; INF= Interferon; CD= Cluster of Differentiation; PHA= phytohaemagglutinin; Con-A= Concanavalin A; URTIs= Upper Respiratory Tract Infections; TNF= Tumor necrosis factor; LPS = Lipopolysaccharide; PMN = polymorphonuclear

† Total study sample size including comparator conditions, if applicable.