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Please cite the final published version:

O'Toole, M. S., Bovbjerg, D. H., Renna, M. E., Lekander, M., Mennin, D. S., & Zachariae, R. (2018). Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, 74, 68-78.
doi:10.1016/j.bbi.2018.04.005

Publication metadata

Title:	Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis
Author(s):	M.S. O'Toole, D.H. Bovbjerg, M.E. Rennac, M. Lekander, D.S. Mennin & R. Zachariae
Journal:	Brain, Behavior, and Immunity
DOI/Link:	https://doi.org/10.1016/j.bbi.2018.04.005
Document version:	Accepted manuscript (post-print)

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Accepted Manuscript

Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis

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PII: S0889-1591(18)30091-6
DOI: <https://doi.org/10.1016/j.bbi.2018.04.005>
Reference: YBRBI 3376

To appear in: *Brain, Behavior, and Immunity*

Received Date: 13 December 2017
Revised Date: 27 February 2018
Accepted Date: 4 April 2018

Please cite this article as: O'Toole, M.S., Bovbjerg, D.H., Renna, M.E., Lekander, M., Mennin, D.S., Zachariae, R., Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis, *Brain, Behavior, and Immunity* (2018), doi: <https://doi.org/10.1016/j.bbi.2018.04.005>

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Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans:**A systematic review and meta-analysis**

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Abstract

The purpose of the present investigation was to systematically review randomized controlled trials examining the effects of psychological interventions on inflammatory biomarkers in adult populations and to quantitatively analyze those effects by meta-analysis. Two researchers independently searched key electronic databases, selected eligible publications, extracted data, and evaluated methodological quality. Nineteen randomized controlled trials examining a total of 1510 participants were included. The overall combined effect size from pre to post psychological intervention on pro-inflammatory biomarker levels was statistically significant, showing an attenuating effect, although of a small magnitude (Hedge's $g = 0.15$, $p = .008$, CI [0.04 - 0.26]). However, this effect was not maintained into the follow-up period ($g < 0.01$, $p = .964$, CI [-0.19 - 0.18]). Looking at the individual biomarkers assessed across studies, only C-reactive protein (CRP) was found to significantly decrease following psychological intervention. A number of moderation analyses were conducted, none of which reached statistical significance. However, the numerically largest – and significant – within-group effect size was obtained for the group of studies that had preselected participants based on elevated psychological distress ($g = 0.29$, $p = .047$). In conclusion, psychological interventions appear efficacious in reducing pro-inflammatory biomarker levels. Future studies are recommended to carefully select individuals based on inflammatory (e.g., the presence of low-grade inflammation) and/or psychological (e.g., psychological distress) criteria.

Keywords: inflammation; psychotherapy; cancer; depression; CRP; cytokines

Highlights

- Nineteen RCTs examined the effect of psychological intervention on inflammatory biomarkers
- The effect size from pre to post intervention was statistically significant but small
- The largest effect size was obtained for the studies preselecting on psychological distress

1. Introduction

Inflammatory processes are increasingly recognized to be important contributors to both mental and physical illness (H. Li et al., 2017; Y. Li et al., 2017; Slavich, 2015; Smith et al., 2018). For instance, systemic levels of C-reactive protein (CRP) as well as certain cytokines and chemokines, e.g. interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), are elevated in individuals with clinical depression (Dantzer and Capuron, 2017; Köhler et al., 2017; Shariq et al., 2018), and it has been suggested that low-grade inflammation is, in part, responsible for the increased rate of coronary heart disease found in this population (Chrysohoou et al., 2018; Halaris, 2017). Likewise, inflammatory processes are a hallmark etiological factor in cancer development and progression and are expressed not only at tumor sites but also peripherally (Chan et al., 2015; Diakos et al., 2014; Hanahan and Weinberg, 2011; J. Li et al., 2017). There is now increasing evidence from clinical studies that peripheral levels of pro-inflammatory biomarkers, (e.g., CRP) are predictive of cancer risk and survival (e.g., Allin et al., 2012; Zheng et al., 2016).

During acute inflammatory responses, the brain recognizes cytokines as molecular signals of sickness. This happens either through indirect, but relatively fast pathways, with cytokines activating afferent neural pathways (e.g., branches of the vagus nerve), or through more direct, but relatively slow pathways, with cytokines acting on a number of cell types in the brain (e.g., macrophage-like cells and endothelial cells of brain vessels) causing local cytokine production (e.g., Dantzer and Capuron, 2017; McCusker and Kelley, 2013). Both of these pathways as well as others less well studied, have been demonstrated to induce a syndrome of common symptoms of sickness, such as anhedonia, loss of appetite, aching joints, fever, sleepiness, fatigue, and withdrawal from social activities (e.g., D'Mello and Swain, 2017; Eisenberger et al., 2017). This behavioral repertoire is regarded as an adaptive, motivational system that reorganizes the organism's priorities to facilitate recovery through conservation of energy, allocation of resources to combat infection, and eliciting support from others (Filiano et al.,

2017; Lotrich, 2012). However, when the organism is exposed to chronically elevated systemic levels of pro-inflammatory cytokines this may result in persistent pernicious alterations in neurotransmitter function and behavior (D'Mello and Swain, 2017; Nasef et al., 2017) and contribute to risk of chronic disease (Slavich, 2015; Xu and Larbi, 2017).

As inflammatory activity is influenced by stress and behavior through a range of neurotransmitters, interventions aimed at reducing stress and targeting specific behavioral problems might be expected to lead to reductions in biomarkers of systemic inflammatory responses. A meta-analysis of 39 RCTs investigated the effect of what the authors characterized as “mind-body therapies” on a number of immune system outcomes (Morgan et al., 2014). The meta-analysis detected a medium and statistically significant effect of these therapies in reducing blood levels of CRP (Cohen's $d = 0.58$), but did not find statistically significant effects for the remaining inflammatory biomarkers investigated (e.g., IL-6, IL-8, TNF- α , IFN- γ). The analyses also revealed considerable heterogeneity among studies, which may reflect the inclusion of a broad variety of interventions. For instance, the proportion of ‘mind vs. body’ in the interventions varied from being mainly based on verbal communication (e.g., imagery), to mostly consisting of physical movement (e.g., yoga). In addition, the type of control group varied, such that some studies had a waitlist control condition while others had an active control group. The potential moderating effects of these between-study differences were not addressed. The lack of effect on inflammatory biomarkers other than CRP may also be due to a lack of effect on the behavioral parameters targeted in the intervention. If the interventions were ineffective at the behavioral level – a question that was not addressed in the meta-analysis – it seems less likely that inflammatory biomarker levels would be altered. Finally, interventions *not* including bodily components were left out of this meta-analysis. However, more traditional psychological interventions show well-documented efficacy in reducing psychological distress, such as anxiety and depression (e.g., Carpenter et al., 2018; Cuijpers et al., 2013), and may therefore also be hypothesized to show effects on inflammatory markers.

Another recent review also investigated the effects of “mind-body therapies” on circulating biomarkers of inflammation (Bower and Irwin, 2016). This review was largely based on the same studies (73% overlap) as the meta-analysis described above (Morgan et al., 2014), although the studies here were limited to those with ‘widely available interventions’, which resulted in the inclusion of 22 studies. This descriptive review concluded that studies of mind-body therapies yielded mixed findings for circulating inflammatory markers, but no meta-analyses were conducted. The type of control condition was again unrestricted, and interventions *not* including bodily components were excluded.

The purpose of the present investigation was to systematically review studies examining the effects of *psychological* interventions on inflammatory biomarkers in adult populations with mental or physical health problems and to quantitatively analyze those effects by meta-analysis. We defined a psychological intervention as an intervention in which verbal communication between a therapist and a participant was the core element or in which a psychological treatment was provided in a printed format or a computer program (e.g., guided self-help or bibliotherapy) that the participant worked through more or less independently, that could include physical elements (e.g., yoga or tai chi) but more than 50% of the intervention had to have a psychological aim, for instance using cognitive behavioral therapy (CBT), mindfulness-based therapy (MBT) or guided imagery (cf. Cuijpers et al., 2009; Farver-Vestergaard et al., 2015; Seekles et al., 2013). This criterion was intended to include mindfulness-based therapies, but exclude interventions primarily based on physical movement and activity (e.g., yoga), since physical activity itself can affect systemic levels of inflammatory biomarkers (e.g., Hojman, 2017; Melo et al., 2017). Furthermore, we wanted to compare the effects of such psychological interventions to non-active control groups in order to limit between-study differences and the potential influence of the comparison group chosen. We planned to evaluate: a) the average effect of psychological interventions on both the combined and individual inflammatory biomarkers immediately following intervention and at a subsequent follow-up; b) the moderating effect of a number of a priori chosen variables (see

below); and, c) the association between the effects on behavioral outcomes (e.g., depression) and inflammatory biomarkers. We specifically hypothesized that psychological interventions would have an attenuating effect on pro-inflammatory biomarkers.

