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# Comparative efficacy of psychological interventions on immune biomarkers: A systematic review and network *meta*-analysis (NMA)

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ABSTRACT

Psychological interventions are viable, cost-effective strategies for improving clinical and psychological impact of inflammation-related conditions. However, their efficacy on immune system function remains controversial. We performed a systematic review and frequentist random-effects network *meta*-analysis of randomised controlled trials (RCTs) assessing the effects of psychological interventions, against a control condition, on biomarkers of innate and adaptive immunity in adults. PubMed, Scopus, PsycInfo, and Web of Science were searched from inception up to Oct 17, 2022. Cohen's *d* at 95% confidence interval (CI) was calculated to assess the effect sizes of each class of intervention against active control conditions at post-treatment. The study was registered in PROSPERO (CRD42022325508). Of the 5024 articles retrieved, we included 104 RCTs reporting on 7820 participants. Analyses were based on 13 types of clinical interventions. Compared with the control conditions, cognitive therapy ($d = -0.95$, 95% CI: −1.64 to − 0.27), lifestyle ($d = -0.51$, 95% CI: −0.99 to − 0.02), and mindfulness-based ($d = -0.38$, 95% CI: −0.66 to − 0.09) interventions were associated with post-treatment reduction of proinflammatory cytokines and markers. Mindfulness-based interventions were also significantly associated with post-treatment increase in anti-inflammatory cytokines ($d = 0.69$, 95% CI: 0.09 to 1.30), while cognitive therapy was associated also with post-treatment increase in white blood cell count ($d = 1.89$, 95% CI: 0.05 to 3.74). Results on natural killer cells activity were non-significant. Grade of evidence was moderate for mindfulness and low-to-moderate for cognitive therapy and lifestyle interventions; however, substantial overall heterogeneity was detected in most of the analyses.

## 1. Introduction

The immune system plays a key role in maintaining physical and mental health, providing specific and non-specific defences against pathogens, and reacting to psychological stressors (Yan, 2018). Dysregulation of the immune system can involve a hyperactivation of inflammatory responses which may result in increased risk of illness, and ultimately, greater disability and mortality (GBD, 2017). Low-grade chronic inflammation, which may be defined by C-reactive protein (CRP) values > 3 mg/l (Pearson et al., 2003), can also be detected in subgroups of individuals with mental disorders that can be effectively treated by psychological interventions such as depressive (Enache et al., 2019; Pitharouli et al., 2021), anxiety (Costello et al., 2019), sleep (Ballesio et al., 2022; Irwin et al., 2016), and psychotic disorders (Khandaker et al., 2015), and in healthy individuals exposed to psychosocial stressors such as adverse life events (Iob et al., 2020), loneliness (Smith et al., 2020), or caregiving (Roth et al., 2019).

Inflammatory responses are mediated by several immune cells, i.e., white blood cells (WBC) such as lymphocytes, (e.g., T and B cells, natural killer (NK) cells), and neutrophils. Higher count of these cells has been detected in individuals with depression, anxiety (Shafiee et al., 2017), and schizophrenia (Jackson and Miller, 2020) compared to healthy controls. Lower KN activity was also detected in depression (Irwin et al., 1987; Jung and Irwin, 1999). Notably, immune cells count and activity may be influenced by stress-related neuroendocrine factors such as corticosteroids in an immune-neuroendocrine network (del Rey and Besedovsky, 2013; Ganea and Skarica, 2013); since a general goal of psychological interventions is to downregulate stress-related factors, (Engel et al., 2022; Lehrer, 2018), it is possible that these interventions may also lead to changes in immune cells count and activity.

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Research on the efficacy of psychological interventions in improving immune system function provided some promising results. To the best of our knowledge, the most updated comprehensive *meta*-analysis on this matter was published by Shields et al. (2020). In their work, authors included 56 randomised controlled trials (RCTs) comparing eight psychological interventions against non-psychological control conditions, and highlighted that standard integrated cognitive-behaviour therapy (CBT) and combined multiple psychosocial interventions were associated with changes in some components of immune function, such as reduction of proinflammatory cytokines, with small-to-moderate effect sizes (Shields et al., 2020). However, several points still require clarification. First, several types of psychological interventions were not considered in previous *meta*-analyses (e.g., Miller and Cohen, 2001; Shields et al., 2020), including third-wave CBT interventions such as mindfulness-based interventions or acceptance and commitment therapy (ACT) which are instead frequently delivered in patients with inflammatory-related conditions (Järvelä-Reijonen et al., 2020; Rådmark et al., 2019). Second, previous *meta*-analyses did not explore the unique contribution of cognitive and behavioural therapies as standalone treatments (e.g., Shields et al., 2020), which remains unexplored, but rather considered both under the label of "CBT". Related to this, the literature on the evidence base of psychological interventions has substantially grown during the last decades, and many interventions are now included in clinical guidelines for the treatment of mental conditions, yet their impact on immune measures remains more controversial (a detailed description of psychological interventions and their efficacy is reported in eAppendix 1). Third, previous *meta*-analyses (e.g., Miller and Cohen, 2001; Shields et al., 2020) might have been underpowered in detecting reliable effects on less-studied aspects of immunity, such as WBC and anti-inflammatory cytokines. Finally, and most important, previous *meta*-analyses (e.g., Miller and Cohen, 2001; Shields et al., 2020; Dunn and Dimolareva, 2022) were based on pairwise comparisons of psychological interventions against non-psychological control conditions. In contrast, the application of more sophisticated network *meta*-analysis (NMA) approach would allow to simultaneously compare the efficacy of multiple experimental treatments (e.g., Rouse et al., 2017), providing an efficacy-based hierarchy of interventions (Ballesio et al., 2018). Moreover, compared with pairwise *meta*-analysis, NMA would permit the visualisation of a larger amount of evidence and a more accurate estimation of the relative efficacy among all treatments under study (Mills et al., 2013). Therefore, NMA increases power and precision as compared to pairwise *meta*-analysis (Linde et al., 2016). For these reasons, we aimed to perform what we believe is the first systematic review and NMA of RCTs assessing the efficacy of available psychological interventions on immunological outcomes in adults.

