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The effect of mindfulness-based interventions on immunity-related biomarkers: a comprehensive meta-analysis of randomised controlled trials

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Abstract

One proposed pathway mindfulness-based interventions (MBIs) may offer a salutogenic effect on somatic disorders is by enhancing immune function. As such, we conducted a meta-analysis of randomised controlled trials examining the effect of MBIs at post-intervention and follow-up for six immune-related biomarkers, including *CD4+ cells*, *C-reactive protein*, *interleukin-6*, *nuclear factor-κB*, *telomere length*, and *telomerase activity*. Potential studies were identified by searching ScienceDirect, Web of Science, Academic Search Complete, AMED, MEDLINE, PsycARTICLES, and PsycINFO. Searches returned 1959 studies, of which 48 (70 effects) were included (N = 4683). Pooled effect sizes indicate a reduction in C-reactive protein (SMCD = -.14, 95% CI [-.26 – -.01]) and interleukin-6 (SMCD = -.35, 95% CI -.67 – -.03]), and an increase in CD4+ (SMCD = .09, 95% CI [-.05 – .22]), telomere length (SMCD = .12, 95% CI [.00 – .24]) and telomerase activity (SMCD = .81, 95% CI [.17 – 1.46]) at post-intervention. At follow-up, results show a reduction in interleukin-6 (SMCD = -.13, 95% CI [-.29 – .03]) and C-reactive protein (SMCD = -.39, 95% CI [-.68 – -.10]) and increase in CD4+ (SMCD = .22, 95% CI [-.08 – .52]). Meta-regression results show that some heterogeneity in effect size can be accounted for by intervention dosage, study population, and study design. Our findings quantify MBIs' potential for improving immune function.

Introduction

Understanding the coalescent nature of psychology and immunity is fundamental to advancing human wellbeing. The link between stress and disease outcomes is well established (Kivimäki et al., 2006; Richardson et al., 2012; Segerstrom & Miller, 2004) and psychology-centred endeavors seeking to improve physical health have focused on interventions with a potential to diminish the impact of stressors on immune function. One approach that has gained traction in recent decades is that of mindfulness-based interventions (MBIs).

At the core of MBI techniques is the concept of *mindfulness*, which can be defined as the ability to observe thoughts, bodily sensations, or feelings in the present moment nonjudgmentally (Bishop et al., 2004; Kabat-Zinn, 1990). Mindfulness practices have been incorporated into a number of therapeutic programs such as Mindfulness-Based Stress Reduction (MBSR) (Kabat-Zinn, 1990), Mindfulness-Based Cognitive Therapy (MBCT) (Segal, Williams & Teasdale, 2002), Dialectical Behavior Therapy (Linehan, 1993), and Acceptance and Commitment Therapy (ACT) (Hayes, Strosahl & Wilson, 1999). Research shows positive outcomes for MBIs targeting depression, anxiety, stress, eating, pain, addiction, sleep, and relapse (Goldberg et al., 2018; Khoury et al., 2013; Kanen, Nazir, Sedky & Pradhan, 2015; Segal, Williams & Teasdale, 2002; Van Gordon et al., 2016). Several mechanisms have been proposed to account for MBIs' impact on psychological functioning, such as alterations to memory, attention, meta-awareness, decentering, rumination, and emotion regulation (Fresco, Segal, Buis & Kennedy, 2007; Hargus, Crane, Barnhofer & Williams, 2010; Segal, Teasdale & Williams, 2004). Despite studies implicating a number of brain regions understood to be involved in these processes (Farb et al., 2007; Hölzel et al., 2011), the role of MBIs in treating somatic disorders is less clear (Black & Slavich, 2016; Khoury et al., 2013). Findings from controlled and randomised controlled trials suggest

changes in immune-related biomarkers may reflect one pathway by which MBIs' impact the prevention, progression, or cessation of disease (Davidson et al., 2003). Specifically, MBIs have been shown to reduce psychological and oxidative stress (Simon et al., 2006; Adachi, Kawamura & Takemoto, 1993), suggesting they may impact somatic disorders by modulating the immunosuppressive effects of stressors on immune function.

A systematic review of 20 RCTs concluded that mindfulness meditation may offer a salutogenic effect on three specific immune system processes: inflammation, cell-mediated immunity, and biological ageing (Black & Slavich, 2016). Concordant with this, studies show that MBSR reduces protein biomarkers of inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6) (Carlson, Speca & Patel, 2003; Oken et al., 2010). Elevation of such inflammatory indicators are linked to multiple psychological disorders and physiological diseases including chronic stress (McDade, Hawkley & Cacioppo, 2006; Wellen & Hotamisligil, 2005), depression (Howren, Lamkin & Suls, 2009; Miller, Maletic & Raison, 2009) breast and prostate cancer (Carlson et al., 2003; Knupfer & Preiss, 2007), tumor growth (D'Anello et al., 2010), and HIV (Robinson, Mathews & Witek-Janusek, 2003; Lau, 2006). Similarly, researchers have examined MBIs' impact on intracellular molecules (transcription factors) such as NF-κB, which act as precursors of proinflammatory cytokines (e.g., IL-6). Tentative findings suggest MBIs may reduce NF-κB activity as measured in peripheral blood mononuclear cells (PBMCs) (Bower et al., 2015; Black, O'Reilly, Olmstead, Breen & Irwin, 2015; Creswell, Irwin & Burklund, 2012).

MBIs have also been shown to positively act on cellular immunity biomarkers such as CD4+ T lymphocytes, which help produce effective immune response to pathogens. For example, research demonstrates that individuals participating in MBIs show increased or improved maintenance of CD4+ cell counts (Balbin, Ironson & Solomon, 1999; Creswell, Myers, Cole & Irwin, 2009; Seyed Alinaghi et al., 2012; Lengacher et al., 2013).

Additionally, MBIs have been linked with improvements to immune cell ageing, measured by means of telomere length (TL) and/or telomerase activity (TA) (an enzyme which helps to diminish cell ageing) (Schutte & Malouff, 2014; Schutte, Malouff & Keng, 2020). Telomeres are protein complexes that function to protect chromosomal ends from deterioration and preserve DNA material (Blackburn, 2000). Short telomere length and reduced telomerase activity have been related to several chronic illnesses such as cardiovascular disease (Calado & Young, 2009; Epel et al., 2006; Fitzpatrick et al., 2006), diabetes (Salpea et al., 2009), and cancer (Willeit et al., 2010).

Overall, the extant literature indicates MBIs may act on physiological markers integral to immune function, such that MBIs could help attenuate inflammation (e.g., CRP, IL-6, NF-κB), improve response to infection (e.g., CD4+ T cells) and diminish immune cell aging (e.g., TL, TA) (Black & Slavich, 2016). This highlights MBIs' potential to improve somatic symptoms related to disease by reducing the impact of psychological and oxidative stress processes on immune function (Salim, 2014). Given this potential, it is crucial to quantitatively summarise the evidence from a growing body of literature that assesses the impact of MBIs on physiological markers of immunity. To our knowledge, only one systematic review of this topic has been carried out (Black & Slavich, 2016) and no comprehensive meta-analysis. The authors of the systematic review conclude that although there is some evidence that MBIs may modulate immune parameters related to inflammation, infection response, and biological ageing (Black & Slavich, 2016), further work is needed to gauge their robustness, generalisability and clinical significance. Additionally, a high degree of heterogeneity across studies has been noted such that disparity in dosage, study population, and study design may obfuscate MBIs true effect of immune-related biomarkers. Thus, the aim of our study is to:

i. Conduct a systematic and comprehensive meta-analysis of RCTs examining the effect of MBIs on three immune parameters: inflammation (*C-reactive protein, interleukin-6, nuclear factor-κB*), infection response (*CD4+ cells*), and biological ageing (*telomere length, telomerase activity*) at post-intervention and follow-up.
ii. Review the quality (i.e., potential levels of bias) of studies in the field.
iii. Explore the role of dosage, study population, and study design in modulating MBIs' impact on the above immune-related biomarkers.

Methods

Eligibility Criteria

Following PRISMA guidelines (Liberati et al., 2009), studies reporting the effect of an MBI on at least one of the following immune-related biomarkers were selected for this meta-analysis: *CD4+*, *CRP*, *IL-6*, *NF-κB*, *TL*, *TA*. The following inclusion criteria were set: (1) article must be written in English (2) use an RCT design (3) include a measure of at least one of six immune-related biomarkers (4) be published in a peer-reviewed journal (5) include a mindfulness-based intervention. The following exclusion criteria were adopted: (1) the article status was 'unpublished' (2) the article was not peer reviewed (3) the design was not an RCT (4) did not include a measure of at least one target biomarker. The full search protocol (registration number: CRD42020187893) can be obtained via the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO) (Dunn & Dimolareva, 2020).

Databases

Seven databases were searched (ScienceDirect, Web of Science, Academic Search Complete, AMED, MEDLINE, PsycARTICLES, and PsycINFO) from their start date until 01.12.2021.

Search

Pre-determined search terms were selected that relate to immunity, mindfulness and design type. Details are provided in the published protocol (Dunn & Dimolareva, 2020).

Selection Process

All searches were conducted by the second author. Selection of articles was completed by both authors. Agreement of inclusion was reached by both authors.

Data Items

The following data were extracted from each study: (1) participant information (*N*, age, medical condition etc); (2) immune indicator; (3) control type (active, waitlist [WL], treatment as usual [TAU]); (4) intervention type (MBSR, MBCT, ACT etc.); (5) number of face-to-face sessions; (6) session duration; (7) point of last follow-up, if applicable; (8) Statistics (*Mean*, *SD*, *Effect size*).

Data Collection Process

The first Author extracted all meta-analysis data, and the second Author checked data accuracy. The participant information and design data were extracted by the first and second Authors separately to reduce likelihood of bias. The first author contacted corresponding authors to collate missing data.

Risk of Bias within Individual Studies

Risk of bias was summarised using the Cochrane collaboration tool (Higgens & Green, 2014) to evaluate general areas of bias inherent to RCTs. The review protocol was adhered to as set out in the Cochrane handbook (Higgens & Green, 2014). Two raters independently assessed risk of bias and any coding discrepancy was discussed until a consensus reached.