2. Material and Methods

2.1 Selection Criteria

Study eligibility was assessed using the PICOS approach (Moher et al., 2015). Population: adults (≥ 18 yrs) with or without a diagnosis of mental or physical disease. Intervention: a) psychological intervention, defined as an intervention in which the main aim and approach were psychological (see above). The intervention could include physical elements (e.g., yoga) but approach and target of the intervention had to be primarily psychological. Comparator: participants randomized to at least one non-active control condition, (e.g., wait list, single psychoeducational meetings). Outcomes: reported at least one quantitative assessment of a systemic inflammatory biomarker post-intervention for both intervention and control groups (e.g., CRP, IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-10, IL-17, TNF- α , IFN- γ), measured in saliva, urine, or blood. Studies were not required to report behavioral outcomes. Study design: randomized controlled trial (RCT); reported in English; results reported such that an effect size could be calculated. Studies were excluded if they only examined the effect on a short-term inflammatory response (i.e., < 3 days) to an acute stressor (e.g., having surgery, being exposed to an experimental challenge) or only reported stimulated levels of cytokines. All papers were evaluated independently by authors MSO and MR, and disagreement on the inclusion/exclusion of a study was resolved by consensus and discussion with a third author (RZ).

2.2 Search strategy

A keyword-based search in the electronic databases of PsychINFO and Pubmed was conducted. Keywords related to inflammation (inflammation OR inflammatory OR cytokine* OR CRP OR “C-reactive protein” OR chemokine* OR interleukin OR IL-1 β OR “IL-1beta” OR IL-2 OR TNF- α OR TNF-alpha OR IL-6

OR IL-8 OR IL-12 OR IL-17 OR IL-4 OR IL-5 OR IL-10 OR interferon OR IFN- γ) were combined with keywords related to psychological intervention (psychotherap* OR "cognitive therap*" OR "Cognitive-behav* therap*" OR "psychol* treatment" OR "psychol* intervention" OR CBT OR "Cognitive behav* therap*" OR mindfulness OR MBSR OR MBCT OR hypnosis OR "imagery" OR "relaxation therapy" OR "applied relaxation" OR ACT OR "Acceptance and commitment therapy" OR DBT OR "dialectic behavior therapy" OR "prolonged relaxation" OR "mind-body therapy" OR "mind-body treatment" OR "mind-body therapy" meditation OR "coping skills" OR "problem-solving" OR "cognitive intervention" OR "behav* intervention" OR "behavi* activation" OR "behav* therap*" OR psychoeducation* OR psychoeducation* OR yoga). Two independent searches were conducted by MSO and MR for the period from the earliest dates available in the databases through January 2018. In addition, a backward search (snowballing) for additional studies to include was conducted using reference lists of identified articles and earlier systematic reviews together with a forward search (citation tracking) until no additional relevant articles were found.

2.3 Data extraction

Means and standard deviations for both inflammatory biomarkers and behavioral outcomes were extracted. When means and standard deviations were not available, the study authors were contacted (see Results). Studies were coded for specific inflammatory biomarkers assessed (e.g., IL-6) and bodily fluids sampled (i.e., blood, urine, or saliva), as well as whether they assessed and analyzed potential confounding variables including timing of sampling to control for diurnal variation (e.g., Nilsson et al., 2016), participant characteristics (e.g., age, gender, race/ethnicity, body mass index [BMI]), clinical diagnosis if any (e.g., cancer, depression, insomnia), intervention characteristics (e.g., treatment format [individual or group], intervention modality [face-to-face, web-based, phone-based, bibliotherapy], number of sessions, intervention period duration [from first to last intervention session]). If studies allocated participants to more than one psychological intervention, an average effect

size was calculated for those particular studies in order not to violate the assumption of independence between observations (Borenstein et al., 2009).

Studies were additionally rated for quality (Jadad score; Jadad et al., 1996) using the 11 original Jadad criteria. Five additional criteria particularly relevant for the type of studies reviewed in the present paper were also rated: 1) Were there clear descriptions of the procedures for the control (comparison) group(s)? 2) Were the statistical methods clearly described? 3) Was the text free of any indications of selective outcome reporting (Sterne et al., 2008)? 4) Were the procedures for collection and assessment of the inflammatory biomarkers clearly described? 5) Was the study pre-registered in a public database, e.g., ClinicalTrials.gov? These criteria address methodological clarity regarding the intervention and potential biases in reporting. Quality criteria were rated on a scale from 0 to 2 (with larger scores indicating higher quality), yielding a total score ranging between 0 and 32. Quality scores were not used as weights when calculating effect sizes, as this is not recommended (Greenland and O'Rourke, 2001).

All codings and ratings were made by the first (MO) and third (MR) author. Disagreements were discussed and resolved by consensus and discussion with the last author (RZ). Literature search and data extraction protocols are available upon request.

2.4 Analytic overview

Meta-analyses were performed for inflammatory biomarkers categorized as primarily pro-inflammatory or anti-inflammatory, based on how the respective biomarkers are generally viewed in the immunological literature (e.g., Banchereau et al., 2012; Gleeson et al., 2011; Sims and Smith, 2010). In addition, when a sufficient numbers of studies ($K \geq 3$) were identified for a given inflammatory biomarker, meta-analyses were performed to determine the effect of psychological interventions on each biomarker. Analyses were conducted for two time periods; that is, from pre- to immediately post-intervention, and from pre-intervention to the last follow-up assessment. These main analyses were based on random-effects models. In addition, planned exploratory moderation analyses were conducted

testing the effect on inflammatory biomarkers of a number of variables. Categorical variables (e.g., primary diagnosis, treatment type, treatment format, treatment recipient) were explored with meta-ANOVAs, whereas continuous variables (i.e., age, % women, % Whites, BMI, quality, number of sessions, duration of treatment, effect on behavioral outcomes) were considered in meta-regression analyses, based on random-effects models and estimated with the Maximum Likelihood method. In the regression analyses, the proposed moderators served as independent variables with the effect size serving as the dependent variable. In order to evaluate the association between the effect of the psychological interventions on inflammatory biomarkers and behavioral outcomes, an effect size for the behavioral outcomes was calculated following the same principles as with the biomarkers, after which the two weighted effects sizes were also explored in a meta-regression analysis.

Effect sizes are expressed as Hedge's g in order to adjust for a potential bias to overestimate the effect size in small samples (Hedges and Olkin, 1985), and values of 0.2, 0.5, and 0.8 were considered small, medium, and large, respectively (Cohen, 1988). A p -value < 0.05 was considered statistically significant. Positive effect sizes indicate that the psychological interventions were associated with lower levels of pro- or anti-inflammatory biomarker. Each effect size was weighted by its precision (inverse variance), so that interventions with larger samples contributed more to the estimate of the overall effect size. Heterogeneity was explored using Q and I^2 statistics. Q -tests concern the probability that results reflect systematic between-study differences. Due to the generally low statistical power of heterogeneity tests, a p -value ≤ 0.10 was used to indicate heterogeneity (Hedges and Pigott, 2001). The I^2 statistic is an estimate of the degree of heterogeneity and is considered unaffected by the number of studies. An I^2 value of 0% indicates no observed heterogeneity. Values of 25%, 50%, and 75% are considered low, moderate, and high, respectively (Higgins and Thompson, 2002).