## 2. Materials and methods

### 2.1. Search strategy and selection criteria

This review was conducted following the preferred reporting items for systematic reviews (PRISMA, Hutton et al., 2015) extension statement for NMA (eTable 1) and registered in the international prospective register of systematic reviews of the University of York (PROSPERO, CRD42022325508). Pubmed, Scopus, PsycInfo, and Web of Science were searched by the first and second authors from inception up to October 17th, 2022, using the string reported in eAppendix 2. Study eligibility was assessed using the participants, intervention, comparators, and outcomes (PICOS) approach. To be included, studies had to fulfil the following inclusion criteria: 1) Population: healthy or clinical adults aged 18 years or older. 2) Intervention: studies had to have included a standardised psychological intervention condition (e.g., cognitive therapy, behavioural interventions, mindfulness, psychophysiological techniques, psychological counselling, etc.); 3) Comparison: RCTs were included if they had a control condition, including an active control like a psychological intervention different from the target intervention condition, medication, treatment as usual, waiting list, placebo, etc; 4) Outcome: studies had to have assessed immune system function and have included postintervention immunologic assessments. The following immune markers were considered: proinflammatory cytokines or markers, anti-inflammatory cytokines or markers, WBC count, NK cells activity, i.e., cytotoxicity, and viral load. If the data were not reported in the original article, authors were asked to provide them.; 5) Study design: RCTs. Only studies published in English, Italian, and Spanish were included. Grey literature was not included as it rarely impacts the statistical or clinical significance of *meta*-analytic findings (Hartling et al., 2017). Abstract and full-text screening was performed in parallel by the first three authors and disagreements were resolved by discussion.

### 2.2. Data extraction

The first and the second author independently extracted the following information from each trial using a standardised spreadsheet: authors; study location; sample size; female percentages; age; ethnicity; type of immunological outcome; intervention type; intervention modality; intervention duration in weeks; clinical status of the sample (i.e., healthy, medical, psychiatric). Data needed for the effect size computations (i.e., post-treatment mean and standard deviations values for both treatment and control groups on the immune biomarkers under investigation) were also extracted. When original articles reported data only in figures and/or graphs, data were converted to numerical values using Plot Digitizer software (http://plotdigitizer.sourceforge.net/). When data were not reported, authors of original papers were contacted to provide them.

### 2.3. Risk of bias and certainty of the evidence

The risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Sterne et al., 2019). Rob2 is structured to provide judgements about the risk of five different sources of bias: bias due to the randomisation process; bias due to the deviations from intended interventions; bias due to missing outcome data; bias due to the measurement of the outcome; and bias in the selection of the reported result. Each domain can be judged as "low risk of bias", "some concerns", and "high risk of bias". The studies were categorised as having an overall low risk of bias if the trial received the judgement of "low risk" for all domains, as having some concerns if the trial was judged to raise "some concerns" in at least one domain, and as having an overall high risk of bias if the trial was judged to be at "high risk" in at least one domain. Two investigators independently performed the quality appraisal and disagreements in the evaluation were resolved by discussion.

The certainty of the evidence pertaining to the primary outcomes was assessed through the grading of recommendations assessment, development, and evaluation (GRADE) approach for NMA, as outlined by Puhan et al. (2014). This proposed system classifies the evidence into four categories of certainty: high, moderate, low, and very low. It conveys the level of confidence in the obtained results and recommends the degree of caution to be exercised while interpreting the findings. The reasons for downgrading the evidence were based on the presence of risk of bias, heterogeneity/inconsistency, intransitivity, imprecision, and publication bias. More details are reported in eTables 5–8.

### 2.4. Data analysis

Preliminarily, a series of pairwise *meta*-analyses comparing the effects of each psychological intervention against non-psychological control conditions on independent biomarkers were conducted by means of jamovi (https://www.jamovi.org) using the MAJOR package (Hamilton, 2018). Since all the outcomes of interest were continuous, standardised mean difference (i.e., Cohen's *d* weighted according to the

relative size of each sample) was used as the effect size metric. Data were synthesised using a random-effects model with DerSimonian-Laird estimator because of the anticipated heterogeneity between studies. Heterogeneity was assessed using Cochran's Q (Cochran, 1954) and $I^2$ statistics, the latter measuring the percentage of variability that cannot be attributed to random error (Higgins and Thompson, 2002). $I^2$ values of 0%, 25%, 50% and 75% suggest no, low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). A minimum number of three studies was set to perform pairwise *meta*-analyses (Crocetti, 2016), whilst funnel plots and tests for funnel plot asymmetry (Egger et al., 1997) were employed only in the presence of at least 10 included studies following Cochrane's recommendations (Higgins and Green, 2011).

