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Does Cognitive Behavior Therapy Affect Inflammation of Depression? A Protocol for the Systematic Review and Meta-analysis

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Keywords:	Depression & mood disorders < PSYCHIATRY, CLINICAL PHYSIOLOGY, IMMUNOLOGY, MENTAL HEALTH

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3 **1 Does Cognitive Behavior Therapy Affect Inflammation of Depression? A Protocol for**
4 **the Systematic Review and Meta-analysis.**
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34 14 **Word count**

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37 15 **Abstract:** 240 words; **Text:** 1518words; **Figures:** 1; **Tables:** 1.
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3 16 **Abstract**
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6 17 **Introduction:** Cognitive behavior therapy (CBT) is becoming the most commonly
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8 18 implemented and standard treatment for depression. Up to date, only a few number of
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10 19 studies have investigated the potentially anti-inflammatory effects of CBT for depression
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12 20 and results are inconsistent between studies. The current study aims to provide a
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14 21 comprehensive, systematic review of the treatment effects of CBT on inflammation of
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16 22 individuals with depression, and clarify the alterations of inflammatory cytokines pre- and
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18 23 post- CBT treatment by meta-analysis.
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23 24 **Methods and analysis:** This study will be conducted in accordance with the *Preferred*
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25 25 *Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines.
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27 26 Electronic databases (CENTRAL, MEDLINE, Web of Science, and PsycINFO) will be
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29 27 searched systematically using predetermined terms. Database searches will be
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31 28 supplemented by expert contact, reference and citation checking, and grey literature.
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33 29 Primary outcomes of interest will be validated measures of levels of inflammatory
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35 30 cytokines pre- and post- CBT treatment in individuals with depression. Hedges' g will be
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37 31 used to express the effect size (ES).
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42 32 **Systematic review registration:** The protocol of current meta-analysis has been registered
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44 33 at the Open Science Framework [<https://doi.org/10.17605/osf.io/tr9yh>].
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47 34 **Ethics and Dissemination:** Formal ethical approval is not required by the National Ethical
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49 35 Review Board in China as primary data will not be collected. The results alterations of
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51 36 inflammatory cytokines pre- and post- CBT treatment in individuals with depression will
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3 37 be disseminated through a peer-reviewed publication and inform the most up-to-date
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5 38 evidence of the roles of CBT treatment for depression.
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11 40 **Keywords:** Depression; Cognitive Behavior Therapy; Inflammation; Cytokines; C-
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13 41 reactive protein
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17 43 **Article Summary**

18 44 *Strengths and limitations of this study*

- 19 45 • This will be the first meta-analysis exploring the treatment effects of CBT on
20 46 inflammation of individuals with depression.
- 21 47 • The results could provide the most up-to-date evidence to assist in shared decision
22 48 making between patients, caregivers, and clinicians in treating the individuals with
23 49 depression by using CBT.
- 24 50 • An insufficient amount of original researches is a possible limitation.
- 25 51 • Potential high heterogeneity may cause selection bias and also decrease the reliability
26 52 of our results.
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54 **Introduction**

55 Depression is a severe and the most prevalent form of mental illness that characterized by
56 neurocognitive deficits and disability ¹. The disorder manifests in millions of individuals
57 worldwide, and a global health priority. The exploration of underlying mechanisms of
58 depression are increasing over the past decades, none of them could clearly clarify the
59 potential triggers of depression ². In recent years, the inflammation processes are
60 recognized to be important contributors to depression ³, the potential bidirectional
61 relationship of depression and inflammation were also clarified ⁴. Evidence from pre-
62 clinical and clinical researches reached a consistency that the concentrations of pro-
63 inflammatory cytokines are significantly increases in individuals or animal models of
64 depression ⁵. The cytokines, considered as molecular signals of sickness, mediated
65 inflammation and decreased neurogenesis in depression ⁶. Previous meta-analyses pointed
66 out that pharmacological interventions could affect the levels of cytokines, for instance,
67 Interleukin (IL)-6, C-reactive protein (CRP) ^{7 8}. Consistent with these findings, anti-
68 inflammatory agents, such as non-steroidal anti-inflammatory drugs, statins and
69 minocyclines, has been pointed out can improved antidepressant treatment effects ^{9 10}.

