**Effects of SSRIs on peripheral inflammatory markers in patients with major depressive disorder:**

**a systematic review and meta-analysis**

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**Abstract**

**Introduction:** Peripheral levels of inflammatory markers are elevated in major depressive disorder (MDD). Selective serotonin reuptake inhibitors (SSRIs) affect levels of inflammatory markers in patients with MDD, but studies have reported inconsistent findings. This systematic review and meta-analysis aims to investigate the effects of SSRI treatment on peripheral levels of a range of inflammatory markers in MDD patients.

**Methods:** Systematic literature search (Pubmed, Web of Science, Embase, Cochrane) for studies published before November 2018. Studies were included if they used SSRI monotherapy and peripheral levels of interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were measured before and after treatment in patients with MDD. Meta-analysis was conducted using Comprehensive Meta-analysis (version 2). Effect sizes were calculated using bias-corrected standardized mean difference (Hedges’ g) between pre- and post-treatment. Sub-group analyses, meta-regression and publication bias estimates were undertaken; sensitivity analyses were performed using different estimated pre- and post-treatment correlations and after removing poor quality studies.

**Results:** Twenty two eligible studies including 827 MDD patients were included in the meta-analysis: fifteen studies for IL-6; eleven for TNF-α; eight for IL-10; seven for IL-1β; six for IL-4; five for IL-2; and four for IFN-γ. The pooled effect estimate indicates SSRI treatment decreased levels of pro-inflammatory markers IL-6 (Hedges’ g, -0.428; 95%CI, -0.699 to -0.158; I2=84.867), TNF-α (Hedges’ g, -0.554; 95%CI, -0.990 to -0.118; I2=95.438) and IL-1β (Hedges’ g=-0.873; 95%CI, -1.702 to -0.043; I2=94.237), and anti-inflammatory marker IL-10 (Hedges’ g=-0.535; 95%CI, -0.987 to -0.084; I2=84.369). There were no significant treatment effects on levels of IL-2, IL-4, or IFN-γ. There was a high level of heterogeneity between studies. Sensitivity analyses indicated the robustness of the primary analyses.

**Conclusions:** The current review and meta-analysis indicates moderate immunomodulating effects of SSRI treatment for MDD, which suggests SSRIs may owe some of their therapeutic effect to their anti-inflammatory properties. High heterogeneity across studies may limit interpretation of the findings and larger randomized clinical trials are warranted.

Key words

major depressive disorder; SSRI; peripheral inflammatory markers; inflammation; immunity; cytokines

**1. Introduction**

There is considerable evidence of interactions between the brain and the immune system. Dysregulations in the immune system and immune response have been reported in various psychiatric disorders, in particular major depressive disorder (MDD). MDD is associated with chronic, low grade inflammation and cell-mediated immune (CMI) activation (Maes et al., 1990; 1991; 1992). The ‘inflammatory response system activation’ theory of major depression and the ‘cytokine-hypothesis of mood disorders’ were proposed because of the evidence of the disturbed inflammatory system and cell-mediated immunity in both MDD and bipolar disorder (Song et al., 1998; van West and Maes, 1999; Schiepers et al., 2005; Beumer et al., 2012; Haarman et al., 2014; Miller et al., 2009; Rosenblat et al., 2014).

Inflammatory responses consist of cellular, cytokine and complement cascades and an acute phase response. Cellular interactions between different immune cells including T lymphocytes and macrophages/monocytes are involved in cell-mediated immunity (Leonard and Maes, 2012). Macrophage-derived cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α are the primary mediators of inflammation. These cytokines activate nuclear factor κB (NFκB) which increases the production of IL-6 and IL-8. IL-1β, IL-6, IL-8 and TNF-α contribute to a rapid local inflammatory response. T cells are further differentiated into Th-1, Th-2, Th-3, Th-17, Th22, Treg, Tr1, etc. The pro-inflammatory cytokines interferon (IFN)-γ and IL-2 are mainly produced by Th-1 cells and have the function of enhancing the cellular immune response. The cytokine IL-12 is produced by monocytes/macrophages, dendritic cells, and antigen-presenting cells and can trigger T cells to produce more IFN-γ (Trinchieri, 2003). Th-3 cells produce transforming growth factor (TGF)-β which has immunosuppressive effects while most Th sub-populations produce the anti-inflammatory cytokine IL-10 in differing amounts (Sabat, 2010). The anti-inflammatory cytokines IL-4 and IL-10 activate the humoral immune response and give negative feedback on immune cell activation (Drexhage et al., 2010; Liao et al., 2011; Shabgah et al., 2014). Pro-inflammatory cytokines enhance the production of positive acute phase proteins such as C-reactive protein (CRP) and down-regulate the production of negative acute phase proteins such as albumin and transferring (Maes, 1993).

Elevated inflammatory marker levels are observed in MDD patients. According to a recent meta-analysis (Goldsmith et al., 2016), levels of IL-6, TNF-α, sIL-2R, and IL-1RA were significantly increased in acutely ill patients with MDD, compared with controls. Three other meta-analyses have shown that inflammatory marker levels such as CRP and IL-1 are increased in depressed patients compared with non-depressed subjects (Haapakoski et al., 2015; Valkanova et al., 2013; Howren et al., 2009). Furthermore, treatment with inflammatory cytokines such as interferon for hepatitis C can lead to an incidence of depression in 25% at 24 weeks and 28% at 48 weeks of treatment, respectively (Udina et al., 2012). In addition, use of anti-inflammatory drugs, such as adalimumab, etanercept, infliximab and tocilizumab, showed significant improvements in depressive symptoms (Kappelmann et al, 2018; Fond et al., 2014; Köhler et al., 2014). Taken together these data indicate that inflammatory processes may be involved in the pathology of depression.

Several studies have shown that antidepressant treatment, mainly selective serotonin reuptake inhibitors (SSRIs), was associated with decreases in the levels of inflammatory markers (Miller et al., 2009). In contrast, results from two other large studies found that use of antidepressants, mainly tricyclic antidepressants (TCA), was associated with elevated inflammation levels (Hamer et al., 2011). Similarly, results from a cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders showed that inflammation levels differ across patients using different classes of antidepressant medications. Male users of SNRI, TCA and tetracyclic antidepressant (TeCA) had increased levels of IL-6, whereas SSRI prescription was associated with significantly lower levels of IL-6 (Vogelzangs et al., 2012). Two meta-analyses of the effect of antidepressant treatment on serum levels of inflammatory markers also showed different results regarding IL-6 levels (Hiles et al., 2012; Hannestad et al., 2011). It is worth noting that SNRIs, TCAs and TeCAs have a combined serotonergic/noradrenergic effect, whereas SSRIs are primarily serotonergic. Evidence has shown that noradrenaline has pro-inflammatory effects on innate immune cells and thus potentiate cytokine production (Thayer and Sternberg, 2010; Elenkov and Chrousos, 2002). Therefore, it is of particular interest to investigate the effects of SSRIs on peripheral inflammatory markers. Using a stratified subgroup analysis, Hannestad et al. found that SSRI treatment may decrease levels of IL-1β, IL-6 and possibly TNF-α (Hannestad et al., 2011). However, this meta-analysis was conducted in 2011 and only a small number of trials using SSRIs were identified: furthermore, only three cytokines (IL-1β, IL-6 and TNF-α) were studied in the abovementioned meta-analysis and the effects of SSRIs on other extensively studied cytokines such as IL-2, IL-4, IL-10 and IFN-γ were not systematically investigated.