Summary Measures

The standardised mean change difference (SMCD) was the primary effect size statistic calculated. The SMCD was derived by calculating the difference between intervention and control effects and dividing by the pooled pretest standard deviation (Becker, 1988; Morris, 2008). A correction factor was used to provide a more precise estimate of the population treatment effect (Morris, 2008; Carlson & Schmidt, 1999). In the instances when a correlation coefficient between pre and post was not reported, a conservative estimate (r = .7) was used (Rosenthal, 1993). Effect sizes were exclusively calculated from *Means* and *SD*s, either reported in the article itself or obtained by way of contacting the authors. All log-transformed *Means* and *SD*s were converted to make them combinable with raw score derived effect sizes (Higgins, White & Anzures-Cabrera, 2008). Pooled effect sizes were calculated for each biomarker at post-intervention and last available follow-up separately. In instances where studies had more than one arm, data were extracted relating to the primary MBI and control condition comparison as defined by the study authors.

Synthesis of Results

All meta-analyses and plots were estimated using the *metafor* and *metaviz* packages in R (Viechtbauer, 2010; Kossmeier, Tran & Voracek, 2020). The standardised mean change, corresponding z and p values, and 95% confidence intervals (95% CI) were calculated. All

meta-analyses were specified as random-effects models using a restricted maximum-likelihood estimator. A random-effects model accounts for within- and between-study variation. Heterogeneity was assessed across studies in each group and sub-group using the I^2 and the *Q*-statistic (Higgins & Thompson, 2002; Higgins, Thompson, Deeks & Altman, 2003). I^2 provides a percentage of effect size variability due to heterogeneity rather than sampling error. The *Q*-statistic (based on χ^2) provides a test of significance of between-study heterogeneity. A random-effects model was used to estimate heterogeneity variance (I^2 and the *Q*-test).

Risk of Bias Across Studies

When three or more studies were available for inclusion, publication bias was assessed through visual inspection of funnel plots, where asymmetry of the distribution of effect size to standard error is suggestive of publication bias (Viechtbauer, 2010). Egger's test was used to assess the significance of asymmetry (Sterne & Egger, 2001). The trim-and-fill method was applied to any identified instances of asymmetry and effect sizes recalculated (Duval & Tweedie, 2000a; Duval & Tweedie, 2000b). Influence diagnostics were carried out to assess whether pooled effects were disproportionately dependent on a single study (Viechtbauer & Cheung, 2010).

Additional Analyses

In line with the objectives of this meta-analysis, meta-regression was used to examine whether dosage, study population, and study design moderated MBI efficacy. Dosage was calculated by multiplying session length in minutes by frequency per week and overall treatment length. For studies that reported session time as a range, the mean of the range was used. Study population related to whether the sample was drawn from a population with a pre-existing medical condition and was coded as 'yes', 'no', or 'not stated'. Study design

related to the type of control group employed and was categorised as either 'active' (e.g., exercise, relaxation therapy) or 'passive' (e.g., TAU, WL). A random-effects model was used to estimate the model coefficients, providing corresponding *z* and *p* values, while the *Q*-statistic was used as the omnibus test of the model coefficients.

Role of Funding Source

This meta-analysis has not received any funding.

Access to Data

Both authors had access to the data.

Results

Study Selection

The search returns from all databases (*N*=1959) were assessed at title and abstract level for their suitability in terms of the inclusion criteria for this meta-analysis (see Figure 1). As the abstract for some papers did not have the details to assess suitability of the research, the full text was assessed for eligibility.

***** place Figure 1. about here *****

Study Characteristics

Study characteristics for 48 qualifying studies are presented in Table 1. The number of effect sizes synthesised for each immune-related biomarker varied, including 12 for CD4+, 22 for CRP, 19 for IL-6, one for NF-κB, seven for TA, and nine for TL. Since only one study was included for NF-κB, it was omitted from any further analysis.

***** place Table 1. about here *****

Risk of Bias within Individual Studies

Risk of individual study bias was deemed to be low to moderate for each biomarker overall (see Figures 2). Specifically, studies presented low risk of bias for random sequence generation, allocation concealment, selective reporting and incomplete data. Outcome assessors were also either explicitly blind to study hypotheses or biomarkers analysed in a manner that limited the potential for bias (e.g., analysed in a third-party laboratory). However, more clarity was needed regarding the blinding of study personnel and whether individuals such as trial coordinators were blind to treatment allocation or study hypotheses.

***** place Figure 2. about here *****

Results of Individual Studies

A meta-analysis for each immune-related biomarker (CD4+, CRP, IL-6, NF-κB, TA, TL) at post-intervention and follow-up (where applicable) is reported below.

Synthesis of Results

MBI effect on immune-related biomarkers. Results showed MBIs had a small effect on CD4+ (SMCD = .09, 95% CI [-.05 – .22]), CRP (SMCD = -.14, 95% CI [-.26 – -.01]) and TL (SMCD = .12, 95% CI [.00 – .24]), a moderate effect on IL-6 (SMCD = -.35, 95% CI [-.67 – -.03]), and a large effect on TA (SMCD = .81, 95% CI [.17 – 1.46]) at post-intervention (see

Table 2 & Figure 3). Follow-up measurements were available for three biomarkers (CD4+, CRP, and IL-6). Results showed a small effect on IL-6 (SMCD = -.13, 95% CI [-.29 – .03]) and moderate effect on CD4+ cells (SMCD = .22, 95% CI [-.08 – .52]) and CRP (SMCD = -.39, 95% CI [-.68 – -.10]) (see Table 2 & Figure 4). Mean follow-up measurement was taken at 26.35 weeks (*SD* = 11.45). Confidence intervals for each pooled biomarker effect are compatible with the idea that MBIs likely offer some benefit to immune function. In particular, inflammatory regulation (CRP, IL-6) and cell aging (TA, TL).

Risk of Bias Across Studies

Results from Egger's test shows potential for publication bias for TA (at post-intervention), CD4+, and CRP (at follow up) meta-analyses (see Table 2). In light of this, the trim-and-fill method was used to estimate the effect sizes of potentially supressed studies (Duval & Tweedie, 2000a; Duval & Tweedie, 2000b). This did not alter the parameter estimates for TA or CRP as no supplementary studies needed to be included according to the non-parametric algorithm implemented in the metaphor package. However, trim-and-fill results reduced the CRP effect size (at follow up) (SMCD = -.14, 95% CI [-.49 – .24)], *SE* = .19, p-value = .50). This suggests potential bias in publication could be driving CRP follow up effects. However, it should be noted that Egger's test is designed to only be indicative of publication bias and alongside the trim-and-fill method performs less well with small sample sizes (Kabat-Zinn, 1990). Heterogeneity at post-intervention was low for TL, moderate for CD4+ and CRP, and high for TA and IL-6 (see Table 2). Heterogeneity at follow up was moderate for CD4+ and IL-6, and high for CRP. Sources of heterogeneity were explored further using meta-regression. Influence diagnostics identified Tolahunase, Sagar, Faiq and Dada (2018) as a study that when excluded from analysis contributed to significant changes in fitted models for both IL-6 (SMCD = -.21, 95% CI [-.40 – -.01], *SE* = .10, p = .04, *Q* = 65.68, τ^2 = .13, I^2 = 82.95%) and TL (SMCD = .08, 95% CI [-.03 – .19], *SE* = .06, p = .17, *Q*

= 10.00, τ^2 = .00, I^2 = 0%). Potential factors that may account for the influence Tolahunase et al.'s (2018) finding had on the fitted models include above average length of intervention (12 weeks), comparatively high frequency of practice (5 days per week), and the physical-focused nature of the intervention (Yoga- and meditation-based lifestyle intervention in comparison to meditation alone).

***** place Table 2. about here *****

Additional Analyses

Meta-regression. The aims of the meta-regression analysis were to i) explore MBI efficacy by way of assessing the relationship between MBI dosage and effect size, and ii) account for between-study sources of heterogeneity using study-specific characteristics. Study characteristics included whether the sample had a medical condition at the time of intervention and/or the control group was 'active' or 'passive'. Moderators were included in a meta-regression model for each biomarker dependent on availability of data. Medical condition as a moderator was replaced with HIV (yes/no) for CD4+ meta-regression analysis, owing to the fact study samples were noticeably divided by HIV and non-HIV participant samples.

The relationship between dosage and each corresponding biomarker was assessed first without additional moderators and showed a significant relationship for TA (z = 2.28, $p<.05$) and TL (z = 1.95, $p<.05$) (see Figure 5). However, both relationships became non-significant when additional moderators were entered into respective models (see Table 3). Moderators failed to explain any variance across CD4+ studies with significant residual heterogeneity (see Table 4). Subgroup analysis showed no significant difference in pooled effects (I^2= 0%,

p=.62) for samples consisting of HIV compared to non-HIV patients (see Figure 6). Since CD4+ count in HIV patients can be significantly influenced by antiretroviral treatment (ART), we compared studies where patients were not currently enrolled on ART (SMCD = .15, 95% CI [-.24 – .54], *SE* = .20, *z* = .75, p = .45, *Q* = 7.18, τ^2 = .09, I^2 = 77.82%, *k* = 3) with those where patients were undergoing ART (SMCD = .21, 95% CI [.15 – .41], *SE* = .10, *z* = 2.11, p = .04, *Q* = 1.70, τ^2 = .00, I^2 = 0%, *k* = 4) and found no significant difference between pooled effect sizes (I^2= 0%, p= .78).

Moderators explained a moderate amount of variance across CRP studies and the test of moderators remained non-significant with no significant residual heterogeneity. Medical condition was a significant predictor (I^2= 86.37%, p <.001) in terms of MBI's impact on CRP levels (see Figure 6). Moderators failed to significantly explain heterogeneity in IL-6 with significant residual heterogeneity. However, subgroup plots show some variation in pooled effect dependent on control group type (passive/active) and participants' medical status (see Figure 6). Moderators explained 100% of heterogeneity for TL with no significant residual heterogeneity, however the test for moderators did not reach significance. Moderators accounted for a small amount of variance in TA studies with a significant amount of residual heterogeneity. Subgroup plots suggest that the type of control group may have potential to impact pooled effect sizes for TA. Meta-regression analysis was not conducted for follow up meta-analyses due to limited sample sizes.