70 Cognitive behavior therapy (CBT) is becoming the most commonly implemented and
71 standard treatment for depression ¹¹. Briefly, CBT is a psychological intervention based on
72 effecting behavioral changes through cognitive aspects. The individuals develop strategies
73 for managing and preventing depressive symptoms by monitoring mood symptoms and
74 utilizing a repertoire of coping skills to manage stress in CBT ¹². A meta-analysis found
75 that there is no difference in treatment effects of CBT and second generation
76 antidepressants, either alone or in combination¹³. Recent published literatures illustrated

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3 77 that similar with antidepressant treatment, CBT may also contribute to reduction of chronic
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5 78 low-grade peripheral inflammation. However, the underlying biological processes of the
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8 79 CBT effects on depression are still very limited.
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11 80 Up to date, only a few number of studies have investigated the potentially anti-
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13 81 inflammatory effects of CBT for depression and results are inconsistent between studies
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15 82 and the results were inconsistent. For example, some researches pointed out that IL-6 was
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17 83 decreased after CBT, while no significant changes were founded in other studies ¹⁴.
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19 84 Additionally, whether the alterations of inflammatory cytokines associated with
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21 85 improvements in depression after CBT treatment is also not well established. So far it is
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23 86 worthy to conduct a systematic review and meta-analysis to summarize the most updated
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25 87 research results for the role of CBT treatment in inflammation of depression.
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31 32 33 89 **Aims and Objectives**

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36 90 The current study aims to provide a comprehensive, systematic review of the treatment
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38 91 effects of CBT on inflammation of individuals with depression, and clarify the alterations
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40 92 of inflammatory cytokines pre- and post- CBT treatment by meta-analysis. From the
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42 93 previous evidence, we hypothesized that some inflammatory cytokines, such as CRP, IL-
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44 94 6, TNF- α , may decrease after the CBT intervention.
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49 50 51 96 **Methods**

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54 97 *Search Strategy*
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3 98 The systematic review and meta-analysis will be conducted and reported in accordance
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5 99 with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*
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8 100 statement¹⁵. **Figure 1** summarizes the study selection as a PRISMA flowchart. Electronic
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10 101 databases (CENTRAL, MEDLINE, EMBASE, and PsycINFO) will be searched
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12 102 systematically using predetermined terms. The keywords of our search strategy will be the
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15 103 key terms mapped to subject headings for (i) depression (major depressive disorder,
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17 104 depression, mood disorder, dysthymic disorder); (ii) CBT (psychotherapy, cognitive
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19 105 therapy, cognitive behavioral therapy); (iii) inflammatory cytokines (cytokine, interleukin,
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21 106 chemokine, interferons, tumor necrosis factor, as well as the specific inflammatory
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24 107 biomarkers). The search strategy of PubMed is shown in **Table 1**.

25 26 27 108 *Selection Criteria*

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29 109 The studies conducted the within-group comparisons of the peripheral levels of
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31 110 cytokines and chemokines in participants with depression at baseline and after CBT will
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34 111 be included in the current meta-analysis. Study eligibility for the inclusion will be assessed
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36 112 by the approach of Population, Intervention, Comparison, Outcome and Study Design
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39 113 (PICOS). Population: adult subjects (≥ 18 years old) meeting the major depression
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41 114 diagnoses by the Diagnostic and Statistical Manual of Mental Disorders (DSM; no
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43 115 restrictions on editions) or International Classification of Diseases and Related Health
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45 116 Problems (ICD) criteria; Intervention and Comparison: assessed the results of
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47 117 inflammatory cytokines (e.g., IL-6, CRP or IL-10) before and after CBT. Outcome:
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49 118 reported mean or median resting levels of inflammatory cytokines in saliva, blood, or urine
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52 119 was reported before and at least once after starting CBT, or the effect size could be
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55 120 calculated from the reported results. Study Design: random controlled trial (RCT), open-

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3 121 label study, or longitudinal study with pre-test-post-test design. Exclusion criteria of the
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5 122 studies will meet if they (1) did not focus on evaluating inflammatory cytokines levels on
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7 123 depression; (2) only reported stimulated levels of cytokines; (3) were repetitive
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9 124 publications from the same datasets by the same or different authors.