Positive and negative findings may not be equally likely to get published, thereby introducing risk of publication bias. The distribution of effect sizes was visually inspected by means of funnel plots

and tested with Egger's test (Egger et al., 1997). When our analyses indicated possible publication bias, an adjusted effect size was estimated using Duval and Tweedie's (2000) trim-and-fill method, which imputes missing results and recalculates the effect size. The file-drawer problem, that is, the possibility that unidentified or unpublished studies with null findings could alter statistically significant meta-analysis results, was evaluated by Rosenthal's fail-safe number (Rosenthal, 1979). If the fail-safe number exceeded $5K + 10$, with K being the number of studies included in the meta-analysis, the file drawer problem was considered sufficiently low to allow acceptance of results as unaffected by that potential source of bias.

All analyses were conducted using the Comprehensive Meta-Analysis program, version 3.3.070 ("Comprehensive meta-analysis," 2014). The study was preregistered in PROSPERO (registration number: CRD42017065639).

3. Results

3.1 Search results and study characteristics

The flow of study selection with reasons for exclusion is presented in [Figure 1](#). The literature searches yielded 1764 unique records. A total of 121 full texts were assessed for eligibility, and 21 studies fulfilled the inclusion criteria. Authors of eleven studies were contacted and requested to provide additional data needed for our analyses. Six authors were able to provide the necessary data. Three authors did not respond. These three studies specifically reported a non-significant effect, so we set the effect size to "0" and included these studies. Since this approach may be too conservative, sensitivity analyses were conducted comparing the results with and without these three studies. Two authors reported that they were unable to locate the data. These two studies were excluded because no meaningful effect size or direction could be calculated. This process resulted in a total of 19 studies that were included in the final meta-analysis.

The included studies reported on a total of 1510 participants (Mean N per study = 79; range: 15 to 322), with data analyzed for 1356 participants. The mean age was 53 years (range: 24 to 73); 82% of the participants were women (range: 46 to 100); and 80% were white (range: 53 to 100). Studies included participants across a variety of clinical populations, including individuals with a history of: a cancer diagnosis ($k=7$), autoimmune disease ($k=4$), depression ($k=3$, of which two samples were at risk for or had an existing heart condition), or sleep disturbances ($k=2$). Non-clinical populations included older adults ($k=2$) and caregivers of family members with dementia ($k=1$). The most common psychological interventions were meditation- and mindfulness-based interventions ($k=8$), followed by CBT ($k=6$). Participants on average received 9.3 (range: 4 to 20) sessions over 10.5 weeks (range: 4 to 37). Four inflammatory biomarkers were assessed in at least three studies at pre- and post-intervention (CRP, IL-1 β , IL-6, TNF- α), and two outcomes were assessed in at least three studies at pre-intervention and follow-up (CRP, IL-6). For study characteristics, see [Table 1](#). All inflammatory biomarkers were classified as pro-inflammatory except for IL-4, IL-5, IL-10, and IL-13, which were classified as anti-inflammatory (e.g., Banchereau et al., 2012; Gleeson et al., 2011; Sims and Smith, 2010). Sixteen studies (84%) relied on biomarker assessment in the blood, three relied on saliva (16%). Five of the 19 studies pre-selected participants based on a measure of psychological distress. The mean modified Jadad score (quality metric) was 21 with a range from 12 to 26. The studies scored lowest on the item examining blinding/masking (sum score on scale from 0 to 26 = 3) that rated the masking of the study condition assignment to the participants and the item on pre-registration in a public depository (sum score = 6). The overall inter-rater reliability for the Jadad items before negotiations was acceptable ($\kappa=0.77$).

3.2 Pooled effect sizes and between-study differences

The overall combined effect size from pre to post psychological intervention on pro-inflammatory biomarker levels was statistically significant, showing an attenuating effect, although of a small magnitude (Hedge's $g=0.15$, $p=.008$, CI [0.04 - 0.26]). See [Table 2](#) and [Figure 2](#). When the studies with

an overall effect size set to zero were excluded, a statistically significant effect, also of small magnitude, continued to be detected ($g = .16$, $p = .007$). The following results are therefore based on all included studies. Only six studies with pre- and post-intervention data controlled for the time of day by restricting sampling time to a certain time range. Analyzed separately, these studies revealed a non-significant effect size ($g=0.13$, $p=.108$).

Four individual pro-inflammatory outcomes were assessed in at least three studies each, and were therefore evaluated separately. The effect of psychological intervention on CRP levels was positive, statistically significant and of small magnitude ($k=10$, $g = 0.23$, $p = .006$), see Forest plot in [Figure 3](#). When the studies not using a high-sensitivity measure of CRP were excluded, the effect was only trend-wise significant, and continued to be of a small magnitude ($k=7$, $g = 0.20$, $p = .078$). The mean average absolute concentration of CRP was calculated from the (6 out of 10) studies providing raw means (i.e., those not just providing test parameters). The mean baseline CRP concentration was 6.8 mg/L (SD=7.0). The effect on IL-6 was not statistically significant ($k=9$, $g = 0.09$, $p = .204$), nor was the effect on IL-1 β ($k=3$, $g = 0.21$, $p = .370$) or TNF- α ($k=6$, $g = 0.11$, $p = .188$).

A number of planned moderation analyses were conducted, none of which were statistically significant. Moderators included diagnosis (i.e., autoimmune disease vs. cancer), treatment type (CBT vs. meditation/mindfulness), treatment format (face-to-face vs. other), treatment recipient (group vs. individual), study quality (i.e. Jadad), mean sample age, percent women, percent Whites, BMI, number of sessions, treatment duration, and effect on behavioral outcomes. See [Tables 2 and 3](#). The overall effect on the behavioral outcomes was large post intervention ($g=0.80$, $p < .001$) but did not correspond to the effect on pro-inflammatory biomarkers ($p = .593$). Due to this finding, it was decided posthoc to also code studies for whether or not participants had been included in the individual studies based on psychological distress criteria. Although this way of grouping the studies did not moderate the outcome, the numerically largest effect size, which turned out to be statistically significant, was obtained for the

group of studies ($k=4$) that had preselected participants based on elevated psychological distress ($g = 0.29, p = .047$).

Concerning effects at follow-up, the mean time from pre-intervention to follow-up was 35 weeks (range: 12 to 70 weeks). The overall combined effect from pre-intervention to follow-up found in the combined pro-inflammatory analysis across the 7 studies with a follow-up assessment of inflammatory biomarkers did not reach statistical significance (Hedge's $g < -.01, p = .964, CI [-.19 - .18]$). At the individual biomarker level, neither the effect on CRP ($g = .18, p = .225$) nor on IL-6 ($g = -.07, p = .469$) reached statistical significance.

Heterogeneity was generally low and statistically non-significant in all analyses, indicating that differences between study effects could largely be due to sampling error despite differences in study characteristics.

Only three studies included outcomes classified as anti-inflammatory, of which only two provided data from pre to post therapy. Thus, a combined variable of anti-inflammatory outcomes was not calculated, and moderation analyses were only conducted on the combined pro-inflammatory biomarkers.

3.4 Publication bias

For all statistically significant results above, the risk of publication bias was evaluated (see Table 2). Four analyses were adjusted for possible publication bias, which did not change the results substantially. Furthermore, all analyses failed to meet the criterion for the fail-safe N, indicating a lack of robustness of the results.

4. Discussion

Based on a systematic review, 19 studies fulfilled the inclusion criteria for the present meta-analysis. Concerning the overall effect of psychological interventions on pro-inflammatory biomarkers, a small

but significant attenuating effect ($g=0.15$) was detected. However, this effect did not last into the follow-up period, where a non-significant and negligible effect was found ($g<-0.01$).

Only four pro-inflammatory biomarkers were assessed in at least three studies (i.e., CRP, IL-6, IL-1 β , TNF- α), which was employed as the criterion for conducting a meta-analysis at the individual biomarker level. When looking at the individual biomarkers, it appeared that the overall effect immediately following the psychological intervention was mainly driven by an attenuating effect on CRP, as this was the only significant analysis at the individual biomarker level. The effect size was estimated to be of a small magnitude ($g=0.23$), which is lower than that detected in the meta-analysis by Morgan et al. (2014), which was of a medium magnitude ($d=0.58$). This divergence is most likely due to a difference – or error - in calculating the effect size from the Oh et al.-study (2010), where Morgan et al. (2014) reports a very large effect size ($d=2.28$), whereas the present analyses detects an effect size of a much lower magnitude ($d=0.41$; based on the final N of 101 individuals, a mean group difference on CRP of 23.17, and a t -value of 2.0). In terms of absolute concentration levels, the mean CRP was 6.8 mg/L ($SD=7.0$). With an effect size of 0.23, psychological interventions decreased CRP levels with 1.6 mg/L immediately following the intervention.