***** place Table 3. about here *****

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Discussion

A growing body of research is concerned with the relation between MBIs and physical health, yet to our knowledge this is the first meta-analysis and meta-regression to comprehensively assess the impact of MBIs across an array of immune-related biomarkers. From analysing collections of RCTs related to several biomarkers, MBIs appear to most notably influence two immune system parameters, i) regulation of circulating protein biomarkers of inflammation and ii) protection against cell ageing. IL-6 and CRP are biomarkers related to systemic inflammatory response (Gabay & Kushner, 1999; Wassel, Barrett-Connor & Laughlin, 2010). IL-6 helps regulate acute-phase immune responses whereas CRP binds to damaged cell membranes (Harris et al., 1999; Alnaas, Moon, Alton, Reed & Knowles, 2017). Elevated IL-6 and CRP levels are associated with injury, ageing, cardiovascular diseases, infection, and autoimmune disorders (Wassel et al.,2010; Finch,

2007). The fact MBIs produced changes to both CRP and IL-6 is not surprising, considering IL-6 have been shown to stimulate the production of CRP (Gabay & Kushner, 1999; McArdle, McMillan, Sattar, Wallace & Underwood, 2004). However, research also shows that CRP can be stimulated by factors other than IL-6 (Baumann et al., 1993), suggesting MBIs' impact on CRP and IL-6 collectively may be disease-specific.

The findings also indicate that MBIs impact telomere length and telomerase activity. Telomeres are protective DNA sequences located at the ends of chromosomes that ensure chromosomal stability and DNA replication (Blackburn, 1991). Telomeres shorten with cell division and therefore immune cell telomere length offers a marker of immune system ageing (Andrews, Fuijii, Goronzy & Weyand, 2010). Telomerase activity is crucial for preserving telomere length and promoting healthy cell function (Blackburn, 2000). Short telomere length and reduced telomerase activity have been related to several chronic illnesses such as cardiovascular disease (Calado & Young, 2009; Epel et al., 2006; Fitzpatrick et al., 2006), diabetes (Salpea et al., 2010), and cancer (Willeit et al., 2010). Telomerase activity can be measured across shorter time intervals (hours/days) compared with telomere length, which may take months or years to detect an observable change. This may explain our findings which show MBIs have a greater impact on telomerase activity over telomere length when measurement is taken at post-intervention (i.e., typically after six weeks). The paucity of longitudinal studies examining telomere biomarkers precludes a better understanding of MBIs' long-term impact on telomere length.

The current meta-analysis offers some evidence that MBIs may positively impact cell immunity, by way of improving CD4+ cell count. Although not statistically significant, examination of forests plots suggests MBIs may have potential to improve CD4+ cells over time and in specific populations (e.g., individuals with HIV). A complication that obfuscates assessing MBIs' impact on CD4+ counts directly is its ancillary role in improving adherence

to treatments such as ART and chemotherapy, which interfere with changes to CD4+ cell count. For example, MBIs may positively act on cell immunity by reducing stress (Kesarwani, Murali, Al-Khami & Mehrotra, 2013; Hubert et al., 2010) or improving treatment adherence by increasing positive affect (Yu et al., 2018; Carrico, Johnson, Colfax & Moskowitz, 2010). Subgroup analysis which aimed to partial out ART treatment effects in HIV patients showed no significant difference in intervention effect between HIV patients enrolled on ART compared to those not enrolled. However, sample sizes were small.

Only one study examining MBIs' impact on NF-κB, which act as precursors of proinflammatory cytokines (e.g., IL-6), could be included. Although several potential studies were identified, NF-κB was typically quantified in terms of gene expression as opposed to average activity or counts, which meant measurements across studies were not combinable. Future research might consider if supplementary forms of measurement metrics could be employed which are more conducive to meta-analytic techniques.

Meta-regression analysis indicated that an individual's medical status may play a role in MBI efficacy. Results showed MBIs' impact on CRP was dependent on whether the sample had a currently diagnosed medical condition (e.g., inflammatory bowel disease/rheumatoid arthritis) or not (e.g., cancer survivors/old age). Specifically, MBIs had no effect on CRP levels for individuals without a medical condition, whereas they reduced CRP for subjects with a medical condition. This is in line with literature demonstrating stressors may accelerate disease pathogenesis by increasing pro-inflammatory cytokines such as CRP (Liu, Wang & Jiang, 2017). Thus, MBI efficacy may improve when acting on conditions where elevation (or suppression) of inflammatory markers is apparent compared with non immune-related disorders. Subgroup plots also caution as to the impact control group type may have on study effects. Specifically, larger effects in favour of MBIs may be

more likely observed when the control group is passive (e.g., waitlist or TAU) compared to active (e.g., exercise or relaxation therapy).

The two immune parameters demonstrated to most saliently benefit from MBIs in this meta-analysis (i.e., inflammatory regulation & cell ageing) offer a link between MBIs and disease. In that, chronic psychological stress is associated with reduced telomerase activity, shortened telomere length and an increase in inflammatory, and oxidative stress processes (Segerstrom & Miller, 2004; Hubert et al., 2010; Damjanovic et al., 2007; Epel et al., 2004; Puterman et al., 2010; Simon et al., 2006). Extant literature shows that MBIs can reduce psychological and oxidative stress (Simon et al.,2006; Adachi, Kawamura & Takemoto, 1993), suggesting MBIs may impact somatic disorders by modulating the immunosuppressive effects of stressors on immune function. This is also in line with our findings that suggest active control interventions such as relaxation and exercise (which are also related to stress reduction) may attenuate comparative gains observed from MBIs.

Recommendations for the Field

To better understand the acute effects of salutary interventions such as MBIs on immune-related biomarkers, hypothesised mechanisms of change (e.g., stress reduction, enhanced mindfulness/attention, improved emotion regulation) ought to be captured alongside intervention outcomes (e.g., immune-related biomarkers). This would allow future research to map theoretical active mechanisms of mindfulness onto specific immune processes. In line with our current findings that support previous literature suggesting a link between dosage and outcome (e.g., Black & Slavich, 2016), it is important for future studies to report total MBI treatment adherence (including private practice) over direct intervention engagement. A greater number of follow-up studies are needed to better understand the long-term impact of MBIs on telomere length and CD4+ cells. Additionally, the beneficial effect

MBIs may have on adhering to immune-impacting treatments such ART and chemotherapy should be explored further. Given sufficient power, moderators such as gender and whether the biomarker of interest was a primary or secondary outcome of the study should also be examined.

Limitations

We did not include full biomarker arrays such as all interleukins, by doing so may provide a more complete picture as to MBIs' impact on immunity. Some subgroup analyses included small sample sizes which likely reduced statistical power.

Conclusion

In summary, findings from 48 randomised controlled trials (N = 4,683) indicate mindfulness-based practices may reduce inflammation and protect against cell ageing, and thus are in line with the idea that mindfulness-based practices can positively impact immune function via a salutogentic pathway (Wirth et al., 2019). It also provides scope for understanding MBIs' broader role in somatic disorders, such that MBIs may help to improve aspects of immune function linked to pathogenesis by modulating stress processes.

Author Contributions

TD contributed to study conceptualisation, data curation, formal analysis, methodology, writing and editing of original draft, project administration and validation. MD contributed to methodology, editing of original draft, investigation and validation.

Declaration of Interests

The Authors declare no conflicts of interest.

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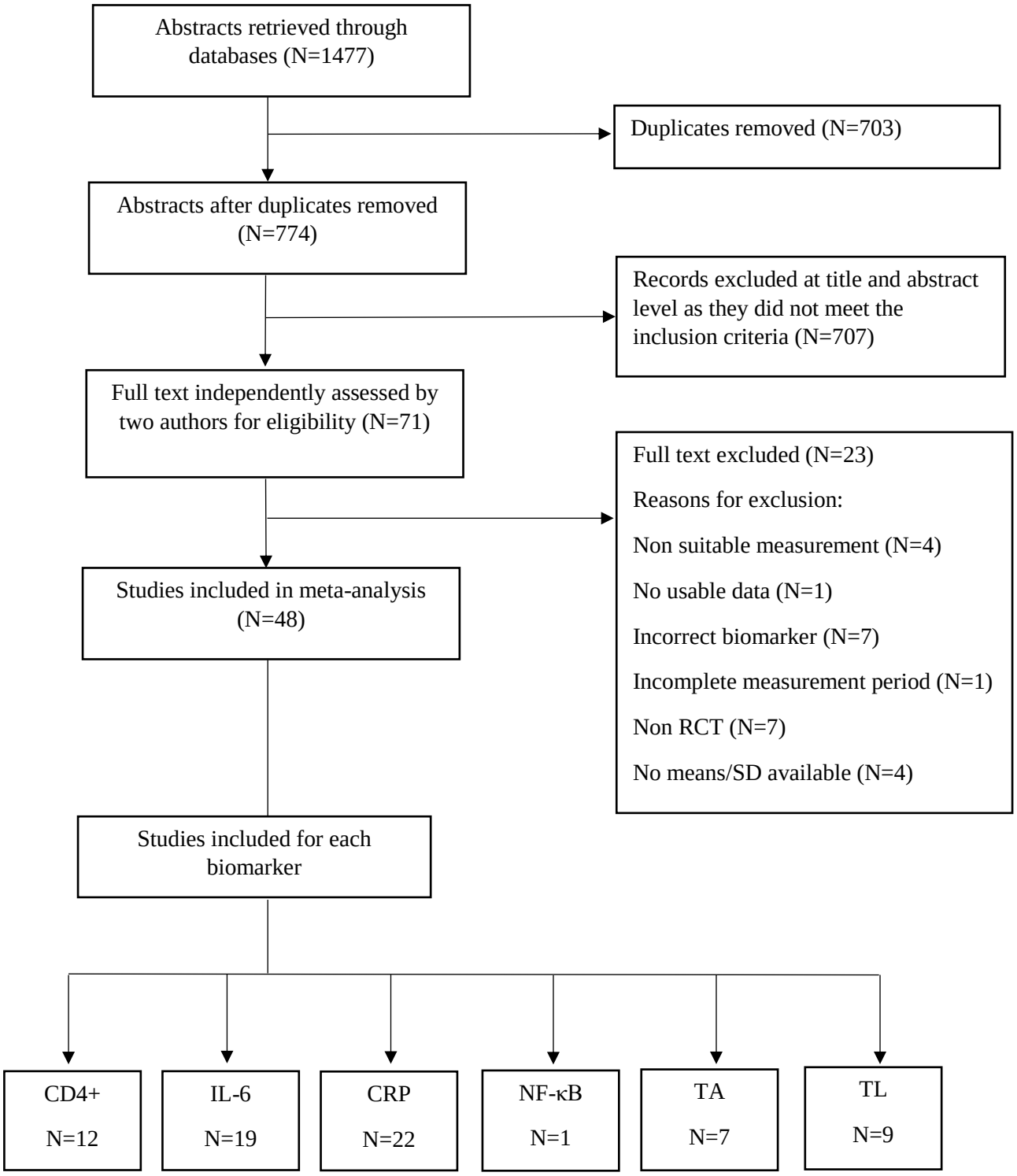