Secondly, random-effects frequentist NMA were conducted to estimate the differential efficacy of the examined interventions on post-treatment levels of immune biomarkers by means of R version 4.1.3 using the *netmeta* package (Rücker et al., 2022). DerSimonian-Laird was used to estimate the between-study variance $\tau^2$ and its square root $\tau$ assuming a common heterogeneity for all treatment comparisons. More specifically, we performed separate NMAs on aggregated measures of: proinflammatory cytokines and markers, WBC count, NK cells activity, and anti-inflammatory cytokines and markers (see Shields et al., 2020). For studies reporting multiple measures for the same category, e.g., interleukin-6 (IL-6), CRP, tumour necrosis factor-α (TNF- α), a mean effect size was calculated following López-López et al. (2018). Indeed, performing separate analyses for each immune outcome would markedly diminish statistical power, as the outcomes evaluated across studies are not uniform (see Shields et al., 2020). Weighted Cohen's d and 95% confidence intervals (CI) were calculated to assess post-treatment differences between each intervention class against the reference condition. Psychoeducation was preferred as the reference condition in all forest plots when possible, following a preliminary examination of the network geometry which showed that psychoeducation was the most commonly employed active control condition in the network (Rouse et al., 2017). When the number of articles included in the NMA did not suffice the use of psychoeducation as a control, we considered placebo as the reference condition (Ballesio et al., 2018). A hierarchy of competing interventions on the basis of their efficacy was established using P-scores, which are considered a frequentist equivalent to the Bayesian network surface under the cumulative ranking curves (SUCRA; Rücker and Schwarzer, 2015). P-scores range from 0 (worst) to 1 (best), measuring the mean extent of certainty that one treatment is better than another, averaged over all competing treatments. The overall degree of statistical heterogeneity/inconsistency in the network was assessed using the $I^2$ statistics and the magnitude of the heterogeneity variance parameter ($\tau^2$). Inconsistency in the networks, a statistical expression of intransitivity, was further globally assessed by considering the Q-statistic in a full design-by-treatment interaction model (Higgins et al., 2012). Furthermore, we formally test local inconsistency through the net-splitting method by separating direct and indirect evidence and then testing their discrepancy (SIDE, Dias et al., 2010; see also Harrer et al., 2021). To ensure the validity of the NMA, the main findings are presented after eliminating each inconsistent comparison, i.e., comparisons for which the z-tests indicate significant discrepancies between direct and indirect estimates. Lastly, we hypothesised that the inclusion of various populations might contribute to heterogeneity/inconsistency across the whole network. Thus, we conducted a series of sensitivity analyses by re-estimating each NMA considering the variability of aggregated markers, the role of clinical status, the treatment modality, and the technique of immunological assessment.

## 3. Results

Of the 5024 records retrieved, 104 (2%) met the inclusion criteria (Alawna and Mohamed, 2022; Alhawatmeh et al., 2022; Andrés-Rodríguez et al., 2019; Antoni et al. 2000, 2005; Arefnasab et al., 2016; Babamahmoodi et al., 2015; Bablis et al., 2022; Barrett et al., 2012; Basso et al., 2013; Berger et al., 2008; Bernateck et al., 2008; Birashk et al., 2018; Black et al., 2015; Carrico et al., 2005; Casarez et al., 2021; Chattopadhyay et al., 2017; Claesson et al., 2006; Coates et al., 1989; Cohen et al., 2011; Creswell et al. 2012, 2012; Diaz et al., 2021; Dolsen et al., 2018; Dunne et al., 2019; Elsenbruch et al., 2005; Ernberg et al., 2018; Euteneuer et al., 2017; Fiedorowicz et al., 2021; Gagrani et al., 2018; Garand et al., 2002; Gardi et al., 2022; González-Moret et al., 2020; Grazzi et al., 2017; Harrigan et al., 2016; Hasson et al., 2005; Hidderley and Holt, 2004; Hoge et al., 2018; Hosaka et al., 2002; Irwin et al., 2015; Janusek et al., 2019; Jedel et al., 2014; Kang and Yoo, 2007; Koh and Lee, 2004; Koh and Lee et al., 2008; Larson et al., 2000; Lekander et al., 1997; Lengacher et al., 2019; Li et al., 2019; Lindsay et al., 2021; Lopez et al., 2013; Lumley et al., 2014; Lutgendorf et al. 1997, 2010; Mackay et al., 2009; Madhombiro et al., 2019; Maduka and Tobin-West, 2013; Malarkey et al., 2013; McCain et al., 2008; McGrady et al., 1992; Memon et al., 2017; Mikocka-Walus et al., 2017; Mirmahmoodi et al., 2020; Montero-Marin et al., 2019; Moore et al., 2013; Naito et al., 2003; Ng et al., 2020; Nijjar et al., 2019; Nkengfack et al., 2014; Oh et al. 2011, 2013; Oken et al., 2010; Oswald et al., 2021; O'Toole et al., 2020; Pakiz et al., 2011; Paredes et al., 2021; Parsons et al. 2007, 2018; Penedo et al., 2021; Reig-Ferrer et al., 2014; Rief et al., 2017; Rigsby et al., 1992; Rodrigues de Oliveira et al., 2021; Ruzyla-Smith et al., 1995; Saban et al., 2022; Sanabria-Mazo et al., 2020; Savard et al., 2005; SeyedAlinaghi et al., 2012; Sharpe and Schrieber, 2012; Sharpe et al., 2001; Simoni et al., 2013; Simos et al., 2019; Smith et al., 2018; Taylor et al., 2009; Theeke et al., 2016; Turner et al., 2020; von Känel et al., 2020; Vučić Lovrenčić et al., 2015; Wang and Yuan, 2020; Wilson et al., 2022; Zabihiyeganeh et al. 2019, 2021; Zautra et al., 2008; Zhao et al., 2016).

These examined the following interventions: 1) cognitive therapy (e.g., cognitive restructuring, imagery techniques) 2) behavioural interventions (e.g., behavioural activation, exposure therapy), 3) integrated CBT interventions, 4) mindfulness-based interventions, 5) relaxation, 6) counselling, 7) lifestyle interventions, 8) cognitive behaviour stress management (CBSM), 9) hypnosis, 10) ACT, 11) psychoeducation, 12) emotion-based interventions, 13) CBT for insomnia. Detailed search flow is reported in Fig. 1. Information on excluded records and the description of the included studies are reported in the eAppendix 3. The overall sample included 7820 participants. The mean age was 49.99 years (SD = 12.29). Of 7820 participants, 63.82% were women, and 70% of 40 studies with reported ethnicity were white. The mean treatment duration was 9.01 weeks. Sixty-seven (65%) studies included a medical sample (most frequently HIV, n = 18 studies, and cancer, n = 14 studies), 10 (9.7%) studies a psychiatric sample (most frequently depression (n = 4 studies) and anxiety (n = 4 studies), and 26 (25%) a non-clinical sample. Detailed description of the studies is reported in eTable2. Risk of bias was high for 61% of the studies (eTable 3).