In terms of psychological issues, there is an increased likelihood (odds ratio = 1.38) of experiencing psychological distress and depression even at relatively low concentrations of CRP (1.01 to 3.00 mg/L; Wium-Andersen et al., 2013). Based on such numbers, a mean reduction in CRP of 1.6 mg/L as evidenced in the present meta-analysis has the potential to be clinically relevant. Furthermore, CRP has been found to be a strong predictor of all-cause mortality (e.g., J. Li et al., 2017; Y. Li et al., 2017; Ridker, 2008). For instance, one study (Marsik et al., 2008) has found that patients with CRP concentrations >5 mg/L at the time of hospital admission had a 50% to 330% increase in risk of death from any cause, rising in magnitude as CRP concentration increases. Although the effect of psychological interventions on CRP could not be statistically detected in a longer follow-up period in the present meta-

analysis, this sub-group analysis only included four studies. Interestingly, although non-significant, the effect remained at the same absolute size ($g=0.18$) despite the small number of papers included. It remains to be determined whether the ability of psychological interventions to significantly reduce CRP concentrations can have a lasting effect, and thus might in turn have a positive impact on morbidity and mortality. Taken together, much more research is needed concerning clinically relevant levels of changes for a broader range of biomarkers in different populations. The present study points to psychological interventions' ability to decrease pro-inflammatory biomarkers - driven by effects on CRP. Additional research is now warranted to explore the relationships between intervention-induced decreases in CRP and improvements in clinically relevant outcomes, as well as to further explore other inflammatory biomarkers. Finding an effect only on CRP may have several explanations. First, where the mean effect size for CRP was of a small magnitude ($g=0.23$), it was even smaller, and negligible, for IL-6 ($g=0.07$). In this regard it should be noted that CRP and cytokines are different types of biomarkers in that IL-6, IL-1 β , TNF- α all induce the synthesis of various acute phase proteins, including CRP (Prasad, 2006). Furthermore, CRP and IL-6 are not always correlated (e.g., Conway et al., 2004) and may be differentially related both in the different conditions tested (e.g., cancer, loneliness) and in their response to psychological intervention. More studies are needed in order to understand such potential differential effects of psychological interventions on various pro-inflammatory biomarkers.

A number of moderation analyses were conducted, none of which were significant, which may in part be explained by the small number of studies, resulting in low statistical power. Although all moderators were non-significant, it should be noted that the numerically largest effect size ($g=0.29$) was found for the studies that pre-selected participants based on elevated psychological distress, either as a clinical diagnosis (e.g., depression, insomnia) or elevated clinical symptomatology. Only five studies in total employed such pre-selection criteria, and even when doing so, it should be underscored that inflammation, although a part of the pathophysiology of one condition, may not be present in all

subjects. For instance, although low-grade inflammation has been detected in major depressive disorder (Dantzer and Capuron, 2017), not all individuals with depression may show such low-grade inflammation (Raison et al., 2013). Furthermore, with only five studies pre-selected participants based on the presence of psychological distress, the overall detected effect should therefore be interpreted in this light, where a floor-effect may be involved simply due to inclusion criteria in the included studies.

Although the psychological interventions did show an overall significant effect in reducing pro-inflammatory biomarkers, the correlation between the size of the intervention effect on behavioral outcomes and pro-inflammatory biomarkers was not significant. Given this finding and the other moderation analyses, it remains a question for whom more specifically this association – between emotional distress and inflammation - can be established.

Limitations of the present meta-analysis include: 1) Only seven studies could be included in the follow-up analysis, at it therefore remains uncertain whether the detected effect immediately following treatment is maintained. 2) The biological measures were only collected once per time point, which must be considered a methodological weakness, potentially obscuring true effects. Related to this, one possible source of bias in these studies is the release of myokines in response to movement, depending on when sampling was made. For instance, IL-6 can be identified in the bloodstream in response to muscle contractions, in which case it is thought to play an *anti*-inflammatory role by, among other things, inhibiting TNF- α (Muñoz-Cánoves et al., 2013). 3) Correlations between saliva and plasma samples have been found to vary depending on the specific biomarker (Williamson et al., 2012). While comparisons of absolute concentrations of biomarkers obtained through different mediums can be problematic, this is less critical when measuring change over time. Exclusion of the three studies relying on biomarker assessment in saliva from the analyses did not appear to change the results ($g=0.015$, $p=.012$). 4) Only seven studies in total controlled for sampling time, which means that the overall effect should be interpreted in light of this uncertainty introduced by not taking diurnal variation into account.

5) Included studies reflect a large heterogeneity both among treated conditions and types of treatment. However, statistical heterogeneity was generally very low and statistically non-significant in all analyses, indicating that differences between study effects could largely be due to sampling error despite differences in study characteristics.

Future studies should pay particularly careful attention to their inclusion strategy, either selecting participants based on the presence of a physical condition known to involve inflammation for all individuals (e.g., an inflammatory disease) and/or elevated psychological or behavioral difficulties. In addition, studies should allow for multiple and controlled sampling of the inflammatory biomarkers of interest.

5. Conclusions

In conclusion, 18 studies fulfilled the inclusion criteria for the meta-analysis, which revealed a statistically significant effect of psychological interventions on pro-inflammatory biomarkers of a small magnitude, which did not last into the follow-up period. Looking at the individual biomarkers, only CRP turned out to significantly decrease following psychological intervention. Although none of the between-group moderation analyses turned out significant, the numerically largest effect size ($g=0.29$) was found for the studies that pre-selected participants based on elevated psychological distress, either as a clinical diagnosis (e.g., depression, insomnia) or elevated clinical symptomatology. Future studies should carefully select individuals based on either inflammatory (e.g., the presence of low-grade inflammation) or psychological (e.g., psychological distress criteria). An important development of the field would be to further study inflammatory correlates to successful psychological treatment in such carefully selected patient samples.

Acknowledgements

We would like to thank Claire Louise Macnamara, School of Psychiatry, University of New South Wales, Australia, for assisting us in the literature searches, record screening and evaluation.

ACCEPTED MANUSCRIPT

References

- Allin, K.H., Bojesen, S.E., Johansen, J.S., Nordestgaard, B.G., 2012. Cancer risk by combined levels of YKL-40 and C-reactive protein in the general population. *Br. J. Cancer* 106, 199–205.
<https://doi.org/10.1038/bjc.2011.501>
- Bae, B.G., Oh, S.H., Park, C.O., Noh, S., Noh, J.Y., Kim, K.R., Lee, K.H., 2012. Progressive muscle relaxation therapy for atopic dermatitis: objective assessment of efficacy. *Acta Derm. Venereol.* 92, 57–61.
<https://doi.org/10.2340/00015555-1189>
- Banchereau, J., Pascual, V., O'Garra, A., 2012. From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines. *Nat. Immunol.* 13, 925–931. <https://doi.org/10.1038/ni.2406>
- Borenstein, M., Hedges, L. V., Higgins, J.P.T., Rothstein, H.R., 2009. *Introduction to meta-Analysis*. John Wiley & Sons, Ltd, Chichester, UK. <https://doi.org/10.1002/9780470743386>
- Bower, J.E., Irwin, M.R., 2016. Mind-body therapies and control of inflammatory biology: A descriptive review. *Brain. Behav. Immun.* 51, 1–11. <https://doi.org/10.1016/j.bbi.2015.06.012>
- Carpenter, J.K., Andrews, L.A., Witcraft, S.M., Powers, M.B., Smits, J.A.J., Hofmann, S.G., 2018. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. *Depress. Anxiety.* <https://doi.org/10.1002/da.22728>
- Chan, D.S.M., Bandera, E. V., Greenwood, D.C., Norat, T., 2015. Circulating C-Reactive Protein and breast cancer risk--Systematic literature review and meta-analysis of prospective cohort studies. *Cancer Epidemiol. Biomarkers Prev.* 24, 1439–1449. <https://doi.org/10.1158/1055-9965.EPI-15-0324>
- Chen, H.-Y., Chiang, C.-K., Wang, H.-H., Hung, K.-Y., Lee, Y.-J., Peng, Y.-S., Wu, K.-D., Tsai, T.-J., 2008. Cognitive-behavioral therapy for sleep disturbance in patients undergoing peritoneal dialysis: a pilot randomized controlled trial. *Am. J. Kidney Dis.* 52, 314.
<https://doi.org/10.1053/j.ajkd.2008.03.012>
- Chrysohoou, C., Kolliou, N., Tousoulis, D., 2018. The link between depression and atherosclerosis through

the pathways of inflammation and endothelium dysfunction. *Maturitas* 109, 1–5.