Figure 1: Study selection

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; NF-KB = nuclear factor-KB; TA = telomerase activity; TL = telomere length

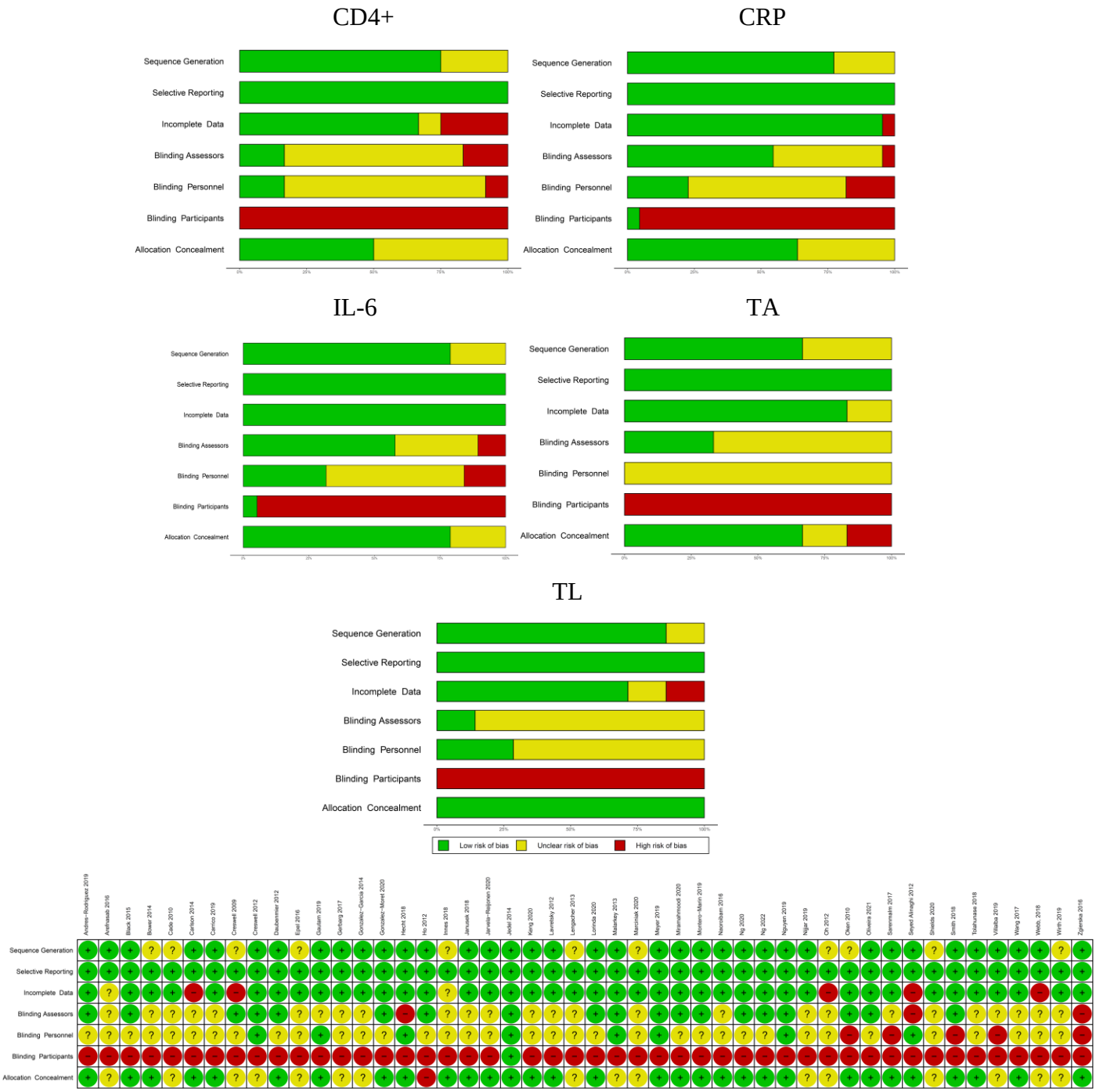
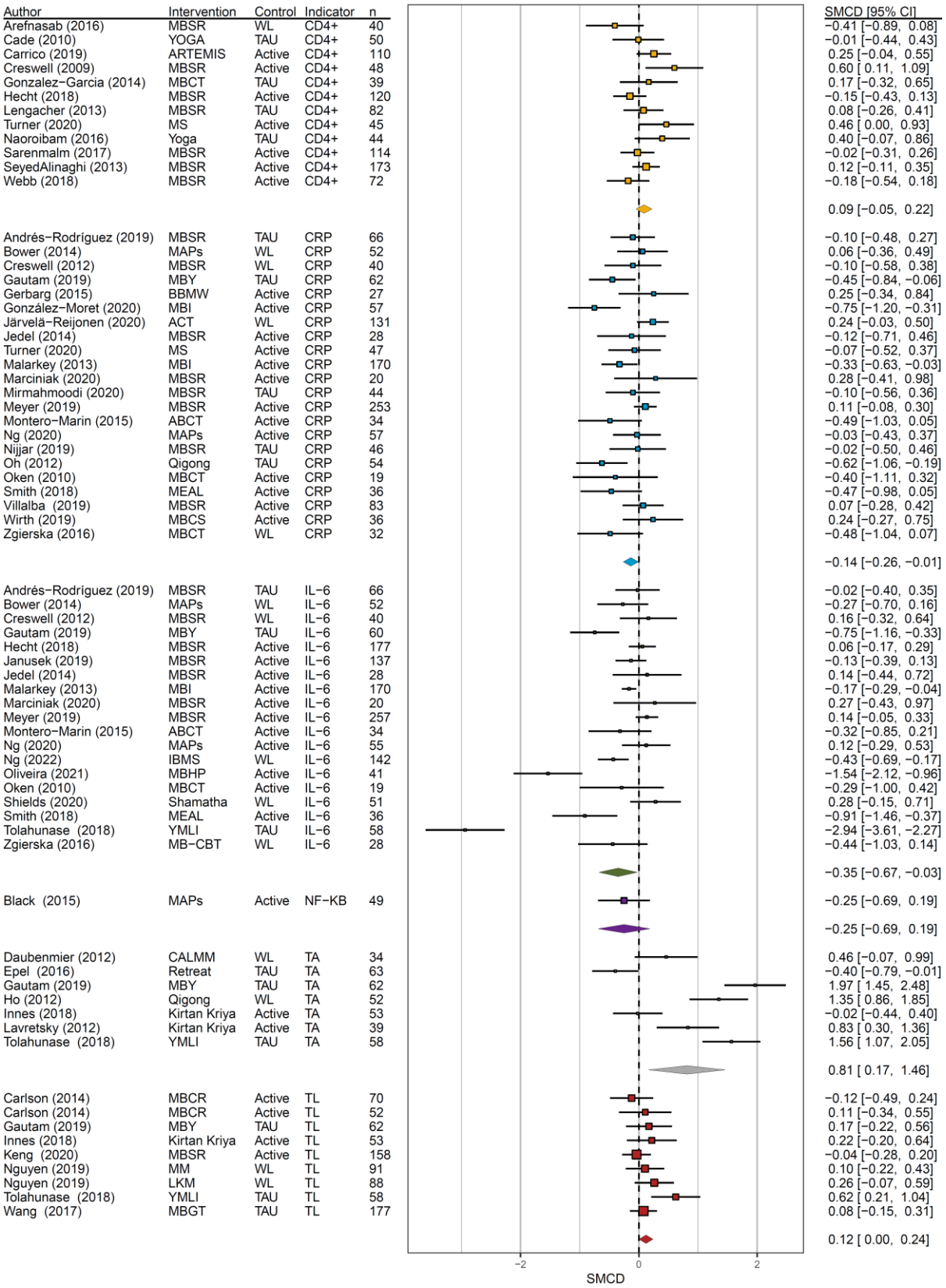


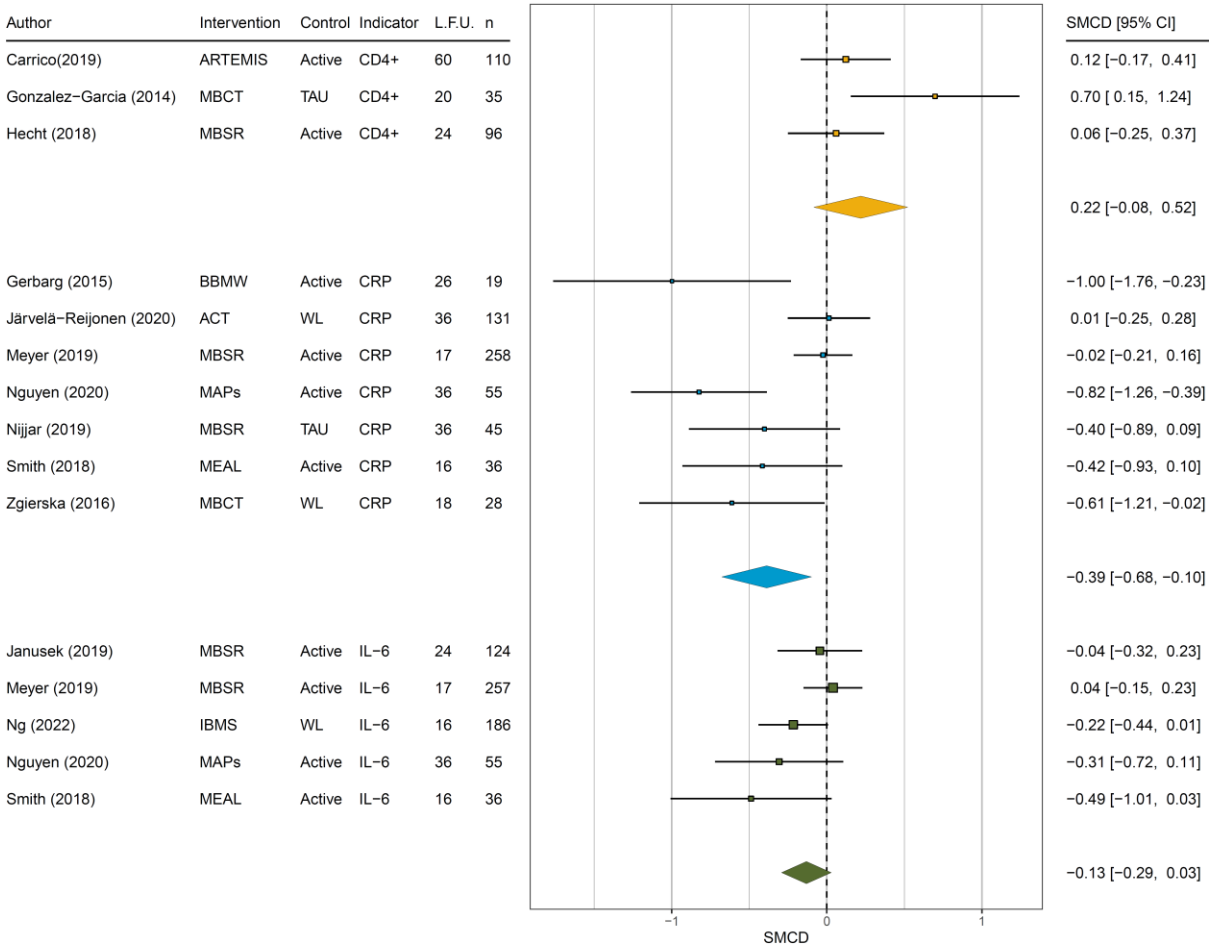
Figure 2: Risk of bias for each biomarker and study