 The aim of this systematic review and meta-analysis was to evaluate current evidence of the effects of SSRIs on peripheral inflammatory markers in patients with MDD.

**2. Methods**

The current systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The current review was to include evidence from clinical trials which had investigated the effects of SSRI treatment on peripheral levels of inflammatory markers in patients with MDD.

**2.1 Eligibility criteria**

We applied the following eligibility criteria:

* Studies with a longitudinal design including both randomized clinical trials and prospective trials which reported levels of inflammatory markers at both pre- and post-treatment points;
* Adult patients of both sexes with major depressive disorder as confirmed by DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-9 or ICD-10 criteria, without major physical illness (i.e. diabetes, heart disease, cancer etc.);
* An intervention with a monotherapy of any of the currently available SSRI agents (including fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine) in an acute treatment phase (treatment duration between 4 weeks and 12 weeks) of a MDD episode;
* As outcomes of interests, studies assessing levels of at least one of the following inflammatory markers: IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ in peripheral blood.

We did not exclude studies on the basis of concomitant drug administration for purposes other than treating depression. Several studies mentioned the use of benzodiazepines as concomitant drugs in a subgroup of patients, and these were included for the systematic review. However, studies which included treatment with more than one antidepressant agent, without a separate evaluation of the effect of SSRI monotherapy, were excluded. We also excluded subjects with medical conditions that can affect the inflammatory pathways, such as hemodialysis or nickel-allergic patients, patients with familial Mediterranean fever and patients undergoing joint replacement surgery.

**2.2 Search methods for identification of studies**

We performed a systematic search of the literature using PubMed, Web of Science, EMBASE and Cochrane Library and included studies published in English before 30th November, 2018 using the following Medical Subject Headings (or similar headings) or text word terms: (Serotonin Uptake Inhibitors OR Fluoxetine OR Paroxetine OR Sertraline OR Citalopram OR Fluvoxamine OR Escitalopram) AND (Cytokines OR [Chemokines](https://www.ncbi.nlm.nih.gov/mesh/68018925) OR [Interferons](https://www.ncbi.nlm.nih.gov/mesh/68007372) OR [Interleukins](https://www.ncbi.nlm.nih.gov/mesh/68007378) OR [Lymphokines](https://www.ncbi.nlm.nih.gov/mesh/68008222) OR [Monokines](https://www.ncbi.nlm.nih.gov/mesh/68015846) OR [Tumor Necrosis Factors](https://www.ncbi.nlm.nih.gov/mesh/68048069)) AND (Depressive Disorder, Major OR Depressive Disorder OR Depression OR Major Depressive Disorder). We also scrutinized and hand-searched the reference lists of all the relevant publications identified to check for any additional studies using EMBASE.

**2.3 Study Selection and Data Extraction**

The titles and abstracts were screened by one investigator (L.W.) to eliminate obviously irrelevant reports. Full texts of the potential relevant articles were further examined for eligibility with inclusion criteria by two investigators (L.W. and R.H.). Disagreements were resolved by consensus and discussion within the research team. Data were extracted using a pre-piloted structured form. In addition to bibliographic information, extraction processes sought the following data: country, participants diagnosis, diagnostic criteria, study design, inpatient or outpatient status, number of subjects (baseline), number of subjects (end point), number of attrition, mean age, sex, severity of symptoms (as measured by scales at pre- and post-treatment points), duration of medication-free period before study, names of SSRIs, treatment duration, concomitant medications, assay type/manufacturer of inflammatory markers, levels of specific inflammatory markers measured (mean with standard deviation, pre- and post-treatment; pre-post correlation). Where not reported, these variables were coded as missing values. One investigator (L.W.) initially extracted these predefined data; another investigator (R.H.) checked the data extraction form. The investigators were not blinded to the study results, authors, or institutions. Disagreements were settled by consensus and discussion within the research team.

Corresponding authors of six studies were directly contacted for further information or clarification. When mean (SD) value of cytokine levels could not be provided by the authors but data were available in the articles in graph format (Gupta et al., 2017; Yoshimura et al., 2013; Mackay et al., 2009; Song et al., 2009), values were extracted using PlotDigitizer software, shown to be a reliable method of data extraction for meta-analysis (Jelicic et al., 2016). One study with the median (inter-quartile range) value reported was provided mean with standard deviation by the author (Manoharan et al., 2016).

**2.4 Quality assessment**

To evaluate the quality of individual studies, the Downs and Black quality assessment method was conducted, which lists 27 criteria to evaluate both randomized and nonrandomized trials (Downs and Black, 1998). This quality assessment scale (QAS) assesses 5 domains including reporting, external validity, internal validity - bias, internal validity - confounding (selection bias) and power (Deeks et al., 2003; Saunders et al., 2003). The scale was modified for use in this review as in previous reviews (Chudyk et al., 2009; Hooper et al., 2008; Samoocha et al., 2010; Marasinghe, 2015). Specifically, the scoring for question 27 dealing with statistical power was simplified by scoring either 1 or 0 point depending on whether there was sufficient power to detect a clinically important effect. The maximum score for item 5, reporting of principal confounders, was 2. Each study can obtain a maximum of 28 points and a higher score reflects better study quality. Downs and Black scale scores were grouped into the following three quality levels: good (≥ 20), fair (15- 19) and poor (≤ 14) (Marasinghe, 2015). In line with the recommendations of the Meta-Analysis of Observational Studies (Stoup et al., 2000), we performed a sensitivity analysis excluding those studies with poor quality.

**2.5 Statistical analysis**

Meta-analysis was conducted using the statistical package Comprehensive Meta-analysis (version 2). Effect sizes were calculated using bias-corrected standardized mean difference (Hedges’ g) from pre- and post-treatment means and standard deviations (SDs) of each inflammatory marker, sample size and the pre- and post-treatment correlation. When the correlation was unknown, we used correlation (r=0.631) reported in one included study (Sutigil et al., 2007) as an estimate (Borenstein et al., 2009). For study which didn’t report means and SDs, t values and sample size were used to calculate the effect size (Lindqvist et al., 2017). For one study where standard deviation was not reported, effect sizes were calculated using the difference in means, sample size and P value (Halaris et al., 2015). For studies which had longer than 12 weeks’ study duration and had more than one follow-up measures of inflammatory markers (Mackay et al., 2009; Hernandez et al., 2008), the follow-up points closest to the median duration of the remaining studies (8 weeks) were selected into the meta-analysis in order to reduce the heterogeneity between studies. For studies where medians and inter-quartile ranges (IQRs) were reported (Brunoni et al., 2018; Brunoni et al., 2014), means and SDs were estimated as medians and IQRs divided by 1.35 (Higgins and Green, 2008). For studies reporting data in two independent groups (i.e., responders & non-responders; Sertraline group & Citalopram group; etc.) (Lindqvist et al., 2017; Gupta et al., 2017; Yoshimura et al., 2013; Eller et al., 2008; Leo et al., 2006; Sluzewska et al., 1995), combined effect sizes were computed for final analysis. In terms of Hamilton Depression Rating Scale (HDRS), scores were combined using the following formulae according to Cochrane handbook (Higgins and Green, 2008) if they were reported in two subgroups. The same approach was used for Montgomery Asberg Depression Rating Scale (MADRS) and mean age (SD).