<https://doi.org/10.1016/j.maturitas.2017.12.001>

Cohen, J., 1988. *Statistical power analysis for the behavioral sciences*, 2nd ed. Lawrence Erlbaum, Hillsdale.

Comprehensive meta-analysis [computer program]. Version 3.3.070. Eaglewood, NJ: Biostat; 2014.

Conway, D.S. g, Buggins, P., Hughes, E., Lip, G.Y.H., 2004. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. *Am. Heart J.* 148, 462–466.

<https://doi.org/10.1016/j.ahj.2004.01.026>

Creswell, J.D., Irwin, M.R., Burklund, L.J., Lieberman, M.D., Arevalo, J.M., Ma, J., Breen, E.C., Cole, S.W., 2012. Mindfulness-Based Stress Reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial. *Brain Behav Immun* 26, 1095–1101.

<https://doi.org/10.1016/j.bbi.2012.07.006>

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., Dobson, K.S., 2013. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Can. J. Psychiatry* 58, 376–385. <https://doi.org/10.1177/070674371305800702>

Cuijpers, P., van Straten, A., van Schaik, A., Andersson, G., 2009. Psychological treatment of depression in primary care: a meta-analysis. *Br. J. Gen. Pract.* 59, 51–60.

<https://doi.org/10.3399/bjgp09X395139>

D’Mello, C., Swain, M.G., 2017. Immune-to-brain communication pathways in Inflammation-associated sickness and depression. *Curr. Top. Behav. Neurosci.* 31, 73–94.

https://doi.org/10.1007/7854_2016_37

Dantzer, R., Capuron, L., 2017. *Inflammation-associated depression : evidence, mechanisms and implications*. Springer International Publishing, Cham, Switzerland.

Diakos, C.I., Charles, K.A., McMillan, D.C., Clarke, S.J., 2014. Cancer-related inflammation and treatment

- effectiveness. *Lancet Oncol.* 15, e493–e503. [https://doi.org/10.1016/S1470-2045\(14\)70263-3](https://doi.org/10.1016/S1470-2045(14)70263-3)
- Doering, L. V, Cross, R., Vredevoe, D., Martinez-Maza, O., Cowan, M.J., 2007. Infection, depression, and immunity in women after coronary artery bypass: a pilot study of cognitive behavioral therapy. *Altern. Ther. Health Med.* 13, 18–21.
- Duval, S., Tweedie, R., 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56, 455–463.
- Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *Br. Med. J.* 315, 629–634.
- Eisenberger, N.I., Moieni, M., Inagaki, T.K., Muscatell, K.A., Irwin, M.R., 2017. In sickness and in health: The co-regulation of inflammation and social behavior. *Neuropsychopharmacology* 42, 242–253. <https://doi.org/10.1038/npp.2016.141>
- Eremin, O., Walker, M.B., Simpson, E., Heys, S.D., Ah-See, A.K., Hutcheon, A.W., Ogston, K.N., Sarkar, T.K., Segar, A., Walker, L.G., 2009. Immuno-modulatory effects of relaxation training and guided imagery in women with locally advanced breast cancer undergoing multimodality therapy: a randomised controlled trial. *Breast* 18, 17–25. <https://doi.org/http://dx.doi.org/10.1016/j.breast.2008.09.002>
- Farver-Vestergaard, I., Jacobsen, D., Zachariae, R., 2015. Efficacy of psychosocial interventions on psychological and physical health outcomes in chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Psychother. Psychosom.* 84, 37–50. <https://doi.org/10.1159/000367635>
- Filiano, A.J., Gadani, S.P., Kipnis, J., 2017. How and why do T cells and their derived cytokines affect the injured and healthy brain? *Nat. Rev. Neurosci.* 18, 375–384. <https://doi.org/10.1038/nrn.2017.39>
- Gallegos, A.M., Hoerger, M., Talbot, N.L., Krasner, M.S., Knight, J.M., Moynihan, J.A., Duberstein, P.R., 2013. Toward identifying the effects of the specific components of Mindfulness-Based Stress Reduction on biologic and emotional outcomes among older adults. *J. Altern. Complement. Med.*

- 19, 787–792. <https://doi.org/10.1089/acm.2012.0028>
- Gleeson, M., Bishop, N.C., Stensel, D.J., Lindley, M.R., Mastana, S.S., Nimmo, M.A., 2011. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat. Rev. Immunol.* 11, 607–615. <https://doi.org/10.1038/nri3041>
- Greenland, S., O'Rourke, K., 2001. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. *Biostatistics* 2, 463–471. <https://doi.org/10.1093/biostatistics/2.4.463>
- Halaris, A., 2017. Inflammation-associated co-morbidity between depression and cardiovascular disease. *Curr. Top. Behav. Neurosci.* 31, 45–70. https://doi.org/10.1007/7854_2016_28
- Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: The next generation. *Cell* 144, 646–674. <https://doi.org/10.1016/j.cell.2011.02.013>
- Hedges, L. V., Olkin, I., 1985. *Statistical methods for meta-analysis*. Academic Press.
- Hedges, L. V., Pigott, T.D., 2001. The power of statistical tests in meta-analysis. *Psychol. Methods* 6, 203–17.
- Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 21, 1539–1558. <https://doi.org/10.1002/sim.1186>
- Hojman, P., 2017. Exercise protects from cancer through regulation of immune function and inflammation. *Biochem. Soc. Trans.* 45, 905–911. <https://doi.org/10.1042/BST20160466>
- Irwin, M.R., Olmstead, R., Carrillo, C., Sadeghi, N., Breen, E.C., Witarama, T., Yokomizo, M., Lavretsky, H., Carroll, J.E., Motivala, S.J., Bootzin, R., Nicassio, P., 2014. Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. *Sleep* 37, 1543–1552. <https://doi.org/10.5665/sleep.4008>
- Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control. Clin.*

Trials 17, 1–12.

- Köhler, C.A., Freitas, T.H., Stubbs, B., Maes, M., Solmi, M., Veronese, N., de Andrade, N.Q., Morris, G., Fernandes, B.S., Brunoni, A.R., Herrmann, N., Raison, C.L., Miller, B.J., Lanctôt, K.L., Carvalho, A.F., 2017. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: Systematic review and meta-analysis. *Mol. Neurobiol.* 1–12. <https://doi.org/10.1007/s12035-017-0632-1>
- Li, H., Liu, W., Xie, J., 2017. Circulating interleukin-6 levels and cardiovascular and all-cause mortality in the elderly population: A meta-analysis. *Arch. Gerontol. Geriatr.* 73, 257–262. <https://doi.org/10.1016/j.archger.2017.08.007>
- Li, J., Jiao, X., Yuan, Z., Qiu, H., Guo, R., 2017. C-reactive protein and risk of ovarian cancer. *Medicine (Baltimore)*. 96, e7822. <https://doi.org/10.1097/MD.00000000000007822>
- Li, Y., Zhong, X., Cheng, G., Zhao, C., Zhang, L., Hong, Y., Wan, Q., He, R., Wang, Z., 2017. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis* 259, 75–82. <https://doi.org/10.1016/j.atherosclerosis.2017.02.003>
- Lotrich, F., 2012. Inflammatory cytokines, growth factors, and depression. *Curr. Pharm. Des.* 18, 5920–5935. <https://doi.org/10.2174/138161212803523680>
- Marsik, C., Kazemi-Shirazi, L., Schickbauer, T., Winkler, S., Joukhadar, C., Wagner, O.F., Endler, G., 2008. C-Reactive Protein and all-cause mortality in a large hospital-based cohort. *Clin. Chem.* 54, 343–349. <https://doi.org/10.1373/clinchem.2007.091959>
- McCusker, R.H., Kelley, K.W., 2013. Immune-neural connections: how the immune system's response to infectious agents influences behavior. *J. Exp. Biol.* 216, 84–98. <https://doi.org/10.1242/jeb.073411>
- Melo, L.C., Dativo-Medeiros, J., Menezes-Silva, C.E., Barbosa, F.T., Sousa-Rodrigues, C.F. de, Rabelo, L.A., 2017. Physical exercise on inflammatory markers in type 2 diabetes patients: A systematic review of randomized controlled trials. *Oxid. Med. Cell. Longev.* 2017, 1–10.