Figure 3: Forest plot showing the effect of MBI on immunity indicators at post-intervention



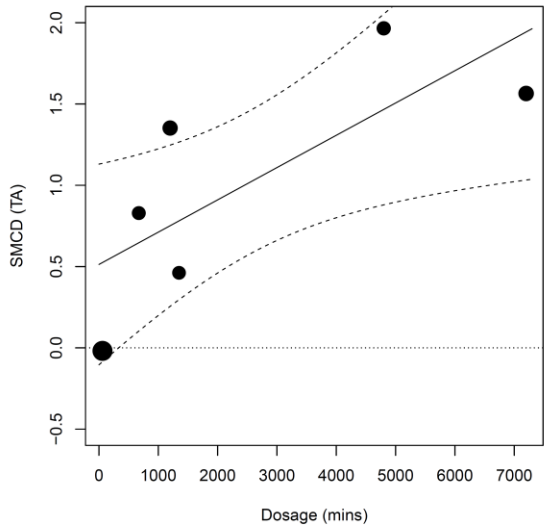
Notes: CRP = C-reactive protein; IL-6 = interleukin-6; NF-KB = nuclear factor-KB; TA = telomerase activity; TL = telomere length; TAU = treatment as usual; WL = waitlist; Active = active control; SMCD = standardized mean change difference

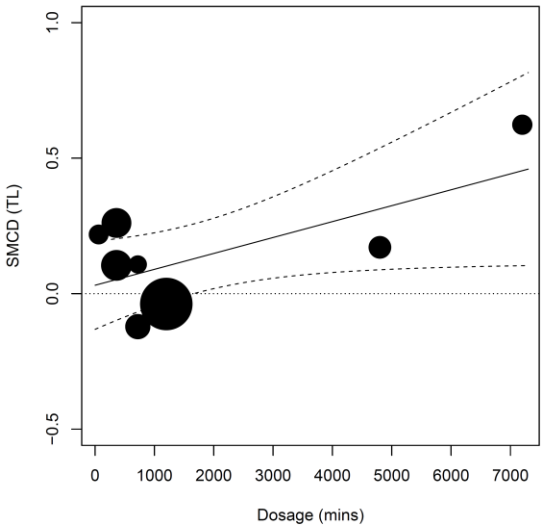
Figure 4: Forest plot showing the effect of MBIs on immunity indicators at follow-up

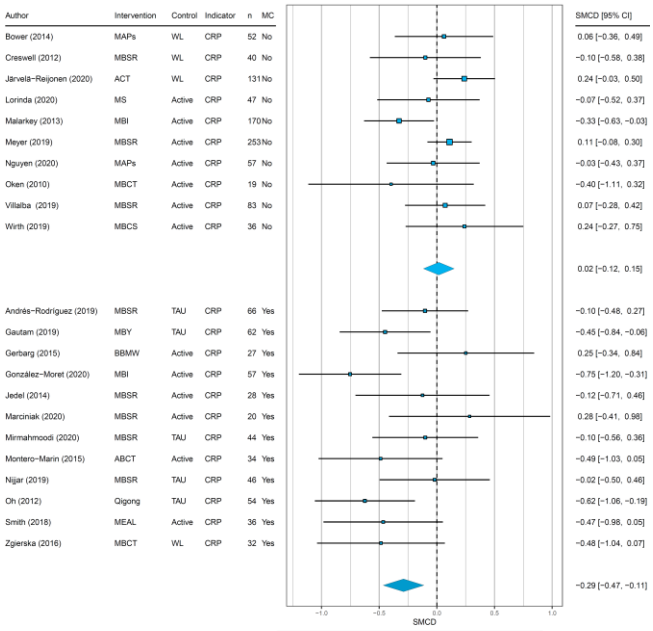


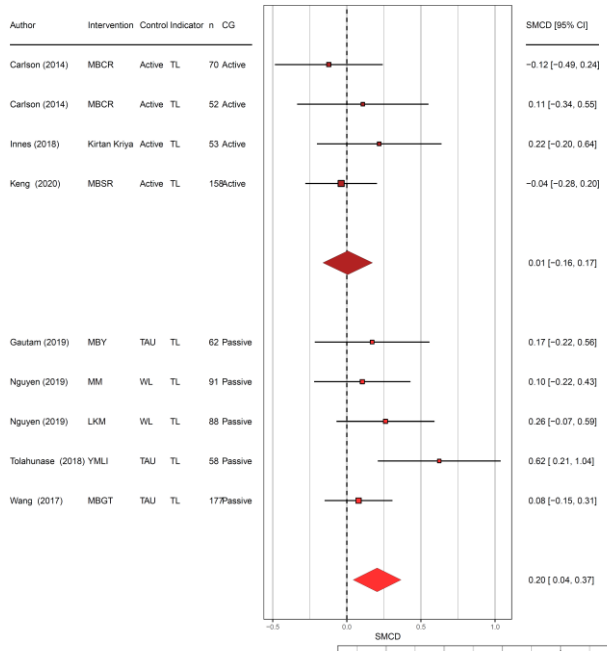
Notes: CRP = C-reactive protein; IL-6 = interleukin-6; TAU = treatment as usual; WL = waitlist; Active = active control; SMCD = standardized mean change difference; L.F.U = last follow-up (weeks)

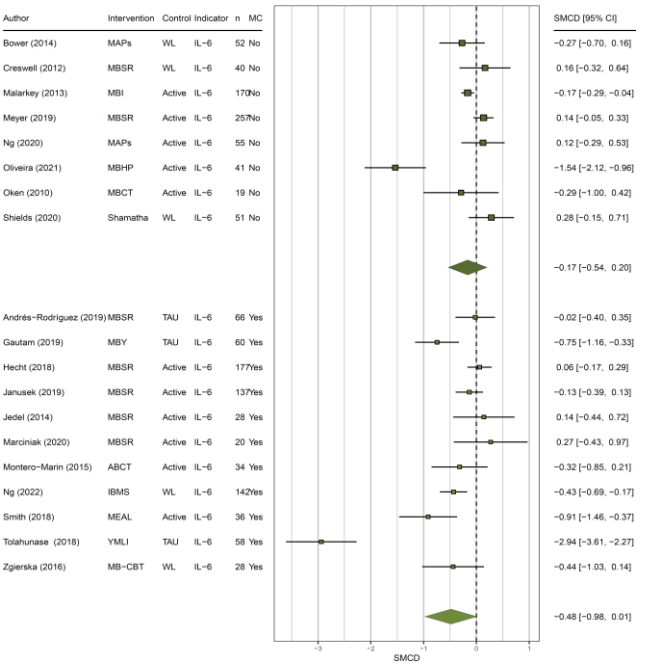
Figure 5: Bubble plots showing the relationship between dosage (mins) and effect size for telomerase activity and telomere length

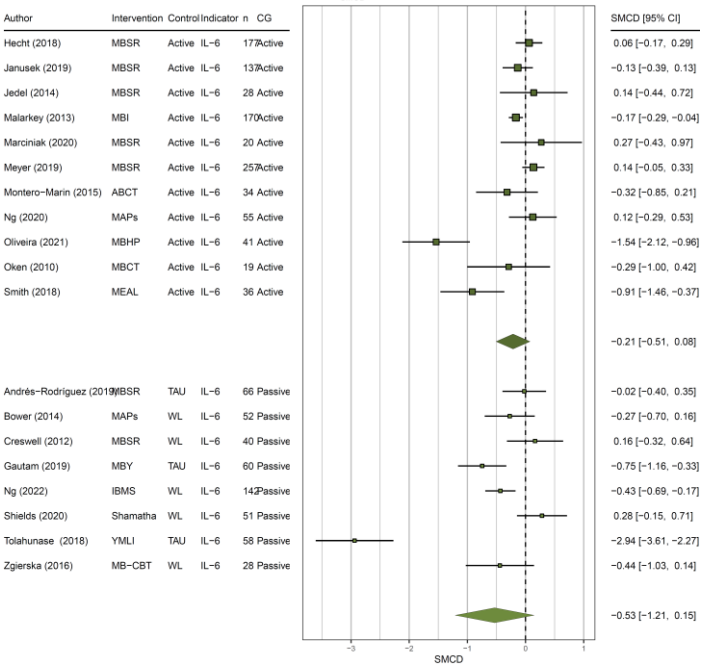

SMCD (TA)
2.0
1.5
1.0
0.5
0.0
−0.5
0
1000
2000
3000
4000
5000
6000
7000
Dosage (mins)


SMCD (TL)
1.0
0.5
0.0
−0.5
0
1000
2000
3000
4000
5000
6000
7000
Dosage (mins)