Formulae for combining groups

|  |  |  |  |
| --- | --- | --- | --- |
|  | Group 1 (e.g. responders) | Group 2 (e.g. non-responders) | Combined groups |
| Sample size | N1 | N2 | N1+N2 |
| Mean  | M1 | M2 |  |
| SD | SD1 | SD2 |  |

Random effects meta-analysis was used to synthesize individual study effect sizes and generate an overall effect size due to the clinical and methodological variation across studies. Random-effects models take into account both within- and between-study variability, and provide a more conservative estimate of effect sizes than can be obtained with the fixed-effect models. A positive effect size indicates an increase in the inflammatory marker over time. Heterogeneity across studies was investigated by calculating the Cochrane Q statistic with P<0.10 considered to represent statistically significant heterogeneity and the I2 statistic with 25%, 50% and 75% considered to indicate low, medium and high heterogeneity respectively.

Subgroup analyses, meta-regression and publication bias were conducted for inflammatory markers measured in at least 10 studies (Higgins and Green, 2008). Subgroup analyses and meta-regression were performed to investigate heterogeneity. Mean age of study population, gender (percentage of female subjects) and study duration were used as covariates in meta-regression. Drug dose (fixed dose vs. variable dose), and study design (RCTs vs. non-RCTs) were used as categorical effect moderators in the subgroup analysis. Publication bias was assessed by visual inspection of funnel plots including Egger’s test (Egger et al., 1997), and Duval and Tweedie’s trim and fill method (Duval and Tweedie, 2000). The fail-safe N analysis was also conducted to assess the robustness of the overall effect size (Rosenthal, 1991; Rosenthal and Rubin, 1988). Sensitivity analyses were performed to examine the robustness of original results using estimated pre- and post-treatment correlations of 0.5 and 0.75 (Borenstein et al., 2009). Sensitivity analyses were also carried out after excluding low quality studies with Downs and Black scores ≤14 and studies reporting medians and IQRs of the inflammatory markers.

**3 Results**

* 1. **Overview of the study selection**

The search of PubMed, Web of Science, EMBASE and Cochrane Library databases resulted in an initial 1597 records, which reduced to 979 records after removal of duplicates. Based on a preliminary screening of titles and abstracts, 939 records were excluded. Eligibility of the remaining 40 records was assessed by a detailed evaluation of the full text articles. Three additional articles were identified by manual search of reference lists. Following full text review, 21 articles were excluded because of the following reasons: six for no separate inflammatory data on SSRIs; five for not measuring peripheral cytokine levels, e.g. cytokine levels in CSF were measured; four for a cross-sectional design of the study; three for no data comparing cytokine levels pre- with post-treatment; one for no separate inflammatory data on MDD patients; one for animal study; and one for study population overlap. A final total of 22 studies met the inclusion criteria and were included in this systematic review and meta-analysis: 15 studies for IL-6; eleven studies for TNF-α; eight studies for IL-10; seven studies for IL-1β; six studies for IL-4; five studies for IL-2; and four studies for IFN-γ. For PRISMA study selection process, see Fig 1.

* 1. **Characteristics of the included studies**

Characteristics of the selected studies are presented in Tables 1 and 2. Of the 22 studies, 7 were RCTs and 15 were non-RCT prospective studies. Fluoxetine monotherapy was used in 6 studies, sertraline and escitalopram in 4 studies respectively, paroxetine and fluvoxamine in 1 study respectively and other 6 studies included more than one SSRI drug. In this review, we collected evidence of the changes of cytokine levels before and after SSRIs treatment. Twenty studies had a treatment duration ranged between 6 weeks and 12 weeks. Two studies had 18 weeks (Mackay et al., 2009) and 52 weeks (Hernandez et al., 2008) duration and we selected 6 weeks and 5 weeks measurements of cytokine levels in the analysis respectively to reduce heterogeneity. The studies had the following geographic distribution: eight in Asia, seven in Europe, four in North America, two in South America and one in Africa.

The 22 studies reported data from a total of 827 participants. The number of participants in the individual studies varied from 14 to 118. All the studies included both male and female participants. With regard to the cytokine assays used, 15 out of 22 studies used enzyme-linked immunosorbent assays (ELISA) to measure peripheral levels of cytokines; however, there was a wide range of manufacturers.

* 1. **Study quality**

The quality of the included studies varied (see Table 2). According to the calculated Downs and Black QAS, all studies were over 13, and all RCTs were over 20. Three studies were rated as being of poor quality, nine studies were rated fair, and ten were rated good. The mean QAS for the included studies was 18.95. Scores were poor on the following items: failure to report adverse events (19 of 22), patient blinding (16 of 22), failure to determine whether patients in different groups were recruited over the same period of time (15 of 22), patient randomizing (14 of 22), intervention assignment concealing (19 of 22), failure to adjust for confounding factors in the analysis (20 of 22), and bias due to losses of patients to follow-up (11 of 22). Furthermore, the randomization method and concealment in the seven RCTs were not described adequately, the internal validity – confounding (selection bias) was relatively poor.

* 1. **Effect of SSRIs on peripheral inflammatory markers**
		1. **IL-6**

Fifteen studies reported or provided IL-6 levels at pre- and post-treatment, allowing calculation of changes of IL-6 based on a total of 565 MDD patients who underwent SSRI treatment. Four studies reported IL-6 levels in two subgroups: Lindqvist et al., 2017 and Yoshimura et al., 2013 reported IL-6 levels in responders to SSRIs and non-responders respectively, Leo et al., 2006 reported IL-6 levels in sertraline and citalopram groups respectively and Sluzewska et al., 1995 reported IL-6 levels in patients with baseline elevated or non-elevated IL-6 levels respectively. Combined effect sizes were computed for final analysis for the 4 abovementioned studies. The random effects meta-analysis yielded a pooled Hedges’ g=-0.418 (95%CI, -0.663 to -0.174; z=-3.357; P=0.001) which indicated SSRIs had significantly reduced IL-6 levels (Fig 2).

There was high heterogeneity (Q=132.220, p＜0.001, I2=89.412), suggesting that systematic differences exist between the studies. Subgroup analyses and meta-regression were therefore conducted respectively to investigate the potential reasons of heterogeneity (Tables 3 and 4). Meta-regression were performed for mean age, gender (percentage of female subjects) and study duration which showed that these three covariates did not modify the effects of SSRIs on IL-6. Separate subgroup analyses were performed for drug dosage and study design which indicated that there were significant effects of SSRI treatment on IL-6 level in studies when participants receiving fixed dosage of SSRIs (p=0.005) and those with a study design of RCT (p=0.006). However, the between group heterogeneity showed no significant difference for each moderator, suggesting that neither of the two moderators were responsible for the heterogeneity.

The funnel plot of standard error by Hedges’ g was asymmetrical indicating a potential publication bias (Fig 3). However, there was no evidence of publication bias via Egger’s test (t=2.141, 2-tailed p=0.052) and Duval and Tweedie’s trim and fill analysis (study trimmed=0).

* + 1. **TNF-α**

Eleven studies reported effects of SSRI treatment on TNF-α level in 431 MDD patients, including three studies which reported TNF-α level in two independent subgroups: Gupta et al., 2017 and Eller et al., 2008 reported in SSRI responders and non-responders respectively, and Leo et al., 2006 reported in sertraline and citalopram groups respectively. Combined effect sizes were computed for the 3 studies. The random effects meta-analysis yielded a pooled Hedges’ g=-0.554 (95%CI, -0.990 to -0.118; z=-2.489; P=0.013) (Fig 4), indicating SSRI treatment had significantly reduced TNF-α levels.