125 *Outcome Measures and Data Extraction*

126 The outcome for this meta-analysis will be the changes of inflammatory cytokines pre-
127 and post- CBT treatment in individuals with depression, as measured by the standard mean
128 differences (SMDs) their concentrations. Paired investigators (Jiatong Xu and Haijing Ma)
129 will independently select the studies, reviewed the main reports and supplementary
130 materials, extracted the relevant information. All reference lists of the retrieved articles
131 will be reviewed to identify the potential studies. The following information will be
132 extracted from each study: first author, publication year, study design, country, geographic
133 location, age, sex, intervention, duration of intervention, inflammatory biomarkers
134 measured, type of sample specimen required for test, sample detection method, sample size,
135 the mean levels of subjects' inflammatory cytokines and standard deviations (SDs) before
136 and after CBT treatment.

137 *Statistical analysis*

138 Only the inflammatory cytokines with sufficient numbers of studies (≥ 3) will be
139 performed the meta-analysis. Analyses will be performed for pre- and post-treatment of
140 CBT. The main analysis will be conducted with a random effects model. Forest plots will
141 be used to estimate the alteration of the levels of inflammatory cytokines pre- and post-
142 treatment CBT, which will be evaluated by SMD with a 95% confidence interval (CI). The
143 effect size (ES) are expressed as Hedges' g in order to adjusted for a potential bias wo

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3 144 overestimate the effect size in small samples. According to the statistical power analysis
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5 145 for the behavioral sciences (2nd edition), the ES is judged using the values of 0.2, 0.5, and
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7 146 0.8 for small, medium and large (Cohen, 1988). The heterogeneity across the studies will
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10 147 be evaluated by chi-square statistics and I-Squared (I^2) test. A value of $P < 0.10$ or $I^2 > 50\%$
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12 148 indicated that the heterogeneity of effect estimates within each group of studies was
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15 149 statistically significant¹⁶, which shows that the percentage of the variability in effect
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17 150 estimates owes to heterogeneity rather than chance. Furtherly, the subgroup analysis and
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19 151 meta-regression will also be performed to investigate the source of the heterogeneity, and
20
21 152 the potential influence of included characteristics of the studies on the pooled effect size.
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24 153 Sensitivity analysis was performed to strengthen the results and investigate whether any
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26 154 single study would have an effect on the heterogeneity of total measurements in each meta-
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28 155 analysis. Additionally, the positive and negative results may not be equally likely to get
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31 156 published, thus the funnel plot with Begg's test and Egger's test will be used for testing the
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33 157 publication bias. If publication bias will be found, then the trim and fill method would be
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35 158 used to both identify and correct the asymmetry of funnel plot. All two-tailed p -values $<$
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37 159 0.05 will be defined as statistical significance. All the data analyses will be conducted using
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40 160 Stata (version 15.0, Stata Corp LP, College Station, TX, USA).

41 42 43 161 *Patient and public involvement*

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46 162 Patients were not involved in the development of this systematic review protocol. The
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48 163 data for this systematic review will be collected from previously published studies.

49 50 51 164 *Ethics and Dissemination*

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54 165 Formal ethical approval is not required as primary data will not be collected with the
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56 166 systematic review and meta-analysis. Data from previously published studies will be

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3 167 retrieved and analyzed. This study including protocol development will run from October
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5 168 2020 to October 2021. The results will be disseminated through a peer-reviewed
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7 169 publication and inform the most up-to-date evidence of the roles of CBT treatment for
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9 170 depression.