### 3.1. Pairwise meta-analysis

Pairwise random effects *meta*-analyses comparing each intervention class against non-psychological control conditions were conducted on the following biomarkers: CRP, IL-6, IL-8, IL-10, TNF-α, CD4, viral load, NK cell count and NK cell activity. Mindfulness-based interventions were associated with a significant post-treatment reduction of CRP (k = 12, $d = -0.19$, 95% CI: −0.35 to − 0.03, $p = 0.018$; $Q = 13.27$, df = 11, $p = 0.276$, $I^2 = 17.13\%$) and IL-6 (k = 18, $d = -0.56$, 95% CI: −0.92 to − 0.20, $p = 0.002$; $Q = 188.74$, df = 17, $p$ less than 0.001, $I^2 = 90.99\%$), and a marginal reduction of IL-8 reaching only trend-level statistical significance (k = 8, $d = -0.21$, 95% CI: −0.47 to 0.03, $p = 0.097$; $Q = 17.39$, df = 7, $p = 0.015$, $I^2 = 59.75\%$); CBSM was associated with a significant reduction of CRP (k = 4, $d = -0.21$, 95% CI: −0.34 to − 0.07, $p = 0.003$; $Q = 0.54$, df = 3, $p = 0.909$, $I^2 = 0.00\%$) and IL-6 (k = 5, $d = -0.14$, 95% CI: −0.28 to − 0.01, $p = 0{\cdot}033$; $Q = 2.39$, df = 4, $p = 0.663$, $I^2 = 0.00\%$); CBT was associated with a significant post-treatment

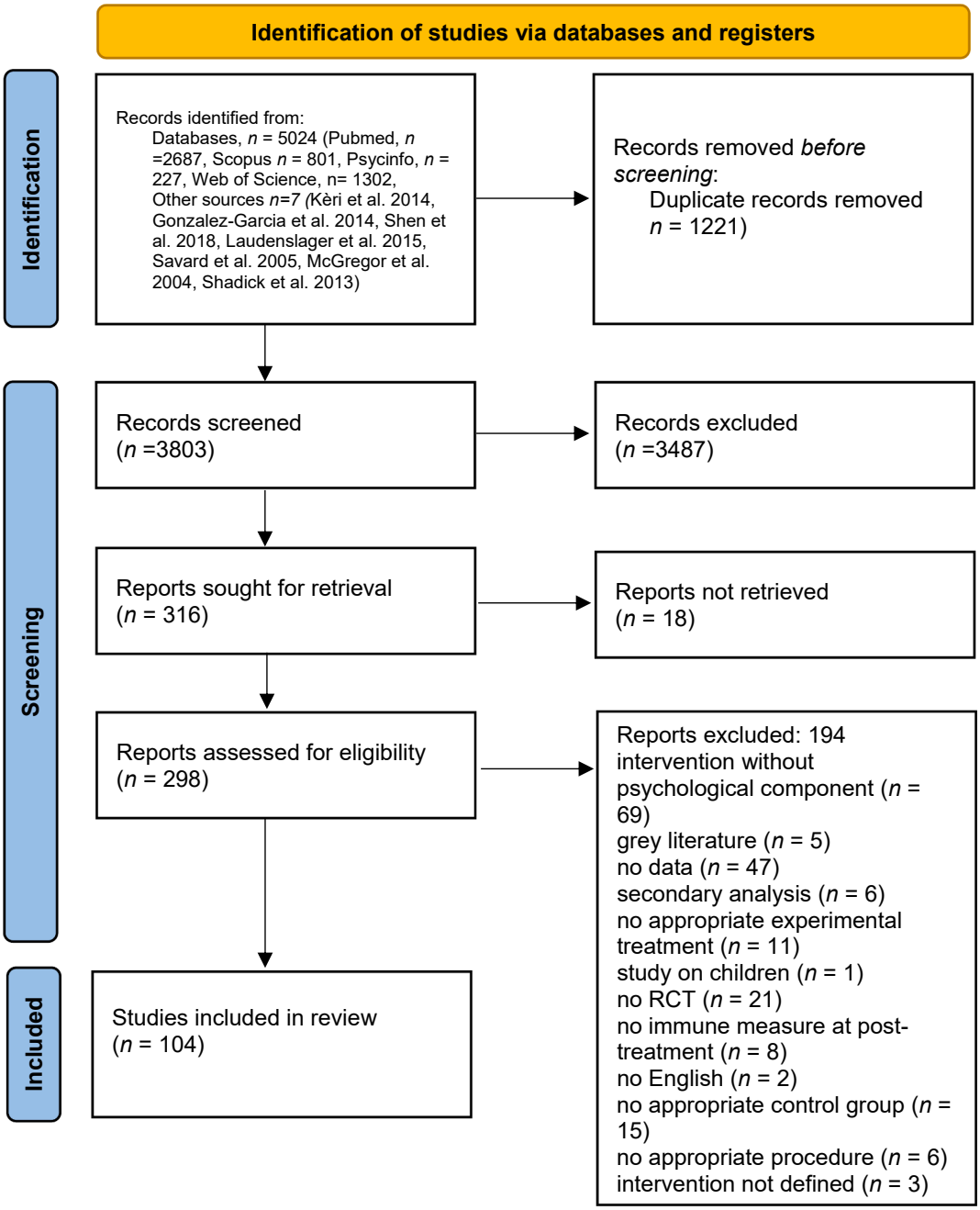


**Fig. 1.** Flow diagram for study selection.

reduction of viral load (k = 3, $d = -0.25$, 95% CI: −0.45 to −0.04, $p = 0.018$; $Q = 1.96$, df = 2, $p = 0.375$, $I^2 = 0\%$) and a marginal reduction of IL-6 reaching only trend-level statistical significance (k = 6, $d = -0.31$, 95% CI: −0.65 to 0.02, $p = 0.072$; $Q = 14.03$, df = 5, $p = 0.015$, $I^2 = 64.38\%$). None of the examined treatment was associated with significant change of IL-10, TNF-α, CD4, NK cell count and NK cell activity in pairwise analysis (eAppendix 4).