High heterogeneity between studies was detected (Q=219.217, p＜0.001, I2=95.438). Hence, subgroup analyses and meta-regression were conducted respectively to investigate the potential effect of modifiers (Tables 3 and 4). Results showed that SSRIs effects on TNF-α levels were significantly increased with the increase of the percentage of female subjects (P=0.004) which indicates gender as a potential modifier for the heterogeneity (Fig 5). Mean age, study duration, drug dosage and study design were not responsible for the heterogeneity.

A potential publication bias was found through the funnel plot of standard error by Hedges’ g which was asymmetrical (Fig 6) and Egger’s test (t=3.762, 2-tailed p=0.004). However, there was no evidence of publication bias via Duval and Tweedie’s trim and fill analysis (study trimmed=0).

* + 1. **IL-1β**

Seven studies reported IL-1β levels before and after treatment with SSRIs in 241 participants. One study reported IL-1β levels in sertraline and citalopram subgroups respectively (Leo et al., 2006) and combined effect sizes were computed in the meta-analysis. Analysis revealed a pooled Hedges’ g=-0.574 (95%CI, -1.014 to -0.135; z=-2.560; P=0.010) which indicated SSRIs significantly reduced IL-1β levels (Fig 7). High heterogeneity between studies was also detected (Q=71.616, p＜0.001, I2=91.622). Subgroup analyses, meta-regression and publication bias estimation were not conducted for IL-1β and the following inflammatory markers, due to the limited numbers of available studies.

* + 1. **IL-2**

Five studies involving 150 MDD patients reported IL-2 levels before and after treatment with SSRIs. Meta-analysis yielded a pooled Hedges’ g=-0.618 (95%CI, -1.703 to 0.467; z=-1.116; P=0.264) (Fig 8). No statistical significance was detected between pre and post-treatment levels of IL-2. This may be due to the extensive heterogeneity between studies (Q=142.311, p＜0.001, I2=97.189).

* + 1. **IL-4**

Six studies reported the effect of SSRIs on IL-4 levels in a total of 161 MDD patients and the random effects meta-analysis yielded a pooled Hedges’ g=0.118 (95%CI, -0.732 to 0.968; z=0.272; P=0.786) (Fig 9). There was no significant treatment effect on IL-4 levels. Heterogeneity between studies was high (Q=131.723, p＜0.001, I2=96.204).

* + 1. **IL-10**

Eight studies reported IL-10 levels in 280 participants. Meta-analysis revealed a pooled Hedges’ g=-0.615 (95%CI, -0.989 to -0.242; z=-3.232; P=0.001) (Fig 10), indicating a significant SSRI treatment effect on IL-10 levels in patients with MDD. High heterogeneity between studies was detected (Q=72.964, p＜0.001, I2=90.406).

* + 1. **IFN-γ**

Four studies reported IFN-γ levels in 123 MDD patients. Analysis revealed a pooled Hedges’ g=-0.440 (95%CI, -0.946 to 1.826; z=0.623; P=0.533) (Fig 11), indicating a non-significant treatment effect. There was high heterogeneity between studies (Q=106.865, p＜0.001, I2=97.193).

* 1. **Sensitivity analyses**

Two studies on IL-6 (Yoshimura et al., 2017; Yoshimura et al., 2013) and one on IL-2 (Mackay et al., 2009) were rated as poor quality according to QAS**.** When fair and good quality studies were included in the analysis, the treatment effect of SSRIs on IL-6 levels remained statistically significant and stable (N=13 studies, Hedges’ g=-0.424, 95%CI=-0.723 to -0.124, p=0.006) and the treatment effect of SSRIs on IL-2 remained non-significant (N=4 studies, Hedges’ g=-0.967, 95%CI=-2.364 to 0.430, p=0.175).

Means and SDs were estimated in two studies which reported medians and IQRs (Brunoni et al., 2018; Brunoni et al., 2014). When analyses excluding these two studies was conducted the SSRIs effect on inflammatory markers remained similar except that on IFN-γ (N=3 studies, Hedges’ g=1.312, 95%CI=0.145 to 2.479, p=0.028) (see Table 5).

A reported correlation coefficient value of 0.631 in one study was used as an estimate for the correlation between pre- and post-treatment inflammatory markers of all the studies. Sensitivity analyses were therefore conducted to examine the robustness of our primary analyses by using different estimated correlations (r=0.5, 0.75). Results showed all the effect sizes remained similar with none producing a large difference (see Table 6).

1. **Discussion**

To our knowledge, the present meta-analysis is the most extensive review of the effect of SSRI treatment on peripheral inflammatory markers in patients with MDD. Evidence from twenty two longitudinal studies with a total of 827 patients was evaluated. SSRIs significantly reduced both the pro-inflammatory makers IL-1β, TNF-α and IL-6 and the anti-inflammatory marker IL-10. However, our meta-analyses found no significant overall effect of SSRI treatment on peripheral levels of IL-2, IL-4 and IFN-γ.

 Extensive research has indicated the presence of inflammatory responses, and in particular, the role of cytokines in major depression. However, inconsistent findings have been reported regarding the effects of SSRIs on inflammatory cytokines: while some studies reported suppression of the production of IL-1β, IL-2, IL-6, IFN-γ and TNF-α (Maes et al., 2005; Diamond et al., 2006; Xia et al., 1996; Maes et al., 1999; Waiskopf et al., 2014; Taler et al., 2007); some studies showed non-significant effect on these cytokines (Kubera et al., 2004; Haastrup et al., 2012; Maes et al., 2005; Diamond et al., 2006); whereas others showed enhanced IL-10 production (Kubera et al., 2009; Maes et al., 1999). Therefore, it is important to conduct the current meta-analysis to review the currently available evidence in the field to guide future research and clinical practice.

 A previous review conducted by Hannestad and colleagues examined the effect of antidepressant treatment on serum levels of IL-6, TNF-α, and IL-1β (Hannestad et al., 2011). Their meta-analysis of 22 studies showed that antidepressant treatment did not affect serum levels of TNF-α, however, they did reduce levels of IL-1β and possibly those of IL-6. Their stratified subgroup analysis showed that SSRI treatment showed a greater reduction in IL-6 levels in comparison to other antidepressants (SMD=-1.45, p=0.02) which is in line with findings from the present meta-analysis. Their meta-analysis did not reveal any significant overall effect of antidepressant treatment on TNF-α levels (n=199, p=0.16), however there was a trend effect of SSRI treatment on TNF-α levels (p=0.06), which is in line with our meta-analysis which revealed significantly reduced TNF-α levels after SSRI treatment (n=431, p=0.01). In line with our meta-analysis, an overall effect of antidepressant treatment on IL-1β levels (SMD=-0.52, P＜0.001) was also reported in their meta-analysis. In another meta-analysis, overall effect sizes were pooled without stratifying medication class and the analysis revealed a significant decrease in IL-6 (d=-0.42, p=0.02) and a non-significant decrease in IL-10 (d=-0.45, p=0.14) (Hiles et al., 2012). The differing treatment effect of antidepressants on IL-10 suggests that SSRIs may have different effects on innate immune cells in comparison to SNRIs and other antidepressants (Thayer and Sternberg, 2010; Elenkov and Chrousos, 2002). Another meta-analysis on inflammation and clinical response to treatment in depression (Strawbridge et al. 2015) found elevated baseline levels of IL-6, TNFα and CRP in depression in comparison to healthy controls. However, there were no significant differences between those subsequently responding or not responding to treatment. The effect of SSRI treatment on IL-1β has also been reported in patients with posttraumatic stress disorder (PTSD) where both citalopram and sertraline significantly reduced the IL-1β levels (Tucker et al., 2004). Evidence from cross-sectional studies reported that the reduction of IL-1β levels were associated with fluoxetine and paroxetine treatment in patients with MDD (Alcocer-Gómez et al., 2017) and IL-6 levels were lower in SSRI male users compared with medication-free depressed men (Vogelzangs et al., 2012).