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14 15 16 172 **Discussion**

17 18 19 173 *Presentation of results and reporting*

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21 174 Our current systematic review and meta-analysis will provide a comprehensive
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23 175 evidence for the treatment effects of CBT on inflammation of individuals with depression.
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25 176 We will use the PRISMA guidelines and checklist in the publication process. The
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27 177 quantitative data will be summarized and presented in tables, forest plots, and charts. The
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29 178 alterations of inflammatory cytokines pre- and post- CBT treatment in individuals with
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31 179 depression will be presented.

32 33 34 35 36 180 *Potential resources of limitations*

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38 181 The current study is anticipated to have some limitations. Firstly, we might not find a
39
40 182 sufficient amount of original researches to perform the analyses. Secondly, the potential
41
42 183 high heterogeneity between studies in the exposure of interest and restriction to studies in
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44 184 English language, which will lead to selection bias and also decrease the reliability of our
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46 185 results.

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50 186 To the best of our knowledge, this will be the first meta-analysis exploring the
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52 187 treatment effects of CBT on inflammation of individuals with depression. From our
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54 188 findings herein, we can provide the most up-to-date evidence to assist in shared decision
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189 making between patients, caregivers, and clinicians in treating the individuals with
190 depression by using CBT and provide a foundation for future studies in this area.

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192 **Author contributors**

193 Cao B, Xu JT and Ma HJ conceived the study and developed the search strategy. Cao
194 B drafted the protocol and tested the search strategies in consultation with a librarian. Li
195 RN and Yang FH provided advice on the protocol. All authors critically revised the
196 protocol for methodological and intellectual content and have read and approved the final
197 manuscript.

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201 analysis or interpretation of this study.

202 **Competing interests**

203 None declared.

204 **Patient consent for publication**

205 Not required.

206 **Data statement**

207 No applicable.

208 **References**

- 209 1. Ang YS, Frontero N, Belleau E, et al. Disentangling vulnerability, state and trait features of
210 neurocognitive impairments in depression. *Brain* 2020 doi: 10.1093/brain/awaa314
211 [published Online First: 2020/11/12]
- 212 2. McIntosh AM, Hall LS, Zeng Y, et al. Genetic and Environmental Risk for Chronic Pain and the
213 Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-
214 Model Analysis. *PLoS Med* 2016;13(8):e1002090. doi: 10.1371/journal.pmed.1002090
215 [published Online First: 2016/08/17]
- 216 3. Osimo EF, Baxter LJ, Lewis G, et al. Prevalence of low-grade inflammation in depression: a
217 systematic review and meta-analysis of CRP levels. *Psychological medicine*
218 2019;49(12):1958-70. doi: 10.1017/S0033291719001454 [published Online First:
219 2019/07/02]
- 220 4. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and
221 Inflammation: Double Trouble. *Neuron* 2020;107(2):234-56. doi:
222 10.1016/j.neuron.2020.06.002 [published Online First: 2020/06/20]
- 223 5. Kim YK, Na KS, Myint AM, et al. The role of pro-inflammatory cytokines in neuroinflammation,
224 neurogenesis and the neuroendocrine system in major depression. *Progress in neuro-
225 psychopharmacology & biological psychiatry* 2016;64:277-84. doi:
226 10.1016/j.pnpbp.2015.06.008 [published Online First: 2015/06/27]
- 227 6. Song C, Wang H. Cytokines mediated inflammation and decreased neurogenesis in animal
228 models of depression. *Progress in neuro-psychopharmacology & biological psychiatry*
229 2011;35(3):760-8. doi: 10.1016/j.pnpbp.2010.06.020 [published Online First: 2010/07/06]
- 230 7. Kohler CA, Freitas TH, Stubbs B, et al. Peripheral Alterations in Cytokine and Chemokine
231 Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic
232 Review and Meta-Analysis. *Molecular neurobiology* 2018;55(5):4195-206. doi:
233 10.1007/s12035-017-0632-1 [published Online First: 2017/06/15]
- 234 8. Wiedlocha M, Marcinowicz P, Krupa R, et al. Effect of antidepressant treatment on peripheral
235 inflammation markers - A meta-analysis. *Progress in neuro-psychopharmacology &
236 biological psychiatry* 2018;80(Pt C):217-26. doi: 10.1016/j.pnpbp.2017.04.026 [published
237 Online First: 2017/04/27]
- 238 9. Kohler-Forsberg O, C NL, Hjorthoj C, et al. Efficacy of anti-inflammatory treatment on major
239 depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta
240 psychiatrica Scandinavica* 2019;139(5):404-19. doi: 10.1111/acps.13016 [published
241 Online First: 2019/03/06]
- 242 10. Husain MI, Strawbridge R, Stokes PR, et al. Anti-inflammatory treatments for mood disorders:
243 Systematic review and meta-analysis. *Journal of psychopharmacology (Oxford, England)*
244 2017;31(9):1137-48. doi: 10.1177/0269881117725711 [published Online First:
245 2017/09/01]
- 246 11. Lopez MA, Basco MA. Effectiveness of cognitive behavioral therapy in public mental health:
247 comparison to treatment as usual for treatment-resistant depression. *Adm Policy Ment
248 Health* 2015;42(1):87-98. doi: 10.1007/s10488-014-0546-4 [published Online First:
249 2014/04/03]
- 250 12. Pearlstein JG, Staudenmaier PJ, West AE, et al. Immune response to stress induction as a
251 predictor of cognitive-behavioral therapy outcomes in adolescent mood disorders: A pilot
252 study. *J Psychiatr Res* 2020;120:56-63. doi: 10.1016/j.jpsychires.2019.10.012 [published
253 Online First: 2019/10/22]
- 254 13. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second
255 generation antidepressants and cognitive behavioral therapies in initial treatment of major