<https://doi.org/10.1155/2017/8523728>

Menzies, V., Lyon, D.E., Elswick, R.K.J., McCain, N.L., Gray, D.P., 2014. Effects of guided imagery on biobehavioral factors in women with fibromyalgia. *J. Behav. Med.* 37, 70–80.

<https://doi.org/10.1007/s10865-012-9464-7>

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)

2015 statement. *Syst. Rev.* 4, 1. <https://doi.org/10.1186/2046-4053-4-1>

Morgan, N., Irwin, M.R., Chung, M., Wang, C., 2014. The effects of mind-body therapies on the immune system: Meta-analysis. *PLoS One* 9, e100903. <https://doi.org/10.1371/journal.pone.0100903>

Muñoz-Cánoves, P., Scheele, C., Pedersen, B.K., Serrano, A.L., 2013. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? *FEBS J.* 280, 4131–48. <https://doi.org/10.1111/febs.12338>

Nasef, N.A., Mehta, S., Ferguson, L.R., 2017. Susceptibility to chronic inflammation: an update. *Arch. Toxicol.* 91, 1131–1141. <https://doi.org/10.1007/s00204-016-1914-5>

Nilsson, G., Lekander, M., Åkerstedt, T., Axelsson, J., Ingre, M., 2016. Diurnal variation of circulating interleukin-6 in humans: A meta-analysis. *PLoS One* 11, e0165799.

<https://doi.org/10.1371/journal.pone.0165799>

Oh, B., Butow, P., Mullan, B., Clarke, S., 2008. Medical qigong for cancer patients: Pilot study of impact on quality of life, side effects of treatment and inflammation 36, 459–472.

<https://doi.org/http://dx.doi.org/10.1142/S0192415X08005904>

Oh, B., Butow, P., Mullan, B., Clarke, S., Beale, P., Pavlakis, N., Kothe, E., Lam, L., Rosenthal, D., 2010. Impact of Medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. *Ann. Oncol.* 21, 608–614. <https://doi.org/10.1093/annonc/mdp479>

Oken, B.S., Fonareva, I., Haas, M., Wahbeh, H., Lane, J.B., Zajdel, D., Amen, A., 2010. Pilot Controlled Trial of Mindfulness Meditation and Education for Dementia Caregivers. *J. Altern. Complement.*

- Med. 16, 1031–1039. <https://doi.org/10.1089/acm.2009.0733>
- Pakiz, B., Flatt, S.W., Bardwell, W.A., Rock, C.L., Mills, P.J., 2011. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. *Int. J. Behav. Med.* 18, 333–341. <https://doi.org/10.1007/s12529-010-9079-8>
- Prasad, K., 2006. C-Reactive Protein (CRP)-Lowering Agents. *Cardiovasc. Drug Rev.* 24, 33–50. <https://doi.org/10.1111/j.1527-3466.2006.00033.x>
- Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression. *JAMA Psychiatry* 70, 31. <https://doi.org/10.1001/2013.jamapsychiatry.4>
- Reich, R.R., Lengacher, C.A., Klein, T.W., Newton, C., Shivers, S., Ramesar, S., Alinat, C.B., Paterson, C., Le, A., Park, J.Y., Johnson-Mallard, V., Elias, M., Moscoso, M., Goodman, M., Kip, K.E., 2017. A randomized controlled trial of the effects of Mindfulness-Based Stress Reduction (MBSR[BC]) on levels of inflammatory biomarkers among recovering breast cancer survivors. *Biol. Res. Nurs.* 19, 456–464. <https://doi.org/10.1177/1099800417707268>
- Richardson, M.A., Post-White, J., Grimm, E.A., Moye, L.A., Singletary, S.E., Justice, B., 1997. Coping, life attitudes, and immune responses to imagery and group support after breast cancer treatment. *Altern Ther Heal. Med* 3, 62–70.
- Ridker, P.M., 2008. High-sensitivity C-reactive protein as a predictor of all-cause mortality: implications for research and patient care. *Clin. Chem.* 54, 234–7. <https://doi.org/10.1373/clinchem.2007.099465>
- Rosenthal, R., 1979. The file drawer problem and tolerance for null results. *Psychol. Bull.* 86, 638–641. <https://doi.org/10.1037/0033-2909.86.3.638>
- Seekles, W., Cuijpers, P., Kok, R., Beekman, A., van Marwijk, H., van Straten, A., 2013. Psychological

- treatment of anxiety in primary care: a meta-analysis. *Psychol. Med.* 43, 351–361.
- <https://doi.org/10.1017/S0033291712000670>
- Shariq, A.S., Brietzke, E., Rosenblat, J.D., Barendra, V., Pan, Z., McIntyre, R.S., 2018. Targeting cytokines in reduction of depressive symptoms: A comprehensive review. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 83, 86–91. <https://doi.org/10.1016/j.pnpbp.2018.01.003>
- Sharpe, L., Schrieber, L., 2012. A blind randomized controlled trial of cognitive versus behavioral versus cognitive-behavioral therapy for patients with rheumatoid arthritis. *Psychother. Psychosom.* 81, 145–152. <https://doi.org/10.1159/000332334> [doi]
- Sharpe, L., Sensky, T., Timberlake, N., Ryan, B., Brewin, C.R., Allard, S., 2001. A blind, randomized, controlled trial of cognitive-behavioural intervention for patients with recent onset rheumatoid arthritis: preventing psychological and physical morbidity. *Pain* 89, 275–283.
- [https://doi.org/http://dx.doi.org/10.1016/S0304-3959\(00\)00379-1](https://doi.org/http://dx.doi.org/10.1016/S0304-3959(00)00379-1)
- Sims, J.E., Smith, D.E., 2010. The IL-1 family: regulators of immunity. *Nat. Rev. Immunol.* 10, 117.
- <https://doi.org/10.1038/nri2691>
- Slavich, G.M., 2015. Understanding inflammation, its regulation, and relevance for health: a top scientific and public priority. *Brain. Behav. Immun.* 45, 13–4.
- <https://doi.org/10.1016/j.bbi.2014.10.012>
- Smith, K.J., Au, B., Ollis, L., Schmitz, N., 2018. The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: A systematic review and meta-analysis. *Exp. Gerontol.* 102, 109–132. <https://doi.org/10.1016/J.EXGER.2017.12.005>
- Sterne, J.A.C., Egger, M., Moher, D., 2008. Addressing reporting biases, in: Higgins, J.P.T., Green, S. (Eds.), *Cochrane Handbook for Systematic Reviews of Intervention*. Wiley-Blackwell Publishing, Chichester, UK, pp. 297–333.
- Taylor, C.B., Conrad, A., Wilhelm, F.H., Strachowski, D., Khaylis, A., Neri, E., Giese-Davis, J., Roth, W.T.,

Cooke, J.P., Kraemer, H., Spiegel, D., 2009. Does improving mood in depressed patients alter factors that may affect cardiovascular disease risk? *J. Psychiatr. Res.* 43, 1246–1252.

<https://doi.org/10.1016/j.jpsychires.2009.05.006>

Walsh, E., Eisenlohr-Moul, T., Baer, R., 2016. Brief mindfulness training reduces salivary IL-6 and TNF- α in young women with depressive symptomatology. *J. Consult. Clin. Psychol.* 84, 887–897.

<https://doi.org/http://dx.doi.org/10.1037/ccp0000122>

Williamson, S., Munro, C., Pickler, R., Grap, M.J., Elswick, R.K., 2012. Comparison of biomarkers in blood and saliva in healthy adults. *Nurs. Res. Pract.* 2012, 1–4. <https://doi.org/10.1155/2012/246178>

Wium-Andersen, M.K., Ørsted, D.D., Nielsen, S.F., Nordestgaard, B.G., 2013. Elevated C-Reactive Protein Levels, Psychological Distress, and Depression in 73 131 Individuals. *JAMA Psychiatry* 70, 176.