 Regarding the most commonly reported cytokine IL-6 (15 out of 22 studies in this review), additional subgroup analyses and meta-regression indicated that the SSRI effect was associated with drug dosage and study design, but not with mean age and gender of participants and study duration: but none of these factors could explain the heterogeneity noted in effect estimation. For studies reporting IL-6, the pooled effect size of RCTs was larger than that of non-RCTs which added to the robustness of the findings of this meta-analysis. While for TNF-α, meta-regression indicated gender as a potential modifier for heterogeneity. The only significant positive linear association after meta-regression analyses revealed more female participants associated with a larger effect of SSRIs on TNF-α. This may be because females tend to have higher response rates to SSRIs treatment in clinical trials (Khan et al., 2005). Subgroup analyses showed that patients taking a fixed SSRI dosage had larger overall effect size on IL-6 levels and the effect size of non-RCTs was larger than that of RCTs on TNF-α. Except for IFN-γ, effect sizes were not affected by the estimate of mean (SD). The instability of the effect size of IFN-γ was probably due to small sample sizes enrolled in the analysis. Sensitivity analyses showed pooled effect sizes of all the seven inflammatory markers were relatively stable, and were neither affected by study qualities nor the estimate of pre-post treatment correlation.

 It should be noted that there was a high level of heterogeneity across all studies. Methodological issues, such as relatively small numbers of studies in each subgroup and risk of bias of the non-RCT studies may explain these differences. The present analysis indicates a probable cumulative effect of patient characteristics on the changes of inflammatory markers. In addition, some other factors may also contribute to the high heterogeneity, such as studies conducted at different clinical settings and in different countries. Sample size, study design and treatment duration varied across studies. MDD patients were enrolled via different ways including outpatients, inpatients, primary and secondary care ambulatories and community recruitment via advertising in local newspapers, radio stations, and websites. Moreover, cytokines are highly unstable proteins and some laboratory procedures such as assay methods, timing of samples collection, storage condition and time spent from collection to the final analysis, may likely affect the measures of cytokines and contribute to the high heterogeneity. It should be noted that factors not reported in some original studies might also account for the high heterogeneity, such as missing information reporting clinical outcomes such as the change of depressive symptoms over time which limit the interpretation about how cytokine changes are associated with long term treatment responses to SSRIs (Hiles et al., 2012).

 Several limitations should be noted when interpreting the findings from the current meta-analysis. First, the mean sample size of the studies was only 38 participants per study, indicating that the trials reviewed were mostly small-scale pilot studies. Large-scale studies are needed to yield more stable and consistent effect sizes. Second, the treatment duration and SSRIs dosage reported across 22 studies varied which may also influence the outcomes of interest. Third, the current review included data from non-RCTs studies, which may result in selection bias, confounding bias, and reporting bias. Fourth, among 22 longitudinal studies, there were few studies which reported the effect of SSRIs on some individual cytokines, such as IFN-γ which was reported in only 4 studies. Hence, publication bias could not be fully examined and pooled effect sizes could be biased. Fifth, due to limited number of studies, we were unable to conduct subgroup analyses to examine inflammatory changes between responders and non-responders, which would have important clinical implications. Sixth, a lack of standard lab procedures to process blood samples may affect the measure of cytokine levels. Moreover, major depressive disorder in itself is a clinically heterogeneous disorder and these differences may extend to differences in inflammation as well. As a result, our findings should be interpreted with caution.

 Research so far has also examined the changes of inflammatory markers between treatment responders and non-responders. While elevated serum levels of IL-6, IL-8, chemokine ligand 2 (CCL2) and vascular endothelial growth factor (VEGF) found in MDD patients, there was no difference between responders and non-responders in terms of baseline IL-4, IL-6 and IL-10 levels (Carvalho et al. 2013; 2014). Cattaneo A, et al. (2013) examined mRNA expression levels of genes relating to inflammation in healthy controls and depressed patients before and after 8 weeks of treatment with escitalopram or nortriptyline. They found higher baseline mRNA levels of IL-1β, macrophage inhibiting factor (MIF), and TNF-α in non-responders. Antidepressants reduced the levels of IL-1β and MIF which were not associated with treatment response, whereas antidepressant responders associated with a reduction in IL-6. Uher et al. (2010) performed a genome-wide association analysis of improvement of depression severity with two antidepressant drugs nortriptyline and escitalopram and identified the IL-11 gene as a marker for treatment response to escitalopram. To predict antidepressant response in MDD, Grosse et al. (2016) investigated circulating leukocyte subsets before venlafaxine or imipramine treatment. They found non-responders associated with increased CD8+ cytotoxic T cell percentages and responders associated decreased natural killer (NK) cell percentages, and both lymphocyte levels were not significantly modulated by treatment. A recent meta-analysis revealed robust improvement in depressive symptoms after anti-inflammatory treatment (monoclonal antibody or cytokine inhibitor) which further supports the role of inflammation in the pathogenesis of depression (Kappelmann et al., 2018). This meta-analysis supports a potentially causal role for cytokines in depression and that cytokine modulators may be novel drugs for depression in chronically inflamed subjects. More recently, Chamberlain et al. (2019) examined treatment-resistant MDD patients in comparison to treatment-responsive patients and healthy volunteers and found elevated CRP in treatment-resistant MDD patients. Their data suggests that MDD patients stratified for pro-inflammatory biomarkers, such as elevated CRP, might have better treatment response to augmentation with anti-inflammatory drugs.

In conclusion, the work reported here provides an up-to-date review of the existing evidence on immumodulating effects of SSRI treatment in MDD. In the current meta-analysis, we included more recent studies and examined more inflammatory markers. Changes of IL-1β, IL-2, IL-4, IL-10 and IFN-γ levels after SSRI treatment were comprehensively reviewed. High heterogeneity between studies may limit our interpretation, but the current meta-analysis indicates moderate immumodulating effects of SSRI treatment for MDD. The pooled effect estimate indicates SSRI treatment reduced levels of pro-inflammatory IL-6, TNF-α and IL-1β, and anti-inflammatory IL-10. To translate these research findings to clinical practice, larger randomized clinical trials with longer term follow-up periods are needed. It would also be of benefit to investigate the effect of individual SSRI agent on inflammatory markers and examine this in subgroups of depression patients with different baseline inflammatory status as well as in subgroups of treatment responders and non-responders, in an attempt to stratify medications and achieve a more ‘personalized medicine’ approach.