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3 256 depressive disorder: systematic review and meta-analysis. *BMJ* 2015;351:h6019. doi:
4 257 10.1136/bmj.h6019 [published Online First: 2015/12/10]
5 258 14. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and
6 259 therapeutic implications. *Neuroscience* 2013;246:199-229. doi:
7 260 10.1016/j.neuroscience.2013.04.060 [published Online First: 2013/05/07]
8 261 15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
9 262 meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097. doi:
10 263 10.1371/journal.pmed.1000097
11 264 16. Cao B, Wang DF, Xu MY, et al. Lower folate levels in schizophrenia: A meta-analysis.
12 265 *Psychiatry Res* 2016;245:1-7. doi: 10.1016/j.psychres.2016.03.003

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3 268 **Figure Legend**
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6 269 **Figure 1.** PRISMA flow diagram of study selection process.
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Table 1. Search strategy for PubMed

Search number	Query
#1	"major depression"[Title/Abstract] OR "major depressive disorder"[Title/Abstract] OR "depressive symptom*"[Title/Abstract] OR "symptom, depressive"[Title/Abstract] OR "depress*"[Title/Abstract] OR "dysphor*"[Title/Abstract] OR "dysthym*"[Title/Abstract] OR "adjustment disorder*"[Title/Abstract] OR "mood disorder*"[Title/Abstract] OR "affective disorder"[Title/Abstract] OR "affective disorders"[Title/Abstract] OR "emotional depression*"[Title/Abstract]
#2	"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh] OR "Depressive Disorder, Major"[Mesh]
#3	#1 OR #2
#4	"Cognitive Behavioral Therapy"[Mesh]
#5	"behavioral therapies, cognitive"[Title/Abstract] OR "behavioral therapy, cognitive"[Title/Abstract] OR "cognitive behavioral Therap*"[Title/Abstract] OR "cognitive behavior therap*"[Title/Abstract] OR "cognitive psychotherap*"[Title/Abstract] OR "behavior modification"[Title/Abstract] OR "behavior therap*"[Title/Abstract] OR "cognitive therap*" [Title/Abstract] OR "psychotherapy*" [Title/Abstract]
#6	#4 OR #5
#7	"Cytokines"[Mesh] OR "Chemokines"[Mesh] OR "Interleukins"[Mesh]
#8	"cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "chemokine*" [Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR "interferon"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "IFN"[Title/Abstract] OR "TNF"[Title/Abstract] OR "CRP"[Title/Abstract] OR "IL-1 β "[Title/Abstract] OR "IL-2"[Title/Abstract] OR "IL-4"[Title/Abstract] OR "IL-6"[Title/Abstract] OR "IL-8"[Title/Abstract] OR "IL-10"[Title/Abstract] OR "IL-12"[Title/Abstract] OR "IL-18"[Title/Abstract] OR "TGF- β "[Title/Abstract] OR "IFN- γ "[Title/Abstract]) OR ("cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "chemokine*" [Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR "interferon"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "IFN"[Title/Abstract] OR "TNF"[Title/Abstract] OR "CRP"[Title/Abstract] OR "IL-1 β "[Title/Abstract] OR "IL-2"[Title/Abstract] OR "IL-4"[Title/Abstract] OR "IL-6"[Title/Abstract] OR "IL-8"[Title/Abstract] OR "IL-10"[Title/Abstract] OR "IL-12"[Title/Abstract] OR "IL-18"[Title/Abstract] OR "TGF- β "[Title/Abstract] OR "IFN- γ "[Title/Abstract])
#9	#7 OR #8
#10	#3 AND #6 AND #9