<https://doi.org/10.1001/2013.jamapsychiatry.102>

Xu, W., Larbi, A., 2017. Immunity and Inflammation: From Jekyll to Hyde. *Exp. Gerontol.*

<https://doi.org/10.1016/J.EXGER.2017.11.018>

Zheng, R.-R., Huang, M., Jin, C., Wang, H.-C., Yu, J.-T., Zeng, L.-C., Zheng, F.-Y., Lin, F., 2016. Cervical cancer systemic inflammation score: a novel predictor of prognosis. *Oncotarget* 7, 15230–42.

<https://doi.org/10.18632/oncotarget.7378>

Table 1: Characteristics of the 19 studies included in the meta-analysis

Author [Jadad sum score, range 0 to 26]	Population <i>Recruited based on psychological distress (randomized N, analyzed N)</i>	Intervention (control)	Number of sessions and duration (follow-ups past post assessment) Delivery mode; face-to-face, audio, video (recipient; group or individual)	Sample demographic characteristics: Age (mean), Gender (% women) Race (% white)	Inflammatory biomarkers (bodily fluid sampled; control for diurnal variation)	Behavioral outcomes
Bae et al., (2012) [15]*	Atopic dermatitis patients <i>No</i> (25, 24)	Progressive muscle relaxation (standard care)	8 practice sessions over 4 weeks (Post, No FUs) At home video and audio programs (individual)	Mean age=24 %Women=46 %White=NA	IL-4, IL-5, IL-13, NPY (Blood; Yes)	Anxiety (STAI, IAS), Depression (BDI-II)
Bower et al., (2016) [26]	Breast cancer survivors <i>No</i> (71,65)	Mindfulness awareness practices (wait-list)	6 sessions over 6 weeks (Post, No FU on inflammatory outcomes) Face-to-face (group)	Mean age=47 %Women=100 %White=76	hs-CRP, IL-6, sTNF-RII (Blood; Yes)	Depression (CES-D), Fatigue (FSI), Fear of recurrence (QLACS), Intrusive thoughts (IES), Meaning and peace (FACIT), Pain (BCPT), Perceived stress (PSS), Positive affect (PANAS), Sleep quality (PSQI)
Chen et al., (2008) [24]	Patients with peritoneal dialysis and insomnia <i>Yes, severe sleep disturbance</i> (26,26)	CBT and sleep hygiene education (sleep hygiene education only)	4 sessions over 4 weeks (Post, No FU) Face-to-face (group)	Mean age=49 %Women=74 %White=NA	IL-1 β , IL-6, IL-18, TNF- α (Blood; No)	Fatigue (FSS), Sleep quality (PSQI)
Creswell et al., (2012) [22]	Lonely older adults <i>No</i> (40,40)	MBSR (wait-list)	9 sessions over 8 weeks (Post, No FU) Face-to-face (group)	Mean age=65 %Women=80 %White=65	hs-CRP, IL-6 (Blood; No)	Loneliness (UCLA-R)
Doering et	Depressed women following	CBT (standard care)	8 sessions over 8 weeks (No	Mean age=60	hs-CRP, IL-6	Depression (BDI)

al., (2007) [17]	coronary artery bypass graft surgery Yes, diagnosis of depression (15,15)		post, 3 and 6 months FUs) Face-to-face at home (individual)	%Women=100 %White=53	(Blood; No)	
Eremin et al., (2009) [20]*	Women with breast cancer undergoing multimodality therapy No (81,71)	Relaxation and guided imagery therapy (standard care)	5 sessions for regular practice (regular FUs up to 37 weeks from baseline) At home audio program (individual)	Mean age=50 %Women=100 %White=NA	IL-1 β , IL-2, IL-4, IL-6, TNF- α (Blood; Yes)	-
Gallegos et al., (2013) [12]	Older adults No (200,200)	MBSR (wait-list)	9 sessions over 8 weeks (Post, 3 and 24 weeks FUs) Face-to-face (group)	Mean age=73 %Women=62 %White=97	IL-6 (Blood; No)	Positive affect (PANAS)
Irwin et al., (2014) [24]	Individuals with late life insomnia Yes, chronic and primary insomnia (75,75)	CBT (sleep hygiene seminar)	Weekly sessions over 4 months (Post, 3 and 12 months FUs) Face-to-face (group)	Mean age=65 %Women=75 %White=86	hs-CRP (Blood; Yes)	Depression (IDS-C), Fatigue (MDFSI), Sleep quality and parameters (PSQI, AIS, PSD), Sleepiness (ESS)
Menzies et al., (2014) [20]	Women with fibromyalgia No (72,64)	Guided imagery (standard care)	Daily practices for 10 weeks (Post, No FUs) At home audio program (individual)	Mean age=47 %Women=100 %White=64	hs-CRP, IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF- α , IFN- γ , GM-CSF, MCP-1 MIP-1 β (Blood; Yes)	Depression (CES-D), Fatigue (BFI), Self-efficacy for managing other symptoms (ASES), Pain (BPI), Perceived stress (PSS)
Oh et al., (2008) [21]	Mixed cancers No (30,18)	Medical Qigong (standard care)	8 to 16 sessions over 8 weeks (Post, No FUs) Face-to-face (group)	Mean age= 54 %Women=75 %White=84	hs-CRP (Blood; No)	Quality of life (EORTC QLQ-C30)
Oh et al., 2010 [25]	Mixed cancers No (162,101)	Medical Qigong (standard care)	20 sessions over 10 weeks (Post, No FUs) Face-to-face (group)	Mean age=60 %Women=58 %White=71	CRP (Blood; No)	Cancer-related fatigue (FACT-F), Mood (PoMS), Quality of life (FACT-G)
Oken et al., (2010) [25]	Caregivers of a close family member with progressive dementia	Meditation intervention based on MBSR and MBCT (attention)	7 sessions over 7 weeks (Post, No FUs) Face-to-face (group)	Mean age=63 %Women=85 %White=90	hs-CRP, IL-6, TNF- α (Saliva; No)	Behavior problems (NPI), Coping strategies (CRI), Depression (CES-D)

	No (20,17)	control)				Energy and fatigue (SF-36), Mindfulness (MAAS, FFMJ), Perceived stress (RMBPC, CAT, PSS), Self-efficacy (GPSES; RMBPC), Sleep quality (PSQI, ESQ)
Pakiz et al., (2011) [24]	Overweight or obese breast cancer survivors No (85,68)	CBT-based weight management (waitlist)	16 sessions over 16 weeks + 8 sessions over an additional 8 months (Post weekly sessions at 16 weeks, no FUs for inflammatory outcomes) Face-to-face (group)	Mean age=56 %Women=100 %White=94	IL-6, IL-8, TNF- α , VEGF (Blood; Yes)	-
Reich et al., (2017) [25]	Breast cancer survivors No (322, 299)	MBSR (wait-list)	6 sessions over 6 weeks (Post, 6 week FU)	Mean age=57 %Women=100 %White=69	IL-6, TNF- α , sTNFR1 (Blood; Yes)	Pain (BPI), fatigue (FSI), depression (CES-D), Anxiety (STAI-S), Stress (PSS), concerns about recurrence (CARS), quality of life (SF-36)
Richardson et al., (1997) [18]*	Breast cancer survivors No (31,31)	Imagery (standard care)	6 sessions over 6 weeks (Post, no FUs) Face-to-face (group)	Mean age=46 %Women=100 %White=70	IL-1 α , IL-1 β , IL-2, IFN- γ (Blood; No)	Coping (WOC-CA), Mood (PoMS-B), Quality of life (FACT-B), Social support (DUFSS)
Sharpe et al., (2001) [21]	Rheumatoid arthritis patients No (45,38)	CBT (standard care)	8 sessions over 8 weeks (Post, 6 month FU) Face-to-face (individual)	Mean age=56 %Women=71 %White=93	CRP (Blood; No)	Anxiety and depression (HADS), Coping (CSQ), Limitation and disability (HAQ), Pain (10-point scale)
Sharpe & Schrieber, (2012) [24]	Rheumatoid arthritis patients No (98,98)	CBT (waitlist)	8 sessions over 8 weeks (Post, 6 month FU) Face-to-face (individual)	Mean age=56 %Women=60 %White=NA	CRP (Blood; No)	Anxiety and depression (HADS), Limitation and disability (HAQ)
Taylor et al., (2009)[19]	Depressed patients with high risk for coronary heart disease	CBT (waitlist)	On average 15 sessions over 6 months (Post, No FUs) Face-to-face and telephone	Mean age=62 %Women=67 %White=96	hs-CRP (Saliva; No)	Depression (HRSD, BDI)