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**Authors’ contributions:**

Drs L. Wang and R. Hou had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: R. Hou and L. Wang. Acquisition, analysis, or interpretation of data: All authors. Critical revision of the manuscript for important intellectual content: R. Hou and L. Wang. Statistical analysis: L. Wang, D. Qiao. Study supervision: R. Hou and L. Wang.

**Conflicts of interest:** The authors declare no conflict of interest.

**Fig 1.** PRISMA flow chart of study selection

1597 records identified by database searching:

* Pubmed: 300
* Web of Science:592
* EMBASE: 576
* Cochrane Library: 129

979 records screened on title & abstract after duplicates removed

939 records excluded:

Not relevant: 622

Reviews/letters to editor: 303

Conference abstract: 14

40 full text articles reviewed

3 additional records identified by reviewing reference lists

43 full text articles assessed for eligibility

21 full text articles excluded:

-No separate data on SSRIs (n=6)

-Not measuring peripheral cytokine levels (n=5)

-Cross-sectional study (n=4)

-No data comparing cytokine levels pre- with post-treatment (n=3)

-No separate data on MDD patients (n=1)

-Animal study (n=1)

-Study population overlap (n=1)

22 full text articles included in systematic review and meta-analysis

**Table 1. Characteristics of the included studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First Author, Year | Sample Size/Female | Age (Year)  | Patients recruitment | Drug Name/Dose(mgs/day) | Study Duration/ Endpoint Included in the analysis (Week) | Rating Scale/Baseline Severity/Endpoint Severitya  | Cytokine(s) Assessed | Assay Type/Manufacturer | Timing of samples collection/Storage |
| EI-Haggar et al., 2018 | 38/ND | 33.09±7.59 | outpatients | Escitalopram/20 | 12/12 | HDRS-17/19.38±1.25/9.96±1.16 | IL-6, IL-10, TNF-α | ELISA/eBioscience | Fasting sample at same time in the morning/ -80℃ |
| Chen et al., 2018 | 50/33 | 43.42±13.17 | Outpatients and inpatients | Paroxetine/10-40 | 8/8 | HDRS-21/26.36±5.64/ND | IL-Iβ,IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α | Mutiplex xMAP Luminex/Novex by Life Technologies | Fasting sample at 7:30-10am/-80℃ |
| Brunoni et al., 2018 | 87/57 | 42.1±12.5 | ND | Escitalopram/10-20 | 10/10 | HDRS-17/21.7±3.5/10.4±5.6 | IL-Iβ,IL-6, IL-10, TNF-α | Cytometric beads array(CBA) assay / Becton and Dickinson | 2-4pm/ -80℃ |
| Yoshimura et al., 2017 | 30/17 | 45.0±14.2 | ND | Fluvoxamine/varied | 8/8 | HDRS-17/24.1±3.1/12.2±2.8 | IL-6 | ELISA/Quantikine HS (R&D Systems) | 8-10am before breakfast/ -80℃ |
| Lindqvist et al., 2017 | 22/15 | 38.99 ± 13.36 | outpatients | Sertraline/25-200Fluoxetine/10-40Citalopram/10-40Escitalopram/10-20 | 8/8 | HDRS-17/12=19.75 ±3.16/ND | IL-6 | high sensitivity multiplexed sandwich immunoassay/(MesoscaleDiscovery | Fasting sample at 8-11am/ND |
| Gupta et al., 2017 | 30/20 | 35.83±9.89 | outpatients | Fluoxetine/20 | 12/12 | HDRS-21/30.83±2.60/13.67±1.79 | TNF-α | ELISA/Krishgen Biosystems | 11am-12 noon / -20℃ |
| Manoharan et al., 2016 | 73/46 | 36.15±9.61 | outpatients | Fluoxetine/20 | 6±1/6±1 | HDRS-17/19.06±3.86/10.85±5.57 | IL-6 | ELISA/AviBion | 9-11am/-20℃ |
| Halaris et al., 2015 | 15/ND | 37.1±11.7 | outpatients | Escitalopram/20-40 | 12/12 | HDRS-17/24/4 | IL-Iβ, IL-4, IL-6, IL-10, TNF-α | Biochip/Evidence InvestigatorTM | Fasting sample at 9-10 am/ -80℃ |
| Brunoni et al., 2014 | 18/11 | 41±1 |  (1) primary and secondary care ambulatories and; (2) spontaneous demand through advertising in local newspapers, radio stations, and websites. | Sertraline/50 | 6/6 | HDRS-17/22±4/14±8 | IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α | Flow Cytometry / BD Biosciences | 2 – 4pm/-80℃ |
| Yoshimura et al., 2013 | 118/67 | 44±12 | inpatients and outpatients | Paroxetine/33±12Sertraline/77±9 | 8/8 | HDRS-17/23.22±7.66/ND | IL-6 | ELISA/Quantikine HS (R&D Systems) | Fasting sample at 8-9am/ND |
| Rawdin et al., 2013 | 17/ND | 37.00±10.77 | clinical referrals | Sertraline/50-200 | 8/8 | HDRS-17/18.71±3.22/10.24±6.32 | IL-6, IL-10 | ELISA/Quantikine HS (R&D Systems) | Fasting sample at 8-10am/-80℃ |
| Abbasi et al., 2012 | 18/ND | 34.2±6.9 | outpatient clinics | Sertraline/200 | 6/6 | HDRS-17/21.3±1.9/±10.05±3.15 | IL-6 | ELISA/Cytimmune Sciences | ND/-70℃ |
| Jazayeri et al., 2010 | 14/10 | 37.00±8.49 | hospital | Fluoxetine/20 | 8/8 | HDRS-24/29.00±6.93/ND | IL-Iβ, IL-6 | ELISA/Bender MedSystems | Fasting sample at 8am/-70℃ |
| Mackay et al., 2009 | 28/23 | 39.0±2.4 | primary care | Fluoxetine/20 | 18/6 | HDRS-21/19.79±1.15/12.01±1.26 | IL-2 | ELISA/Oxford Biosystems | ND/ND |
| Song et al., 2009 | 24/14 | 34±13 | outpatients | Fluoxetine/20 | 6/6 | HDRS-21/22.16±2.16/11.34±6.62 | IL-Iβ, IL-4, IL-10, IFN-γ, TNF-α | ELISA/Gene May | 7-9am/-20℃ |
| Hernandez et al., 2008 | 31/22 | 32.00±9.40 | outpatients | Fluoxetine/20Paroxetine/20Sertraline/100 | 52/5 | HDRS-21/20.28±2.07/10.10±1.11 | IL-Iβ, IL-2, IL-4, IL-10, IFN-γ | ELISA/DuoSet (R&D Systems) | 8-9am/-70℃ |
| Eller et al., 2008 | 100/65 | 32.1±11.9 | outpatients | Escitalopram/10-20 | 12/12 | MADRS/28.76±5.55/9.26±9.71 | TNF-α | Chemiluminescence/Immulite | 9-11:30am/ND |
| Sutcigil et al., 2007 | 23/11 | 34.78±7.42 | outpatients  | Sertraline/50-100 | 8/8 | HDRS-ND/28.39±4.53/13.57±2.21 | IL-2, IL-4, TNF-α | ELISA/Bender MedSystems | Fasting sample at 9am (±30 minutes) /-80℃ |
| Leo et al., 2006 | 20/11 | ND | day hospital program and outpatients | Sertraline/100Citalopram/20 | 6/6 | HDRS-21/23.50±3.83/14.35±2.09 | IL-Iβ, IL-6, TNF-α | ELISA/Quantikine HS (R&D Systems) | Fasting sample at 8-9am/-80℃ |
| Basterzi et al., 2005 | 23/20 | 33.8±12.8 | ND | SSRIs/ND | 6/6 | HDRS-17/20.9±3.8/10.7±3.9 | IL-6 | ELISA/Cytimmune Sciences | ND/-70℃ |
| Tuglu et al., 2003 | 26/11 | 39.38±14.56 | inpatients | Sertraline/50-100Citalopram/20-40Fluoxetine/20-40Fluvoxamine/100-200Paroxetine/20 | 6/6 | HDRS-17/27.07±5.39/8.96±3.92 | TNF-α | Chemiluminescence/Immulite | Fasting sample at 7-8am/-20℃ |
| Sluzewska et al., 1995 | 22/20 | 41.98±5.61 | inpatients | Fluoxetine/20 | 8/8 | HDRS-17/23.22±3.37/ND | IL-6 | ELISA/ND | ND/ND |