### 3.2. Network meta-analysis

Network graphs are shown in Fig. 2. Forest plots for the mean change in immune biomarkers for psychological interventions and control conditions are shown in Fig. 3. P-score rankings are reported in eTable4. Grading of certainty of the evidence is reported in eTables 5–8.

A first NMA was conducted on proinflammatory cytokines and markers (IL-1, IL-2, IL-6, IL-8, IL-12, IL-17, interferon- γ (IFN-γ), TNF-α, CRP, fibrinogen, faecal calprotectin, and monocyte chemoattractant protein (MCP)-1) and included 71 studies and 86 pairwise comparisons. Compared to psychoeducation as reference condition, cognitive therapy alone ($d = -0.95$, 95% CI: −1.64 to −0.27, $p = 0.006$, certainty of the evidence: moderate, eTable 5), lifestyle ($d = -0.51$, 95% CI: −0.99 to −0.02, $p = 0.042$, certainty of the evidence: low, eTable 5), and mindfulness-based interventions ($d = -0.38$, 95% CI: −0.66 to −0.09, $p = 0.009$, certainty of the evidence: moderate, eTable 5) were associated with a significant medium-to-large posttreatment reduction in these outcomes. As shown in Fig. 3, duloxetine was the only intervention associated with an increase in proinflammatory cytokines. However, this effect reflected the result of one single RCT directly comparing duloxetine to CBT and showing a post-treatment reduction of IL-6, IL-8, and TNF-α following both interventions without between-group differences (Zabihiyeganeh, Amini Kadijani, and Vafaee Afshar et al., 2021), so this result should be interpreted cautiously as discussed below. The

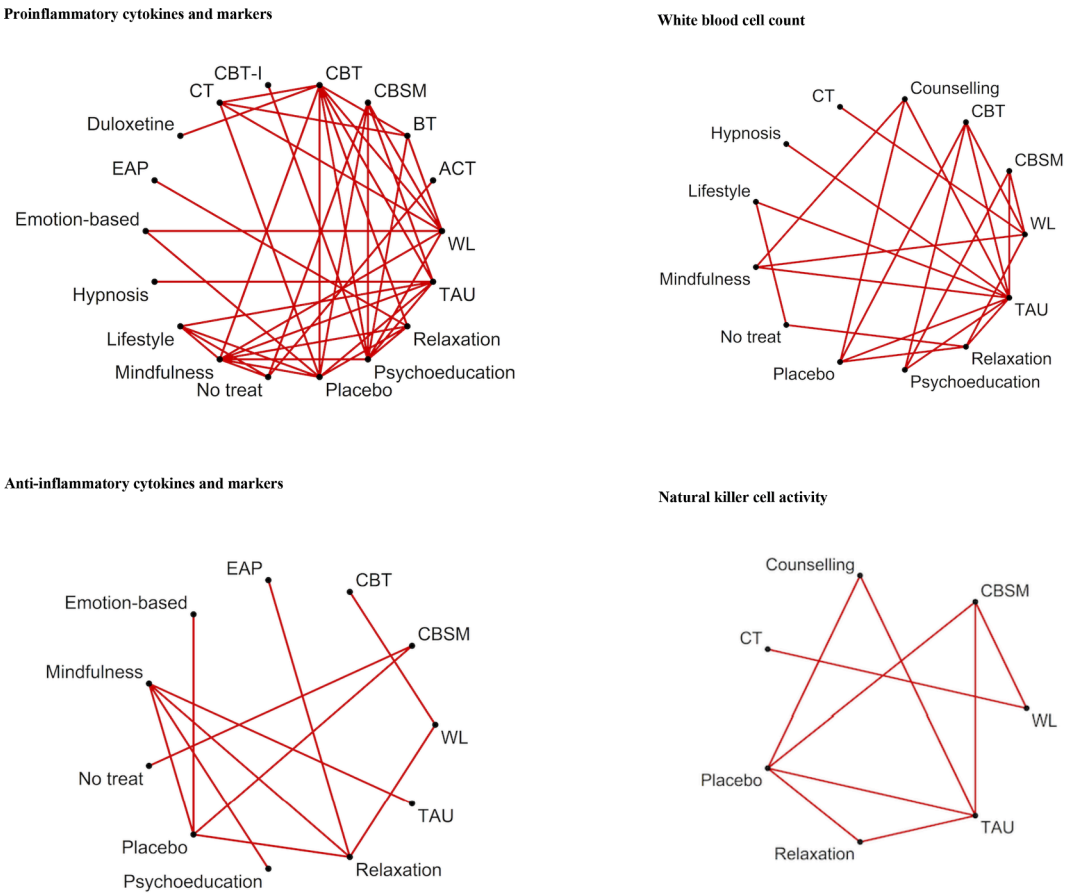


**Fig. 2.** Network graphs for proinflammatory cytokines and markers, white blood cell count, anti-inflammatory cytokines, and natural killer cell activity. ACT: acceptance and commitment therapy; BT: behaviour therapy; CBT: standard cognitive behaviour therapy; CBT-I: cognitive behaviour therapy for insomnia; CBSM: cognitive behaviour stress reduction; CT: cognitive therapy; EAP: electroacupuncture; TAU: treatment as usual; WL: waiting list.

overall heterogeneity/inconsistency was high: $I^2 = 78.4\%$ [72.6%-82.9%]; $\tau 2 = 0.201$. The design-by-treatment interaction model did not indicate global inconsistency in the network ($Q = 29.55$, df = 27, p = 0.334).