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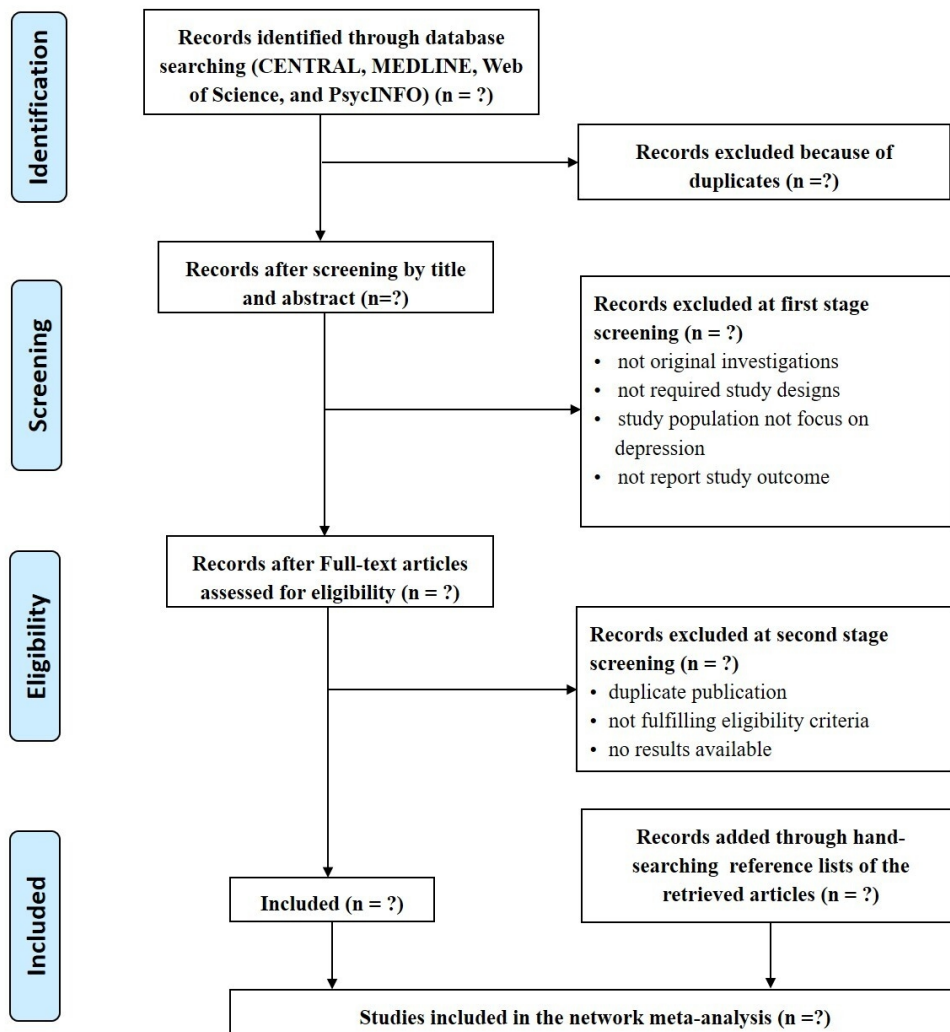


Figure 1. PRISMA flow diagram of study selection process.