ELISA, enzyme-linked immunosorbent assay; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg's Depression Rating Scale; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; SSRIs, Serotonin reuptake inhibitors; ND, no data.

a. Total scores of the rating scales at the time points which were considered in the meta-analyses.

**Table 2.** Quality assessment of the included studies

|  |  |  |  |
| --- | --- | --- | --- |
| First Author, Year | Country | Study Design | Quality Assessment (Downs and Black Checklist) |
| Reporting | External validity | Internal validity - bias | Internal validity - confounding (selection bias) | Power | Total Score |
| EI-Haggar et al., 2018 | Egypt | RCT | 10 | 2 | 7 | 5 | 1 | 25 |
| Chen et al., 2018 | Taiwan, China | Prospective | 10 | 3 | 5 | 4 | 1 | 23 |
| Brunoni et al., 2018 | Brazil | RCT | 8 | 2 | 7 | 5 | 1 | 23 |
| Yoshimura et al., 2017 | Japan | Prospective | 6 | 0 | 4 | 2 | 1 | 13 |
| Lindqvist et al., 2017 | US | Prospective | 9 | 2 | 5 | 3 | 1 | 20 |
| Gupta et al., 2017 | India | Prospective | 9 | 2 | 5 | 4 | 1 | 21 |
| Manoharan et al., 2016 | India | Prospective | 8 | 2 | 5 | 1 | 1 | 17 |
| Halaris et al., 2015 | US | Prospective | 7 | 3 | 6 | 1 | 1 | 18 |
| Brunoni et al., 2014 | Brazil | RCT | 8 | 3 | 7 | 3 | 1 | 22 |
| Yoshimura et al., 2013 | Japan | Prospective | 7 | 1 | 5 | 0 | 1 | 14 |
| Rawdin et al., 2013 | US | Prospective | 7 | 2 | 5 | 1 | 1 | 16 |
| Abbasi et al., 2012 | Iran | RCT | 10 | 3 | 7 | 3 | 1 | 24 |
| Jazayeri et al., 2010 | Iran | RCT | 9 | 3 | 7 | 2 | 1 | 22 |
| Mackay et al., 2009 | UK | Prospective | 5 | 2 | 5 | 1 | 1 | 14 |
| Song et al., 2009 | China | RCT | 6 | 3 | 6 | 4 | 1 | 20 |
| Hernandez et al., 2008 | Mexico | Prospective | 8 | 3 | 6 | 1 | 1 | 19 |
| Eller et al., 2008 | Estonia | Prospective | 9 | 2 | 5 | 1 | 1 | 18 |
| Sutcigil et al., 2007 | Turkey | Prospective | 8 | 2 | 5 | 1 | 1 | 17 |
| Leo et al., 2006 | Italy | RCT a | 8 | 3 | 5 | 3 | 1 | 20 |
| Basterzi et al., 2005 | Turkey | Prospective | 9 | 2 | 5 | 1 | 1 | 18 |
| Tuglu et al., 2003 | Turkey | Prospective | 8 | 2 | 5 | 2 | 1 | 18 |
| Sluzewska et al., 1995 | Poland | Prospective | 6 | 2 | 5 | 1 | 1 | 15 |

RCT=randomized-controlled trials.
a. The part of the study included in the meta-analysis is designed as RCT.

**Table 3.** Result of subgroup analysis for IL-6 and TNF-α

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Inflammatory marker | Subgroup | N | Overall Effect | p-value | Between group Heterogeneity |
| Hedges' ga (95% CI) | Q-value | p-value |
|  IL-6 | Drug Dose | fixed | 7 | -0.687 (-1.171 to -0.203) | 0.005 | 2.951 | 0.086 |
| variable | 8 | -0.203 (-0.469 to 0.063) | 0.135 |
| Study Design | RCTs | 6 | -0.689 (-1.182 to -0.196) | 0.006 | 2.312 | 0.128 |
| non-RCTs | 9 | -0.249 (-0.529 to 0.031) | 0.081 |
|  TNF-α | Drug Dose | fixed | 5 | -0.718 (-1.606 to 0.171) | 0.114 | 0.356 | 0.551 |
| variable | 6 | -0.411 (-0.882 to 0.060) | 0.087 |
| Study Design | RCTs | 5 | -0.494 (-1.291 to 0.304) | 0.225 | 0.056 | 0.814 |
| non-RCTs | 6 | -0.614 (-1.218 to -0.010) | 0.046 |

N, number of studies included in the meta-analysis; CI, confidence interval; IL, interleukin; TNF, tumor necrosis factor; RCT, randomized-controlled trial.

a. According to the random-effects model. A positive effect indicates increase of the inflammatory markers.

**Table 4.** Result of Meta-regression for IL-6 and TNF-α

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Inflammatory marker | Covariate | N | Point estimate | Standard error | Lower limit | Upper limit | Z-value | P-valuea |
|  IL-6 | Mean age | Slope | 14 | 0.015 | 0.038 | -0.059 | 0.089 | 0.396 | 0.692 |
| Intercept | -1.022 | 1.499 | -3.961 | 1.916 | -0.682 | 0.495 |
| Gender (% of female) | Slope | 11 | -1.225 | 1.280 | -3.734 | 1.284 | -0.957 | 0.338 |
| Intercept | 0.345 | 0.865 | -1.351 | 2.041 | 0.399 | 0.690 |
| Study duration | Slope | 15 | -0.014 | 0.068 | -0.147 | 0.119 | -0.207 | 0.836 |
| Intercept | -0.308 | 0.560 | -1.405 | 0.789 | -0.551 | 0.582 |
|  TNF-α | Mean age | Slope | 10 | 0.070 | 0.071 | -0.068 | 0.209 | 0.998 | 0.318 |
| Intercept | -3.155 | 2.646 | -8.341 | 2.030 | -1.193 | 0.233 |
| Gender (% of female) | Slope | 9 | 5.929 | 2.046 | 1.919 | 9.938 | 2.898 | 0.004 |
| Intercept | -3.843 | 1.221 | -6.236 | -1.449 | -3.147 | 0.002 |
| Study duration | Slope | 11 | -0.066 | 0.092 | -0.246 | 0.114 | -0.721 | 0.471 |
| Intercept | 0.033 | 0.853 | -1.639 | 1.704 | 0.038 | 0.969 |

N, number of studies included in the meta-analysis; IL, interleukin; TNF, tumor necrosis factor.

a. According to the random-effects model. For the slope, P-value being less than 0.05 indicates the factor is a potential modifier for the outcome effect.