A second NMA was conducted on WBC count (lymphocytes, basophils, neutrophils, monocytes, NK cell count, and total WBC count) and included 34 studies and 36 pairwise comparisons. Compared to psychoeducation as reference group, cognitive therapy alone was associated with a large post-treatment increase in this outcome ($d = 1.89$, 95% CI: 0.05 to 3.74, $p = 0.044$, certainty of the evidence: low, eTable 6). The overall heterogeneity/inconsistency was high: $I^2 = 89\%$ [84.9%-92.00%]; $\tau 2 = 0.498$. The design-by-treatment interaction model did not indicate global inconsistency in the network ($Q = 1.41$, df = 10, p = 0.999).

A third NMA was conducted on anti-inflammatory cytokines and markers (IL-1 receptor antagonist, IL-4, and IL-10). This analysis was based on 13 studies and 13 pairwise comparisons. Compared to psychoeducation as reference group, none of the included interventions was associated with significant posttreatment change in this outcome. However, since only one out of 13 studies included psychoeducation condition, limiting the robustness of the finding, we replicated the analysis considering placebo as reference group which was present in 5 studies. Results showed that mindfulness-based interventions ($d = 0.69$, 95% CI: 0.09 to 1.30, $p = 0.024$, certainty of the evidence: moderate, eTable 7) were associated with a significant and large posttreatment increase in anti-inflammatory cytokines; The overall heterogeneity/inconsistency was moderate: $I^2 = 72.1\%$ [21%-90.2%]: $\tau 2 = 0.190$. The design-by-treatment interaction model did not indicate global inconsistency in the network ($Q = 2.16$, df = 1, p = 0.141).

Finally, a fourth NMA was conducted on NK cells activity and was based on 8 studies and 12 pairwise comparisons. None of the included interventions was associated with significant posttreatment change in this outcome compared to placebo as reference group. The overall heterogeneity/inconsistency was moderate: $I^2 = 69.1\%$ [20.8%-88.00%]; $\tau 2 = 0.226$. The Q statistic to assess consistency under the assumption of a design-by-treatment interaction model was significant ($Q = 13.55$, df = 4, p = 0.008).

### 3.3. Sensitivity analysis

A series of sensitivity analyses were conducted considering whether various methodological factors including the variability of aggregated markers, the clinical status of participants, the treatment modality administration, and the biomarkers assessment procedure might have influenced the heterogenous results found on proinflammatory markers and WBC count. Findings confirmed the efficacy of cognitive therapy and mindfulness interventions, but failed to explain the high heterogeneity (eAppendix 5).

## 4. Discussion

This *meta*-analysis sought to detect effective psychological interventions capable to positively impact immune system biomarkers in adults. To this aim, we performed 1) pairwise analyses that estimated the independent efficacy of each intervention under study against a control condition on single biomarkers of immune function, and 2) network analyses that simultaneously compared the efficacy of each intervention on aggregated biomarkers of proinflammatory cytokines or