Author Intervention Control Indicator n MC SMCD [95% CI]
Bower (2014) MAPs WL CRP 52 No 0.06 [−0.36, 0.49]
Creswell (2012) MBSR WL CRP 40 No −0.10 [−0.58, 0.38]
Järvelä−Reijonen (2020) ACT WL CRP 131 No 0.24 [−0.03, 0.50]
Lorinda (2020) MS Active CRP 47 No −0.07 [−0.52, 0.37]
Malarkey (2013) MBI Active CRP 170 No −0.33 [−0.63, −0.03]
Meyer (2019) MBSR Active CRP 253 No 0.11 [−0.08, 0.30]
Nguyen (2020) MAPs Active CRP 57 No −0.03 [−0.43, 0.37]
Oken (2010) MBCT Active CRP 19 No −0.40 [−1.11, 0.32]
Villalba (2019) MBSR Active CRP 83 No 0.07 [−0.28, 0.42]
Wirth (2019) MBCS Active CRP 36 No 0.24 [−0.27, 0.75]
0.02 [−0.12, 0.15]
Andrés−Rodríguez (2019) MBSR TAU CRP 66 Yes −0.10 [−0.48, 0.27]
Gautam (2019) MBY TAU CRP 62 Yes −0.45 [−0.84, −0.06]
Gerbarg (2015) BBMW Active CRP 27 Yes 0.25 [−0.34, 0.84]
González−Moret (2020) MBI Active CRP 57 Yes −0.75 [−1.20, −0.31]
Jedel (2014) MBSR Active CRP 28 Yes −0.12 [−0.71, 0.46]
Marciniak (2020) MBSR Active CRP 20 Yes 0.28 [−0.41, 0.98]
Mirmahmoodi (2020) MBSR TAU CRP 44 Yes −0.10 [−0.56, 0.36]
Montero−Marin (2015) ABCT Active CRP 34 Yes −0.49 [−1.03, 0.05]
Nijjar (2019) MBSR TAU CRP 46 Yes −0.02 [−0.50, 0.46]
Oh (2012) Qigong TAU CRP 54 Yes −0.62 [−1.06, −0.19]
Smith (2018) MEAL Active CRP 36 Yes −0.47 [−0.98, 0.05]
Zgierska (2016) MBCT WL CRP 32 Yes −0.48 [−1.04, 0.07]
−0.29 [−0.47, −0.11]
−1.0 −0.5 0.0 0.5 1.0
SMCD


Author Intervention Control Indicator n CG SMCD [95% CI]
Carlson (2014) MBCR Active TL 70 Active −0.12 [−0.49, 0.24]
Carlson (2014) MBCR Active TL 52 Active 0.11 [−0.34, 0.55]
Innes (2018) Kirtan Kriya Active TL 53 Active 0.22 [−0.20, 0.64]
Keng (2020) MBSR Active TL 158 Active −0.04 [−0.28, 0.20]
0.01 [−0.16, 0.17]
Gautam (2019) MBY TAU TL 62 Passive 0.17 [−0.22, 0.56]
Nguyen (2019) MM WL TL 91 Passive 0.10 [−0.22, 0.43]
Nguyen (2019) LKM WL TL 88 Passive 0.26 [−0.07, 0.59]
Tolahunase (2018) YMLI TAU TL 58 Passive 0.62 [0.21, 1.04]
Wang (2017) MBGT TAU TL 177 Passive 0.08 [−0.15, 0.31]
0.20 [0.04, 0.37]
−0.5 0.0 0.5 1.0
SMCD


Author Intervention Control Indicator n MC SMCD [95% CI]
Bower (2014) MAPs WL IL−6 52 No −0.27 [−0.70, 0.16]
Creswell (2012) MBSR WL IL−6 40 No 0.16 [−0.32, 0.64]
Malarkey (2013) MBI Active IL−6 170 No −0.17 [−0.29, −0.04]
Meyer (2019) MBSR Active IL−6 257 No 0.14 [−0.05, 0.33]
Ng (2020) MAPs Active IL−6 55 No 0.12 [−0.29, 0.53]
Oliveira (2021) MBHP Active IL−6 41 No −1.54 [−2.12, −0.96]
Oken (2010) MBCT Active IL−6 19 No −0.29 [−1.00, 0.42]
Shields (2020) Shamatha WL IL−6 51 No 0.28 [−0.15, 0.71]
−0.17 [−0.54, 0.20]
Andrés−Rodríguez (2019) MBSR TAU IL−6 66 Yes −0.02 [−0.40, 0.35]
Gautam (2019) MBY TAU IL−6 60 Yes −0.75 [−1.16, −0.33]
Hecht (2018) MBSR Active IL−6 177 Yes 0.06 [−0.17, 0.29]
Janusek (2019) MBSR Active IL−6 137 Yes −0.13 [−0.39, 0.13]
Jedel (2014) MBSR Active IL−6 28 Yes 0.14 [−0.44, 0.72]
Marciniak (2020) MBSR Active IL−6 20 Yes 0.27 [−0.43, 0.97]
Montero−Marin (2015) ABCT Active IL−6 34 Yes −0.32 [−0.85, 0.21]
Ng (2022) IBMS WL IL−6 142 Yes −0.43 [−0.69, −0.17]
Smith (2018) MEAL Active IL−6 36 Yes −0.91 [−1.46, −0.37]
Tolahunase (2018) YMLI TAU IL−6 58 Yes −2.94 [−3.61, −2.27]
Zgierska (2016) MB−CBT WL IL−6 28 Yes −0.44 [−1.03, 0.14]
−0.48 [−0.98, 0.01]
−3 −2 −1 0 1
SMCD


Author Intervention Control Indicator n CG SMCD [95% CI]
Hecht (2018) MBSR Active IL−6 177 Active 0.06 [−0.17, 0.29]
Janusek (2019) MBSR Active IL−6 137 Active −0.13 [−0.39, 0.13]
Jedel (2014) MBSR Active IL−6 28 Active 0.14 [−0.44, 0.72]
Malarkey (2013) MBI Active IL−6 170 Active −0.17 [−0.29, −0.04]
Marciniak (2020) MBSR Active IL−6 20 Active 0.27 [−0.43, 0.97]
Meyer (2019) MBSR Active IL−6 257 Active 0.14 [−0.05, 0.33]
Montero−Marin (2015) ABCT Active IL−6 34 Active −0.32 [−0.85, 0.21]
Ng (2020) MAPs Active IL−6 55 Active 0.12 [−0.29, 0.53]
Oliveira (2021) MBHP Active IL−6 41 Active −1.54 [−2.12, −0.96]
Oken (2010) MBCT Active IL−6 19 Active −0.29 [−1.00, 0.42]
Smith (2018) MEAL Active IL−6 36 Active −0.91 [−1.46, −0.37]
−0.21 [−0.51, 0.08]
Andrés−Rodríguez (2019) MBSR TAU IL−6 66 Passive −0.02 [−0.40, 0.35]
Bower (2014) MAPs WL IL−6 52 Passive −0.27 [−0.70, 0.16]
Creswell (2012) MBSR WL IL−6 40 Passive 0.16 [−0.32, 0.64]
Gautam (2019) MBY TAU IL−6 60 Passive −0.75 [−1.16, −0.33]
Ng (2022) IBMS WL IL−6 142 Passive −0.43 [−0.69, −0.17]
Shields (2020) Shamatha WL IL−6 51 Passive 0.28 [−0.15, 0.71]
Tolahunase (2018) YMLI TAU IL−6 58 Passive −2.94 [−3.61, −2.27]
Zgierska (2016) MB−CBT WL IL−6 28 Passive −0.44 [−1.03, 0.14]
−0.53 [−1.21, 0.15]
−3 −2 −1 0 1
SMCD

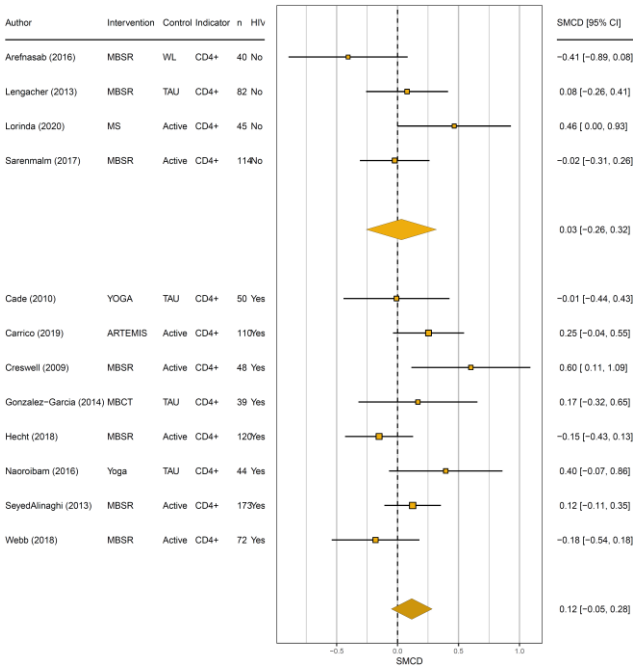


Figure 6: Subgroup meta-analyses of studies assessing CRP, IL-6, and TL grouped by medical condition and/or control group type

Notes: MC = medical condition; CG = control group type

Table 1

Study characteristics of the articles included in the meta-analysis

First Author Year	*Participant Information*				*Treatment Details*	*Control Details*	*Medication*	*Clinical Sample*	*Biomarker (Measure)*	*Findings*
	N T(otal) C(ontrol) I(ntervention / Treatment)	*Medical Condition*	*Sample Mean Age (SD)*	*Sex*						
Arefnasab 2016	T= 40 I= 20 C= 20	Mild-Moderate Pulmonary Injury	M= 49.4 Range= 42-59	M= 40 F= 0	MBSR 8 x 120 min 1 x daily home practise	WL 0 sessions	No	No	CD4+ (%)	N/S
Cade	T= 60 I= 34 C= 26	HIV	Range= 18-70 years	M= 45 F= 15	Yoga 2-3 x 60 min sessions per week for 20 weeks	TAU	cART	Yes	CD4+ (count)	N/S
Carrico	T= 110 I=55 C= 55	HIV	43.2 (8.9)	M=110	ARTEMIS 5x 60 min sessions	Attention-control (Active control)	ART	Yes	CD4+ (count)	N/S
Creswell 2009	T= 67 I= 41 C= 26	HIV	NP	M= 43 F= 5	MBSR 8 x 120 min 30 min daily home practise 6h day retreat	1-day MBSR 1 session x 360 min	No	Yes	CD4+ (count)	Control- sig decrease MBSR- no sig change