**Table 5.** Results of sensitivity analysis after excluding studies with estimated mean (SD) of inflammatory markers

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Inflammatory marker | N | Overall Effect | p-value | Heterogeneity |
| Hedges' ga (95% CI) | Q-value | p-value | I2(%) |
| IL-6 | 13 | -0.380 (-0.650 to -0.110) | 0.006 | 112.249 | 0.000 | 89.309 |
| TNF-α | 9 | -0.688 (-1.262 to -0.114) | 0.019 | 209.363 | 0.000 | 96.179 |
| IL-1β | 6 | -0.715 (-1.312 to -0.119) | 0.019 | 69.598 | 0.000 | 92.816 |
| IL-2 | 4 | -0.205 (-1.300 to 0.889) | 0.713 | 105.910 | 0.000 | 97.167 |
| IL-4 | 5 | 0.475 (-0.396 to 1.347) | 0.285 | 104.181 | 0.000 | 96.161 |
| IL-10 | 6 | -0.728 (-1.275 to -0.181) | 0.009 | 66.414 | 0.000 | 92.472 |
| IFN-γ | 3 | 1.312 (0.145 to 2.479) | 0.028 | 46.892 | 0.000 | 95.735 |

N, number of studies included in the meta-analysis; CI, confidence interval; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

a. According to the random-effects model. A positive effect indicates increase of the inflammatory markers.

**Table 6.** Results of sensitivity analysis about pre-post treatment correlations for inflammatory markers

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Inflammatory marker | Pre- post Correlation | N | Overall Effect | p-value | Heterogeneity |
| Hedges' ga (95% CI) | Q-value | p-value | I2(%) |
| IL-6 | 0.631 | 15 | -0.418 (-0.663 to -0.174) | 0.001 | 132.220 | 0.000 | 89.412 |
|  | 0.50 | 15 | -0.425 (-0.676 to -0.174) | 0.001 | 102.062 | 0.000 | 86.283 |
|  | 0.75 | 15 | -0.401 (-0.635 to -0.167) | 0.001 | 181.703 | 0.000 | 92.295 |
| TNF-α | 0.631 | 11 | -0.554 (-0.990 to -0.118) | 0.013 | 219.217 | 0.000 | 95.438 |
|  | 0.50 | 11 | -0.563 (-1.013 to -0.113) | 0.014 | 168.491 | 0.000 | 94.065 |
|  | 0.75 | 11 | -0.534 (-0.952 to -0.117) | 0.012 | 303.762 | 0.000 | 96.708 |
| IL-1β | 0.631 | 7 | -0.574 (-1.014 to -0.135) | 0.010 | 71.616 | 0.000 | 91.622 |
|  | 0.50 | 7 | -0.547 (-0.993 to -0.100) | 0.016 | 53.446 | 0.000 | 88.774 |
|  | 0.75 | 7 | -0.605 (-1.036 to -0.174) | 0.006 | 104.117 | 0.000 | 94.237 |
| IL-2 | 0.631 | 5 | -0.618 (-1.703 to 0.467) | 0.264 | 142.311 | 0.000 | 97.189 |
|  | 0.50 | 5 | -0.616 (-1.736 to 0.505) | 0.282 | 108.633 | 0.000 | 96.318 |
|  | 0.75 | 5 | -0.609 (-1.644 to 0.425) | 0.248 | 198.961 | 0.000 | 97.990 |
| IL-4 | 0.631 | 6 | 0.118 (-0.732 to 0.968) | 0.786 | 131.723 | 0.000 | 96.204 |
|  | 0.50 | 6 | 0.118 (-0.771 to 1.006) | 0.795 | 102.209 | 0.000 | 95.108 |
|  | 0.75 | 6 | 0.112 (-0.682 to 0.907) | 0.782 | 179.231 | 0.000 | 97.210 |
| IL-10 | 0.631 | 8 | -0.615 (-0.989 to -0.242) | 0.001 | 72.964 | 0.000 | 90.406 |
|  | 0.50 | 8 | -0.622 (-1.004 to -0240) | 0.001 | 55.541 | 0.000 | 87.397 |
|  | 0.75 | 8 | -0.601 (-0.962 to -0241) | 0.001 | 102.448 | 0.000 | 93.167 |
| IFN-γ | 0.631 | 4 | 0.440 (-0.946 to 1.826) | 0.533 | 106.865 | 0.000 | 97.193 |
|  | 0.50 | 4 | 0.421 (-1.012 to 1.854) | 0.565 | 80.508 | 0.000 | 96.274 |
|  | 0.75 | 4 | 0.468 (-0.847 to 1.783) | 0.486 | 151.812 | 0.000 | 98.024 |

N, number of studies included in the meta-analysis; CI, confidence interval; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

a. According to the random-effects model. A positive effect indicates increase of the inflammatory markers.



**Figure 2** Forest plot of change in IL-6 after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). ‘Combined’ indicates study reporting data in two independent groups and combined effect sizes were computed for final analysis. Negative effect sizes represent a decrease in IL-6 following SSRIs treatment. The red diamond at the bottom of the effect size plot represents the overall pooled effect size for standardized change in IL-6 (Hedges’ g, 95%CI).



**Figure 3** Funnel plot of standard error by Hedges’ g for IL-6. Asymmetry indicates a potential publication bias.



**Figure 4** Forest plot of change in tumor necrosis factor (TNF)-α after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). ‘Combined’ indicates study reporting data in two independent groups and combined effect sizes were computed for final analysis. Negative effect sizes represent a decrease in TNF-α following SSRIs treatment. The pooled effect size is provided as the red diamond at the bottom of the figure.



**Figure 5** Scatter plot of regression of gender (% of female subjects) on Hedges’ g. The center line shows the predicted values which indicates the effect sizes increase as the percentage of female subjects increases.



**Figure 6** Funnel plot of standard error by Hedges’ g for TNF-α. Asymmetry indicates a potential publication bias.



**Figure 7** Forest plot of change in IL-1β after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). ‘Combined’ indicates study reporting data in two independent groups and combined effect sizes were computed for final analysis. Negative effect sizes represent a decrease in IL-1β following SSRIs treatment. The pooled effect size is provided as the red diamond at the bottom of the figure.



**Figure 8** Forest plot of change in IL-2 after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). Negative effect sizes represent a decrease in IL-2 following SSRIs treatment. The pooled effect size is provided as the red diamond at the bottom of the figure.



**Figure 9** Forest plot of change in IL-4 after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). Negative effect sizes represent a decrease in IL-4 following SSRIs treatment. The pooled effect size is provided as the red diamond at the bottom of the figure.



**Figure 10** Forest plot of change in IL-10 after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). Negative effect sizes represent a decrease in IL-10 following SSRIs treatment. The pooled effect size is provided as the red diamond at the bottom of the figure.



**Figure 11** Forest plot of change in IFN-γ after SSRIs treatment for each study including study name identifier, results of bias-corrected standardized mean difference calculation (Hedges’ g, 95%CI, Z-value, P-value). Negative effect sizes represent a decrease in IFN-γ following SSRIs treatment. The pooled effect size is provided as the red diamond at the bottom of the figure.

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