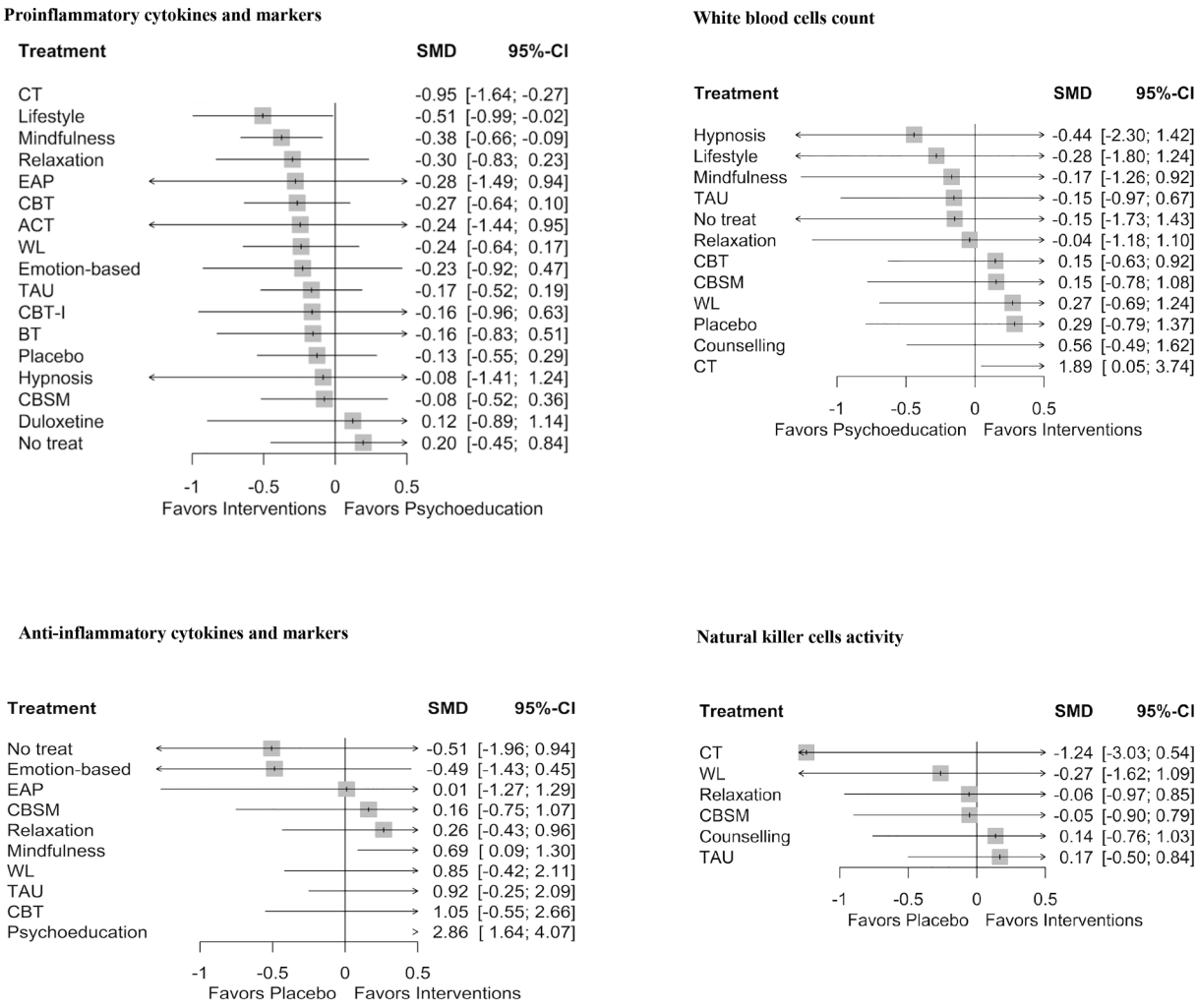


**Fig. 3.** Forest plots for network *meta*-analyses. Results are reported as standardised mean differences (SMD), i.e., Cohen's d and 95% confidence intervals (CI). ACT: acceptance and commitment therapy; BT: behaviour therapy; CBT: standard cognitive behaviour therapy; CBT-I: cognitive behaviour therapy for insomnia; CBSM: cognitive behaviour stress reduction; CT: cognitive therapy; EAP: electroacupuncture; TAU: treatment as usual; WL: waiting list.

markers, anti-inflammatory cytokines or markers, WBC count, and NK cells activity. Importantly, to the best of our knowledge, this was the first *meta*-analysis combining both pairwise and NMA on this topic. Results of pairwise analyses showed that, compared to non-psychological control conditions, mindfulness-based, CBSM, and integrated CBT interventions were all associated with small to moderate reduction of IL-6, and that mindfulness-based and CBSM interventions were also associated with reduction of CRP. Integrated CBT was significantly associated with reduction of viral load in individuals with HIV, with a small sized and homogeneous effect. In terms of direction and size of the effects, these results are in line with previous pairwise *meta*-analyses on the same outcomes (Dunn and Dimolareva, 2022; Miller and Cohen, 2001; Shi et al., 2019; Shields et al., 2020).

Likely due to small sample size and reduced statistical power, none of the interventions under study were associated with post-treatment changes in IL-10, TNF-α, CD4, NK cell activity when considered independently in pairwise analyses. Conversely, in network analyses, with the greater power and the more accurate efficacy estimation (Linde et al., 2016; Mills et al., 2013), we showed that cognitive therapy alone, lifestyle, and mindfulness-based interventions were associated with moderate to large reduction in proinflammatory cytokines and markers. Importantly, the certainty of the evidence using the GRADE approach was estimated as moderate for cognitive therapy and mindfulness, and low for lifestyle interventions.

Results are in line with two recently published pairwise *meta*-analyses on mindfulness and lifestyle interventions on IL-6 and CRP (Dunn and Dimolareva, 2022; Rahimi et al., 2022) and extend the investigation to other proinflammatory cytokines and markers (e.g., IL-1, IL-2, IL-8, IL-12, IL-17, IFN-γ, TNF-α, MCP-1, fibrinogen). Additionally, we provide new *meta*-analytic evidence for cognitive therapy alone (i.e., cognitive restructuring, imagery techniques) in reducing proinflammatory cytokines, as previous *meta*-analytic reviews on CBT approaches did not differentiate between cognitive and behavioural subcomponents of the therapies (e.g., Shields et al., 2020). Moreover, results yield novel evidence for the efficacy of mindfulness-based interventions in increasing anti-inflammatory cytokines levels, as previous *meta*-analyses were restricted to pro-inflammatory molecules (e.g., Dunn and Dimolareva, 2022).

It should be noted that cognitive therapy as standalone treatment was also associated with increased post-treatment counts of WBC. This may suggest that confronting with one's difficulties may, in the short-term, increase inflammation. However, the grading of evidence for this result was estimated as low, and the large heterogeneity of the effects distribution, alongside the impossibility of analysing WBC subcomponents due to the small number of studies included in this analysis precluded a clear interpretation of this finding.

The mechanisms of action that may mediate the interventions efficacy remain to be clarified. For instance, these may potentially include increased vagal/parasympathetic activity such as increased heart rate variability (e.g., Nijjar et al., 2014) for cognitive therapy and

mindfulness-based interventions and changes in dietary/exercise patterns (e.g., Khosravi et al., 2019) for lifestyle interventions. Heart rate variability is considered a measure of physiological regulation which is negatively associated with inflammatory markers (Williams et al., 2019), that could increase following interventions that include mindfulness practices and cognitive therapy (Jang et al., 2017; Pascoe et al., 2017). Moreover, lifestyle interventions targeting dietary/exercise patterns may influence hormonal factors including leptin (Jadhav et al., 2021), which is associated with inflammatory markers such as CRP (Ble et al., 2005). These mediating factors need to be tested in future RCTs.

These results may have several implications. Higher levels of peripheral pro-inflammatory cytokines or cytokines-induced acute phase proteins such as CRP may be longitudinally associated with the onset of mental disorders such as depression, anxiety, and psychosis across the lifespan (Ballesio et al., 2022; Costello et al., 2019; Enache et al., 2019; Khandaker et al., 2014; Pitharouli et al., 2021). In parallel, the experimental injection of anti-inflammatory IL-10 has been recently associated with improvements in depressive symptoms in mice models (e.g., Worthen et al., 2020), and anti-inflammatory treatment has been effectively employed to reduce depressive symptoms in human (Köhler et al., 2014). Moreover, higher baseline pro-inflammatory cytokines and acute phase proteins are associated with resistance to monoaminergic treatments (e.g., Carvalho et al., 2013; Chamberlain et al., 2019; Cattaneo et al., 2020). In this scenario, results of our *meta*-analysis may suggest that in psychiatric patients with elevated inflammation, the administration of a psychological intervention such as cognitive therapy, lifestyle, mindfulness, or CBSM/CBT, preliminarily or at the same time of medical treatment, may be potentially associated with increased response to the latter. It should be noted, however, that while inflammation may be trandisgnostically associated with several disorders (e.g., Khandaker et al., 2015; Irwin et al., 2016; Costello et al., 2019; Enache et al., 2019; Pitharouli et al., 2021; Ballesio et al., 2022), and that the most of mental disorders can be effectively treated by psychological interventions, each condition is characterised by a specific psychopathology that should be carefully considered. In particular, it is possible that the proposed anti-inflammatory action of psychotherapies might contribute differently to the therapeutic improvements in different disorders. Additionally, current knowledge in immunopsychiatry suggests that inflammation may be relevant for only a subset of patients with mental disorders such as the 27% of those with major depression who show CRP $>$ 3 mg/L. (Osimo et al., 2019).