100x106mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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Reporting Item			Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10

Amendments

1		#4	If the protocol represents an amendment of a previously completed or	NA
2			published protocol, identify as such and list changes; otherwise, state	
3			plan for documenting important protocol amendments	
4				
5				
6	Support			
7				
8	Sources	#5a	Indicate sources of financial or other support for the review	10
9				
10	Sponsor	#5b	Provide name for the review funder and / or sponsor	10
11				
12	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any,	10
13	funder		in developing the protocol	
14				
15				
16				
17	Introduction			
18				
19	Rationale	#6	Describe the rationale for the review in the context of what is already	4-5
20			known	
21				
22	Objectives	#7	Provide an explicit statement of the question(s) the review will	5
23			address with reference to participants, interventions, comparators, and	
24			outcomes (PICO)	
25				
26				
27				
28	Methods			
29				
30	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting,	6-7
31			time frame) and report characteristics (such as years considered,	
32			language, publication status) to be used as criteria for eligibility for	
33			the review	
34				
35	Information sources	#9	Describe all intended information sources (such as electronic	6-7
36			databases, contact with study authors, trial registers or other grey	
37			literature sources) with planned dates of coverage	
38				
39	Search strategy	#10	Present draft of search strategy to be used for at least one electronic	6-7
40			database, including planned limits, such that it could be repeated	
41				
42	Study records - data	#11a	Describe the mechanism(s) that will be used to manage records and	7
43	management		data throughout the review	
44				
45	Study records -	#11b	State the process that will be used for selecting studies (such as two	7
46	selection process		independent reviewers) through each phase of the review (that is,	
47			screening, eligibility and inclusion in meta-analysis)	
48				
49	Study records - data	#11c	Describe planned method of extracting data from reports (such as	7
50	collection process		piloting forms, done independently, in duplicate), any processes for	
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		obtaining and confirming data from investigators	
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3	Data items	#12 List and define all variables for which data will be sought (such as	7
4		PICO items, funding sources), any pre-planned data assumptions and	
5		simplifications	
6			
7			
8	Outcomes and	#13 List and define all outcomes for which data will be sought, including	7
9	prioritization	prioritization of main and additional outcomes, with rationale	
10			
11	Risk of bias in	#14 Describe anticipated methods for assessing risk of bias of individual	8
12	individual studies	studies, including whether this will be done at the outcome or study	
13		level, or both; state how this information will be used in data synthesis	
14			
15			
16			
17	Data synthesis	#15a Describe criteria under which study data will be quantitatively	7-8
18		synthesised	
19			
20			
21	Data synthesis	#15b If data are appropriate for quantitative synthesis, describe planned	7-8
22		summary measures, methods of handling data and methods of	
23		combining data from studies, including any planned exploration of	
24		consistency (such as I ² , Kendall's τ)	
25			
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28	Data synthesis	#15c Describe any proposed additional analyses (such as sensitivity or	7-8
29		subgroup analyses, meta-regression)	
30			
31	Data synthesis	#15d If quantitative synthesis is not appropriate, describe the type of	NA
32		summary planned	
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35	Meta-bias(es)	#16 Specify any planned assessment of meta-bias(es) (such as publication	8
36		bias across studies, selective reporting within studies)	
37			
38			
39	Confidence in	#17 Describe how the strength of the body of evidence will be assessed	8
40	cumulative	(such as GRADE)	
41	evidence		
42			
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BMJ Open

Does Cognitive Behavior Therapy Affect Inflammation of Depression? A Protocol for the Systematic Review and Meta-analysis