<i>Yes, diagnosis of depression</i> (48,42)		calls (individual)			
Walsh et al., Young women with (2016) [20] depressive symptoms <i>Yes, mild to moderate</i> <i>depressive symptoms</i> (64,64)	Mindfulness-based intervention (contact control group)	4 sessions over 4 weeks (Post, No FUs) Face-to-face (group)	Mean age=19 %Women=100 %White=86	IL-6, TNF- α (Saliva; No)	Depressive symptoms (CES-D)

Note. *=imputed effect size of Hedge's $g=0.0$; AIS= Athens Insomnia Scale; ASES=Arthritis Self-Efficacy Scale; BCPT=Breast Cancer Prevention Trial Symptom Checklist; BDI=Beck Depression Inventory; BFI=Brief Fatigue Inventory; BPI=The Brief Pain Inventory; CARS=Concerns about recurrence scale; CAT=Caregiver Appraisal Tool; CBT=cognitive behavioral therapy; CES-D=The Center Epidemiologic Depression Scale; CRI=Coping Response Inventory; CRP=C-reactive protein; CSQ=Coping Strategy Questionnaire; DUFSS=The Duke-UNC Functional Social Support Questionnaire; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; ESQ=Epworth Sleep Questionnaire; ESS=Epworth Sleepiness Scale; FACIT=Functional Assessment of Chronic Illness Therapy; FACT-B=The Functional Assessment of Cancer Treatment-Breast; FACT-G=Functional Assessment of Cancer Treatment-General; FACT-F= Functional Assessment of Cancer Treatment-Fatigue; FU=follow-up; FFNJ=Nonjudgmental factor derived from several mindfulness scales; FSI=Fatigue Symptom Inventory; FSS=Fatigue Severity Scale; GM-CSF=Granulocyte macrophage colony-stimulating factor; GPSES=General Perceived Self-Efficacy Scale; HADS=Hospital Anxiety and Depression Scale; HAQ=Health Assessment Questionnaire; HRSD=Hamilton Rating Scale for Depression; hs-CRP= high sensitivity CRP; IAS=Interaction Anxiousness Scale; IDS-C=Inventory of Depressive Symptomatology; IES=Impact of Events Scale; IL=Interleukin; MAAS=Mindful Attention Awareness Scale; MCP=Monocyte chemotactic protein; MDFSI=Multidimensional Fatigue Symptom Inventory; MIP=Macrophage inflammatory protein; NPI=Neuropsychiatric Inventory; NPY= neuropeptide Y; PANAS=Positive and negative Affect Schedule; PoMS-B=The Profile of Mood States-Brief; PSQI=Pittsburgh Sleep Quality Index; PDS=Pittsburgh Sleep Diary; PSS=Perceived Stress Scale; QLACS= Quality of Life in Adult Cancer Survivors; RMBPC=Revised Memory and Behavior Problems Checklist; post=immediately following the acute treatment; SF-36=Short Form Health Survey; STAI=State(s)-Trait(t) Anxiety Inventory; TNF=Tumor necrosis factor; UCLA-R=UCLA-R Loneliness Scale; VEGF=Vascular endothelial growth factor; WOC-CA=Ways of Coping with Cancer.

Table 2: Pooled effect sizes across outcomes and levels of categorical moderator variables.

	Sample size		Heterogeneity				Global effect sizes ^a			Failsafe N ^d	Criterion
	K	N	Q ^c	df	p	I ²	Hedge's g	95 % CI	p		
Outcome from pre to post treatment^b											
Combined pro-inflammatory outcomes	17	1401	9.8	16	.878	0.0	.15	.04 - .26	.009	14	95
Adjusted for publication bias	(17)						.15	.04 - .26			
CRP	10	558	6.0	9	.744	0.0	.23	.06 - .41	.008	10	60
Adjusted for publication bias	(10)						.23	.06 - .41			
IL-1 β	3	121	2.8	2	.244	29.2	.21	-.25 - .66	.370	-	-
IL-6	9	843	3.9	8	.862	0.0	.09	-.05 - .22	.204	-	-
TNF- α	6	538	1.6	5	.902	0.0	.11	-.06 - .28	.188	-	-
Outcome from pre-treatment to follow-up^b											
Combined pro-inflammatory outcomes	7	796	8.1	6	.229	26.1	<-.01	-.19 - .18	.964	-	-
CRP	4	226	2.6	3	.460	0.0	.18	-.11 - .47	.225	-	-
IL-6	4	585	3.8	3	.288	20.4	-.07	-.27 - .12	.469	-	-
Categorical moderators											
<u>Primary diagnosis</u>											

Autoimmune disease	4	224	0.3	3	.968	0.0	.11	-.17 - .38	.457	-	-
Cancer	6	582	5.8	5	.327	13.6	.17	-.02 - .36	.083	-	-
Between-group difference			0.1	1	.710						
<u>Treatment type</u>											
CBT	6	347	4.1	5	.539	0.0	.18	-.05 - .41	.117	-	-
Meditation/mindfulness	6	685	0.7	5	.980	0.0	.11	-.04 - .26	.152	-	-
Between-group difference			0.3	1	.596						
<u>Psychological distress selection criteria</u>											
Yes	4	207	1.5	6	.673	0.0	.29	<.01 - .57	.047	1	30
Adjusted for publication bias	(4)						.29	<.01 - .57			
No	13	1194	7.0	12	.858	0.0	.13	.01 - .25	.042	1	75
Adjusted for publication bias	(13)						.13	.01 - .25			
Between-group difference			1.1	1	.303						
<u>Treatment format</u>											
Face-to-face	14	1271	9.3	13	.752	0.0	.16	.04 - .28	.008	14	80
Adjusted for publication bias	(15)						.15	.03 - .27			
Other	3	130	0.1	2	.932	0.0	.07	-.27 - .41	.684	-	-

Between-group difference			0.2	1	.639						
<u>Treatment recipient</u>											
Group	12	1135	8.8	10	.553	0.0	.16	.04 - .28	.012	12	70
<i>Adjusted for publication bias</i>		(13)					.15	.02 - .27			
Individual	5	266	0.3	4	.990	0.0	.12	-.14 - .37	.369	-	-
Between-group difference			0.1	1	.750						

Note. *K* and *N* do not necessarily add up due to exclusion of non-independent samples/studies from the comparison analyses. Statistically significant results are highlighted in **bold**. *A*=Effect size = Hedge's *g*. Standardized mean difference, adjusting for small sample bias. A positive value indicates an effect size indicates an attenuating effect of psychological intervention; *b*=Possible publication bias was examined with funnel plots and Egger's test, followed by imputation of missing studies (Duval & Tweedie, 2000). (*K*) = *K* + number of imputed studies; *c*=*Q*-statistic: *p*-values < 0.1 taken to suggest heterogeneity; *d*=In case of statistically significant effect sizes, it was planned to examine the robustness of findings by calculating the Failsafe *N* (number of non-significant studies that would bring the *p*-value to non-significant (*p* > 0.05) (Rosenthal, 1979).

Table 3: Results from meta-regression-based moderation analyses

Moderator	B	SE	p
<i>Study quality characteristics</i>			
Jadad	0.01	0.01	.296
<i>Participant characteristics</i>			
Mean sample age	<0.01	<0.01	.849
% women	<-0.01	<0.01	.447
% Whites	<0.01	0.01	.602
BMI	<-0.01	<0.01	.636
<i>Intervention characteristics</i>			
# sessions	<-0.01	<0.01	.929
Treatment duration	<0.01	0.01	.917
Effects on behavioral outcomes	-0.04	0.08	.593

Figure 1: Flow chart of study selection

Figure 2. Forest plot of effect sizes for the combined pro-inflammatory biomarker outcomes.

Figure 3. Forest plot of effect sizes for CRP.

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Highlights

- Nineteen RCTs examined the effect of psychological intervention on inflammatory biomarkers
- The effect size from pre to post intervention was statistically significant but small
- The largest effect size was obtained for the studies preselecting on psychological distress

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