Gonzalez-Garcia 2014	T= 40 I= 20 C= 20	HIV	49.4 (5.1)	M= 20 F= 19	MBCT 8 x 150 min 6x 45 min/ week home practise	TAU 0 sessions	NP	Yes	CD4+ (count)	Control- N/S MBCT: Post-int: N/S Follow-up: Sig increase
Hecht 2018	T= 177 I= 89 C= 88	HIV	NP	M= 171 F= 6	MBSR 8x 150 min 6x 45 min home practise/ week 8hr silent retreat	Education 8 x 150 min	No	Yes	CD4+ (count)	N/S
Lorinda	T= 54 I= 27 C= 27	None	18+	M= 16 F= 38	MSS 8x 75-90 min weekly sessions	TAU	No	No	CD4+ (%)	N/S
Lengacher 2013	T= 84 I= 41 C= 43	Cancer	58 (9)	M= 0 F= 84	MBSR 6 x 120 min	TAU 0 sessions	NP	No	CD4+ (count)	N/S
Naoroibam	T= 44 I= 22 C= 22	HIV	35.14 (6.84)	M= 24 F= 20	Yoga 6x 60min per week for 1 month	TAU	ART	Yes	CD4+ (count)	N/S

Sarenmalm 2017	T= 177 I= 66 C(A)= 57 C(N)= 54	Cancer	57.2 (10.2)	M= 0 F= 177	MBSR 8 x 120 min Homework	Self-instruction MBSR 0 sessions	NP	Yes	CD4+ (%)	N/S
Seyed Alinaghi 2012	N= 245 I= 120 C= 125	HIV	35.1 (6.5)	M= 118 F= 53	MBSR 8 sessions (duration NP) 6-7h retreat	TAU + education & support 2 sessions (duration NP)	No	Yes	CD4+ (count)	Control-N/S MBSR: Post-int: Sig increase Follow-up: decrease back to baseline
Webb 2018	T= 96 I= 48 C= 45	HIV	18.71 (2.31)	M= 38 F= 33	MBSR 9 sessions (duration NP)	HealthEd 9 sessions (duration NP)	NP	Yes	CD4+ (count)	N/S
Andres-Rodriguez 2019	T= 70 I= 35 C= 35	FM	NP	M= 0 F= 70	MBSR (&TAU) 8x 150 sessions 45 min/ day home practise 6h retreat	TAU 0 sessions	No	Yes	CRP	N/S

Bower 2014	T= 71 I= 39 C= 32	Cancer (survivors)	NP	M= 0 F= 71	MAPs 6 x 120 min 5-20 mins/day home practise	WL 0 sessions	NP	No	CRP	N/S
Creswell 2012	T= 40 I= 20 C= 20	None	65 (7)	M= 8 F= 32	MBSR 8x 120 min 30 min/day, 6 days/ week home practise 7h retreat	WL 0 sessions	No	No	CRP	N/S
Gautam 2019	T= 72 I= 36 C= 36	Rh Arthritis	NP	M= 16 F= 56	MBY 40 x 120 min	TAU 0 sessions	NP	Yes	CRP	MBY sig decrease
Gerbarg 2017	T= 29 I= 16 C= 13	IBD	53.92 (15.22)	M= 12 F= 17	BBMW 2x consecutive days (9h) 6x weekly 90 min sessions, then monthly for 5 months 20 mins/ day home practice	ES 2 x consecutive days (9h) 6 x weekly education sessions	Yes, info collected	Yes	CRP	BBMW sig decrease

Gonzalez-Moret 2020	T= 57 I= 37 C= 20	Inflammatory bowel disease	NP	M= 19 F= 38	MBI & SMT 4x 120 min 4 online modules	SMT 0 sessions	No	Yes	CRP	MBI & SMT sig decrease
Jarvela-Reijonen 2020	T= 254 I= 84 I (O)= 85 C= 85	None	NP	M= 33 F= 171	ACT 8 x 90 min Homework (duration NP)	No Treatment 0 sessions	NP	No	CRP	ACT face to face sig decrease
Jedel 2014	T= 55 I= 27 C= 28	Inactive Ulcerative Colitis	NP	M= 24 F= 31	MBSR 8x 120- 150 min 45 min/day, 6 days/ week home practise	Time/ Attention Intervention 8x120 min	NP	Yes	CRP	N/S
Lorinda	T= 54 I= 27 C= 27	None	18+	M= 16 F= 38	MSS 8x 75-90 min weekly sessions	TAU	No	No	CRP	N/S

Malarkey 2013	T= 186 I= 93 C= 93	None	NP	M= 23 F= 161	MBI 8x 60 min 20 min/day home practise 2h retreat	Lifestyle Education Program 8x 60 min 30 min/ day home practise 2h retreat	NP	No	CRP	N/S Post-int: MBI-Id decreased
Marciniak	T= 28 I= 18 C= 10	Mild Cognitive Impairment	74 (6.9)	M= 7 F= 13	MBSR 150 min per week for 8 weeks 6 hour retreat Home practise	Cognitive Training 150 min per week for 8 weeks	NP	Yes	CRP	N/S
Meyer 2019	T=413 I= 138 C(A)= 137 C(N)= 138	None	49.7 (11.6)	M= 92 F= 293	MBSR 8x150 min Home practise (duration NP) Half day retreat	Exercise 8 x 150 min Half day retreat	NP	No	CRP	MBSR sig increase
Mirmahmoodi 2020	T= 44 I= 22 C=22	Breast cancer	44.89 (10.65)	M= 0 F= 44	8x 90 min weekly sessions	TAU	NP	Yes	CRP	NS

Montero-Marin 2019	T= 64 I= 23 I (O)= 22 C= 19	FM	NP	M= 0 F= 64	ABCT 8 x 120 min Daily homework (duration NP)	Relaxation Therapy 8x 120 min Daily homework (duration NP)	No	Yes	CRP	ABCT sign decrease
Ng 2020	N= 55 I= 28 C= 27	Mild Cognitive Impairment	71.28 (6)	M= 14 F= 41	MAPs 18x 60 min	Health Ed 18 x 60 min	NP	No	CRP	Post-int: N/S Follow up: MAPS sig decrease
Nijjar 2019	T= 47 I= 31 C= 16	Cardiac Patients	58.6 (10.8)	M= 29 F= 18	MBSR N & duration NP	TAU 0 sessions	NP	Yes	CRP	N/S
Oh 2012	T= 81 I= 37 C= 44	Cancer	NP	M= 38 F= 38	MQ & TAU 20 x 90 min Home practise (duration NP)	TAU 0 sessions	NP	Yes	CRP	MQ sig decrease
Oken 2010	T= 31 I= 10 I (O)= 10 C= 11	None	NP	M= 6 F= 25	MBCT 7 x 90 min Home practise (duration NP)	Dementia Education 7 x 90 min	NP	No	CRP	N/S

Smith 2018	T= 40 I= 20 C= 20	Obesity	58.46 (4.87)	M= 0 F= 40	MEAL 16 x 120 min	CONT 16 x 120 min	No	Yes	CRP	Post-int: N/S Follow up: MEAL sig decrease
Villalba 2019	T= 137 I (MO)= 53 C= 30 Another int= 54	None	38 (13)	M= 45 F= 92	MBSR 14 x 280 sessions 3-10 min/ day home practise	No Treatment 0 sessions	No	No	CRP	N/S
Wirth 2019	T= 36 I= 19 C= 17	Cancer (survivors)	63.9 (10.1)	NP most F	MBCS Home practise (duration NP)	Breathing 1 session (duration NP)	No	No	CRP	N/S
Zgierska 2016	T= 35 I= 21 C= 14	Chronic Low Back Pain	51.8 (9.7)	NP	MB-CBT 8x 120 min 30 min/ day, 6 days/week home practise	WL 0 sessions	NP	No	CRP	N/S
Andres-Rodriguez 2019	T= 70 I= 35 C= 35	FM	NP	M= 0 F= 70	MBSR (&TAU) 8x 150 sessions 45 min/ day home practise 6h retreat	TAU 0 sessions	No	Yes	IL-6	N/S

Bower 2014	T= 71 I= 39 C= 32	Cancer (survivors)	NP	M= 0 F= 71	MAPs 6 x 120 min 5-20 mins/day home practise	WL 0 sessions	NP	No	IL-6	N/S
Creswell 2012	T= 40 I= 20 C= 20	None	65 (7)	M= 8 F= 32	MBSR 8x 120 min 30 min/day, 6 days/ week home practise 7h retreat	WL 0 sessions	No	No	IL-6	N/S
Gautam 2019	T= 72 I= 36 C= 36	Rheumatoid Arthritis	NP	M= 16 F= 56	MBY 40 x 120 min	TAU 0 sessions	NP	Yes	IL-6	MBY sig decreases
Janusek 2018	T= 192 I= 96 C= 96	Cancer	NP	M= 0 F= 192	MBSR 8x 150 min 6h mindfulness retreat	Health Education 8x 120 mins	No	Yes	IL-6	Control sig increase
Jedel 2014	T= 55 I= 27 C= 28	Inactive Ulcerative Colitis	NP	M= 24 F= 31	MBSR 8x 120- 150 min 45 min/day, 6 days/ week home practise	Time/Attention Intervention 8x120 min	NP	Yes	IL-6	Post-int: N/S Follow up: N/S

Malarkey 2013	T= 186 I= 93 C= 93	None	NP	M= 23 F= 161	MBI 8x 60 min 20 min/day home practise 2h retreat	Lifestyle Education Program 8x 60 min 30 min/ day home practise 2h retreat	NP	No	IL-6	N/S
Marciniak 2020	T= 28 I= 18 C= 10	Mild Cognitive Impairment	74 (6.9)	M= 7 F= 13	MBSR 150 min per week for 8 weeks 6 hour retreat Home practise	Cognitive Training 150 min per week for 8 weeks	NP	Yes	IL-6	N/S
Meyer 2019	T=413 I= 138 C(act)= 137 C(notreat)= 138	None	49.7 (11.6)	M= 92 F= 293	MBSR 8x150 min Home practise (duration NP) Half day retreat	Exercise 8 x 150 min Half day retreat	NP	No	IL-6	Post-int: N/S Follow up: N/S
Montero-Marin 2019	T= 64 I= 23 C= 19 Other Int: 22	FM	NP	M= 0 F= 64	ABCT 8 x 120 min Daily homework (duration NP)	Relaxation Therapy 8x 120 min Daily homework	No	Yes	IL-6	N/S