Our results support and foster the implementation of future RCTs combining pharmacological and psychological interventions and assessing inflammation biomarkers as treatment outcomes. Particularly, our results suggests that among those under study, mindfulness-based interventions may improve inflammatory status combining both the reduction of pro-inflammatory cytokines, and the increase of anti-inflammatory cytokines and could be therefore potentially beneficial in individuals with physical and/or psychiatric conditions and concomitant inflammation. However, a high heterogeneity made the mean effects estimate uncertain and pledge further clarification.

### 4.1. Limitations

This study has several limitations. The high heterogeneity detected in most of the analyses imposes to consider the results of the present review cautiously. As for Shields et al. (2020) *meta*-analysis, our pairwise analyses were based on a relatively small set of studies that precluded to clearly estimate treatments efficacy on several independent biomarkers including WBC subcomponents. Also, we aggregated systemic (e.g., interleukins, acute phase proteins) and local (e.g., faecal calprotectin) markers of inflammation in order to increase power but this may limit the generalisability of the findings. Reassuringly, our sensitivity analyses showed that excluding potential outliers due to the aggregation of multiple pro-inflammatory (e.g., IL-6, IL-8, CRP), and WBC (e.g., lymphocytes, granulocytes) biomarkers within the same NMA did not substantially change the results nor impact the heterogeneity/inconsistency of effect distribution (eAppendix 5).

We restricted our review to adult studies. However, several medical chronic inflammatory conditions have their onset in youth (e.g., inflammatory bowel disease, Ashton et al., 2017) and paediatric inflammation has been shown to increase the risk of depression, anxiety, and psychotic symptoms in early adulthood in the Avon Longitudinal Study of Parents and Children (ALSPAC) (e.g., Khandaker et al., 2014). Additionally, although for each observed pairwise comparison the presence of publication bias was not detected through the standard approach (e.g., Salanti et al., 2014), it should be noted that we were unable to run funnel plots for publication bias detection in several pairwise *meta*-analyses with less than 10 included studies (Higgins and Green, 2011). Finally, since this NMA was focused on psychological interventions, pharmacological treatment studies were not systematically included and were therefore under-represented. This led a spurious increase of pro-inflammatory cytokines following duloxetine treatment (Fig. 3) that should be cautiously interpreted. This effect reflects, in fact, the data of one single RCT comparing duloxetine to CBT and showing a post-treatment reduction of IL-6, IL-8, and TNF-α following both interventions (Zabihiyeganeh, Amini Kadijani, and Vafaee Afshar et al., 2021). In our NMA, however, we choose psychoeducation as the reference condition; thus, the location of duloxetine in the forest-plot reflects indirect evidence only.

### 4.2. Future directions and conclusions

Several issues still remain unresolved. Neither the clinical status of participants, the treatment modality administration (e.g., individual or group interventions), nor the biomarkers assessment procedures seem to have influenced the results as tested in sensitivity analyses; thus, future RCTs are encouraged to explore further potential moderators of interventions efficacy. Related to this, future RCTs may benefit from a rigorous selection of participants with high baseline inflammation in order to avoid floor effect; alternatively, authors may report the results separately for participants with high vs. low baseline inflammation. The selection of individuals with specific baseline patterns of altered inflammatory-immune function (i.e., immunophenotyped individuals, Kasten-Jolly and Lawrence, 2022) and the exploration of post-treatment specific changes in these patterns would be in line with the translation of a precision medicine approach to the field of psychological interventions. Potential risk of bias was detected in most of the studies, especially in the domain of participants and personnel (therapists) blinding. Future RCTs are encouraged to prevent the risk of such bias using recommended procedures (Sterne et al., 2019). Finally, some of the interventions under study were under-represented in our *meta*-analysis. For instance, psychological interventions for sleep problems (e.g., CBT for insomnia) or emotion-based interventions were tested only in two and three trials, respectively. It is known that up to 20% of individuals with chronic sleep problems show low-grade chronic inflammation as defined by CRP $>$ 3 mg/l (Carroll et al., 2015), and that impaired sleep may be prospectively associated with increased inflammation (e.g., Ballesio et al., 2022). While the efficacy of CBT for insomnia has been widely tested on sleep and psychological outcomes (e.g., Ballesio et al., 2018; Ballesio et al., 2021), the impact of this intervention on immune outcomes remains unclear. Similarly, negative emotions and emotion dysregulation have been associated with poorer immune function including weaker antibody response to vaccination (e.g., Phillips et al., 2005) and increased inflammation following pathogen exposure (Brown et al., 2020). Therefore, an effort should be made to implement RCTs testing sleep and emotion-based interventions on immune outcomes in order to advance the knowledge in this field.

To summarise and conclude, this *meta*-analysis contributes to establish the beneficial role of psychological interventions on immune system. Some interventions (e.g., mindfulness-based interventions) compared to others seem more consistently and robustly associated with

favourable effects not only in reducing pro-inflammatory markers, but also in increasing anti-inflammatory cytokines and markers. These results should be considered when planning clinical psychological interventions in populations with or at risk of inflammation-related conditions or altered immune function.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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