						(duration NP)				
Ng 2020	T= 55 I= 28 C= 27	Mild Cognitive Impairment	71.28 (6)	M= 14 F= 41	MAPsF 18x 60 min	Health Ed 18 x 60 min	NP	No	IL-6	Post-int: N/S Follow up: N/S
Ng 2022	T= 281 I(IBMS)= 93 C= 93	Sleep disturbance and depression	55.49 (10.10)	M=66 F=215	IBMS 8x 180min	WL	No	Yes	IL-6	IBMS = reduction in IL-6
Oken 2010	T= 31 I= 10 I(O)= 10 C= 11	None	NP	M= 6 F= 25	MBCT 7 x 90 min Home practise (duration NP)	Dementia Education 7 x 90 min	NP	No	IL-6	N/S
Oliveira 2021	T= 76 I= 38 C= 38	None	44.71 (8.29)	M=0 F= 76	MBHPEduca 8 x 120mins Plus 10-30 min/day meditation	Neuro-Educa 8 x 120mins Plus 10-30 min/day reading/ music	No	No	IL-6	MBHPEduca= lower IL-6
Shields 2020	T=60 I= 30 C= 39	None	47.85 (14)	M= 28 F=32	Meditation Training 6/7 hours per day for 3 months	WL	No	No	IL-6	N/S
Smith 2018	T= 40 I= 20 C= 20	Obesity	58.46 (4.87)	M= 0 F= 40	MEAL 16 x 120 min	CONT 16 x 120 min	No	Yes	IL-6	N/S Intervention = reduction

Tolahunase 2018	T= 58 I= 29 C= 29	Major Depressive Disorder	NP	M= 27 F= 31	YMLI 60 x 120 mins	TAU 0 sessions	No	Yes	IL-6	YMLI sig decrease
Zgierska 2016	T= 35 I= 21 C= 14	Chronic Low Back Pain	51.8 (9.7)	NP	MB-CBT 8x 120 min 30 min/ day, 6 days/week home practise	WL 0 sessions	NP	No	IL-6	N/S
Black 2015	T= 49 I= 24 C= 25	None	55.3 (7.4)	M= 16 F= 33	MAPS 6x120 min 5-20 min home practise	Sleep Hygiene education 6 x 120 mins 5-20 min home practise	NP	No	NF-KB	N/S
Daubenmier 2012	T= 47 I= 24 C= 23	None	NP	M= 0 F= 47	CALMM 9 x 150 min 30min/ day home practise 7h silent retreat	WL 0 sessions	NP	No	TA	N/S

Epel 2016	T= 70 I= 33 C= 31	None	47 (8.1)	M= 0 F= 70	Week-long Meditation Retreat (duration NP)	Vacation Week-long vacation (duration NP)	NP	No	TA	Regular meditators sig increase
Gautam 2019	T= 72 I= 36 C= 36	Rh Arthritis	NP	M= 16 F= 56	MBY 40 x 120 min	TAU 0 sessions	NP	Yes	TA	MBY sig increase
Ho 2012	T= 70 I=35 C= 35	Fatigue/ CFS	NP	M= 13 F= 51	Qigong 10 x 120 min 30 min/day home practise	WL 0 sessions	NP	Yes	TA	Qigong sig increase
Innes 2018	T= 53 I= 25 C= 28	Subjective Cognitive Delay	60.47 (1.17)	M= 7 F= 46	Kirtan Kriya meditation 5 x 12 min	Music Listening once/ day (duration NP)	NP	Yes	TA	N/S
Lavretsky 2012	T= 45 I= 25 C= 20	None	NP	M= 2 F= 37	Kirtan Kriya 56 x 12 min	Relaxation (music) 56 x 12 min	NP	No	TA	Kirtan Kiya sig increase
Tolahunase 2018	T= 58 I= 29 C= 29	Major Depressive Disorder	NP	M= 27 F= 31	YMLI 60 x 120 mins	TAU 0 sessions	No	Yes	TA	YMLI sig increase

Carlson 2014	T= 128 I= 53 *C(SET)= 49* C(SMS)= 26	Cancer (survivors)	NP	M= 0 F= 128	MBCR 8 x 90 mins 6h retreat	SET 12 x 90 min	No	No	TL	N/S
Carlson 2014	T= 128 I= 53 C(SET)= 49 *C(SMS)= 26*	Cancer (survivors)	NP	M= 0 F= 128	MBCR 8 x 90 mins 6h retreat	SMS 1 x 360 min	No	No	TL	N/S
Gautam 2019	T= 72 I= 36 C= 36	Rh Arthritis	NP	M= 16 F= 56	MBY 40 x 120 min	TAU 0 sessions	NP	Yes	TL	N/S
Innes 2018	T= 53 I= 25 C= 28	Subjective Cognitive Delay	60.47 (1.17)	M= 7 F= 46	Kirtan Kriya meditation 5 x 12 min	Music Listening once/ day (duration NP)	NP	Yes	TL	N/S
Keng 2020	T= 158 I= 79 C= 79	None	27.24 (5.24)	M= 58 F= 100	MBSR 8 x 150 min 30-40 min home practise	MTSR (Music) 8 x 150 min 30-40 min daily music half day music retreat	NP	No	TL	N/S
Nguyen 2019	T= 176 I (LKM)= 62 I (MM)= 63 C= 51	None	NP	M= 43 F= 99	MM 6 x 60 min Doily home practise encouraged (duration NP)	WL 0 sessions	NP	No	TL	N/S

Nguyen 2019	T= 176 I (LKM)= 62 I (MM)= 63 C= 51	None	NP	M= 43 F= 99	LKM 6 x 60 min Doily home practise encouraged (duration NP)	WL 0 sessions	NP	No	TL	KLM sig shortening
Tolahunase 2018	T= 58 I= 29 C= 29	Major Depressive Disorder	NP	M= 27 F= 31	YMLI 60 x 120 mins	TAU 0 sessions	No	Yes	TL	N/S
Wang 2017	T= 181 I= 88 C= 89	Depression, Anxiety, Stress	48.9 (11.1)	M= 22 F= 159	MBGT Number of sessions and duration NP	TAU (CBT) Number of sessions and duration NP	No	Yes	TL	N/S

Notes: ABCT Attachment based compassion therapy; ACT Acceptance and commitment therapy; BBMW Breath body mind workshop; CALMM: MBSR and MB Eating awareness training; CONT An Active Control; ES education seminar; IBMS Integrative Body-Mind-Spirit; LKM Loving-kindness meditation; MAPs Mindful awareness practices; MBCR MB cancer recovery; MB-CBT Mindfulness-based cognitive behaviour therapy; MBCS Mindfulness-based cancer survivorship; MBCT mindfulness based cognitive therapy; MBGT Mindfulness-based group therapy; MBHPEduca Mindfulness-based health program for educators; MBI Mindfulness based intervention; MBSR mindfulness based stress reduction; MBY Yoga based mind-body intervention; MEAL Mindful eating and living; MM Mindfulness meditation; MQ Medical Qigong; Neuro-Educa Neuroscience for education; SET Supportive-expressive group therapy; SMS stress management seminar; SMT standard medical therapy; TAU treatment as usual; WL waitlist control; YMLI Yoga and meditation based lifestyle intervention

Table 2. Meta-analyses of MBI and immune-related biomarkers at post intervention and follow-up

	SMDC (SE)	**p value**	**Heterogeneity**			**Egger's test Z-statistic (p-value)**
			Q-statistic (*df*;p value)	τ^2	I^2	
Post intervention						
CD4+	.09 (.07)	.20	19.55 (11; .05)	.02	40.36%	.91 (.37)
CRP	-.14 (.07)	.04*	42.23 (21;<.01)	.04	50.08%	-1.05 (.29)
IL-6	-.35 (.18)	.03*	132.63 (16;<.01)	.46	94.26%	-1.71 (.09)
NF-KB	-.25 (.22)	.26	-	-	-	-
Telomerase activity	.81 (.33)	.01*	84.44 (6; <.01)	.70	92.24%	2.29 (.02)
Telomere length	.12 (.06)	.04*	10.12 (8; .25)	.00	13.25%	1.57 (.12)
Follow-up						
CD4+	.22 (.15)	.16	4.21 (2;.12)	.04	52.37%	1.99 (<.05)
CRP	-.39 (.15)	<.01*	20.92 (6;<.01)	.10	72.81%	-3.76 (<.01)
IL-6	-.13 (.08)	.11	6.40 (4;.17)	.01	36.67%	1.88 (.06)

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; NF-KB = nuclear factor-KB; SE = standard error; df = degrees of freedom; '' = p< .05; '†' = p<.10*

Table 3. Moderator parameter estimates for meta-regression models

	Estimate (*SE*)	***Z*-value**	***P* value**
CD4+			
Dosage (mins)	-.00 (.00)	-.64	.52
HIV (yes/no[R])	-.21 (.22)	-.92	.36
Control (passive[R]/active)	-.05 (.23)	-.22	.82
CRP			
Dosage (mins)	.00 (.00)	.13	.90
Medical condition (yes[R]/no)	-.33 (.13)	-2.60	<.01*
Control (passive[R]/active)	.06 (.12)	.49	.62
IL-6			
Dosage (mins)	.00 (.00)	.38	.71
Medical condition (yes[R]/no)	-.24 (.36)	-.67	.50
Control (passive[R]/active)	-.32 (.37)	-.84	.40
Telomerase			
Dosage (mins)	.00 (.00)	.92	.36
Medical condition (yes/no[R])	.13 (.67)	.20	.84
Control (passive/active)	.46 (.76)	.61	.54
Telomere Length			
Dosage (mins)	.00 (.00)	.39	.70
Medical condition (yes[R]/no)	.17 (.20)	.88	.38
Control (passive/active)	.19 (.14)	1.35	.18

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; SE = standard error; '' =p< .05; '†' = p<.0; 'R' = reference category*

Table 4. Meta-regression models for immune-related biomarkers

	Test of Moderators			**Variance accounted for**	**Test for Residual Heterogeneity**		
	Q_M statistic	*df*	p value		Q_E statistic	*df*	p value
CD4+	1.38	3	.71	0%	14.70	6	.02*
CRP	6.89	3	.08†	46.67%	25.54	16	.06
IL-6	1.43	3	.70	0%	116.09	15	.00*
TA	3.56	3	.31	12.14%	15.30	2	.00*
TL	6.61	3	.09†	100%	3.39	4	.50

Notes: CRP = C-reactive protein; IL-6 = interleukin-6; df = degrees of freedom; '' =p< .05; '†' = p<.10*