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health
Keywords:	Depression & mood disorders < PSYCHIATRY, CLINICAL PHYSIOLOGY, IMMUNOLOGY, MENTAL HEALTH

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3 **1 Does Cognitive Behavior Therapy Affect Inflammation of Depression? A Protocol for**
4 **the Systematic Review and Meta-analysis.**
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9 3 Bing Cao ¹, Ruonan Li ¹, Ling Ding², Jiatong Xu ¹, Haijing Ma ¹, Jie Liu^{2,*}

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34 **14 Word count**
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3 16 **Abstract**
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6 17 **Introduction:** Cognitive behavior therapy (CBT) is becoming the most commonly
7
8 18 implemented and standard treatment for depression. Up to date, only a few number of
9
10 19 studies have investigated the potentially anti-inflammatory effects of CBT for depression
11
12 20 and results are inconsistent between studies. The current study aims to provide a
13
14 21 comprehensive, systematic review of the treatment effects of CBT on inflammation of
15
16 22 individuals with depression, and clarify the alterations of inflammatory cytokines pre- and
17
18 23 post- CBT treatment by meta-analysis.
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23 24 **Methods and analysis:** This study will be conducted in accordance with the *Preferred*
24
25 25 *Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. A
26
27 26 systematic search of predetermined terms will be conducted with electronic databases of
28
29 27 CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to July 2021. Database
30
31 28 searches will be supplemented by expert contact, reference and citation checking, and grey
32
33 29 literature. Primary outcomes of interest will be validated measures of levels of
34
35 30 inflammatory cytokines pre- and post- CBT treatment in individuals with depression.
36
37 31 Hedges' g will be used to express the effect size (ES).
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42 32 **Systematic review registration:** The protocol of current meta-analysis has been registered
43
44 33 at the Open Science Framework [<https://doi.org/10.17605/osf.io/tr9yh>].
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47 34 **Ethics and Dissemination:** Formal ethical approval is not required by the National Ethical
48
49 35 Review Board in China as primary data will not be collected. The results alterations of
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51 36 inflammatory cytokines pre- and post- CBT treatment in individuals with depression will
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3 37 be disseminated through a peer-reviewed publication and inform the most up-to-date
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5 38 evidence of the roles of CBT treatment for depression.
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8 39

10
11 40 **Keywords:** Depression; Cognitive Behavior Therapy; Inflammation; Cytokines; C-
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13 41 reactive protein
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18 43 **Article Summary**

20 44 *Strengths and limitations of this study*

- 22
23 45 • This will be the first meta-analysis exploring the treatment effects of CBT on
24
25 46 inflammation of individuals with depression.
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27
28 47 • The results could provide the most up-to-date evidence to assist in shared decision
29
30 48 making between patients, caregivers, and clinicians in treating the individuals with
31
32 49 depression by using CBT.
33
34
35 50 • An insufficient amount of original researches is a possible limitation.
36
37 51 • Potential high heterogeneity may cause selection bias and also decrease the reliability
38
39 52 of our results.
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42 53

54 **Introduction**

55 Depression is a severe and the most prevalent form of mental illness that characterized by
56 neurocognitive deficits and disability ¹. The disorder manifests in millions of individuals
57 worldwide, and is a global health priority. The exploration of underlying mechanisms of
58 depression are increasing over the past decades, none of them could clearly clarify the
59 potential triggers of depression ². In recent years, the inflammatory processes are
60 considered to be important contributors to depression. A systematic review and meta-
61 analysis confirmed that a high proportion of depressed individuals showed signs of
62 inflammation³. The potential bidirectional relationship of depression and inflammation
63 were also clarified ⁴. For instance, early infection and autoimmune diseases are highly
64 associated with high risk of depressive disorders in adulthood ⁵; evidence from preclinical
65 and clinical researches reached a consistency that the concentrations of pro-inflammatory
66 cytokines are significantly increases in individuals or animal models of depression ⁶. The
67 inflammatory cytokines as mediators of environmental and genetic factors that may
68 contribute to the development of depression from a biological perspective⁷. A previous
69 study suggested that inflammation may be involved in some certain medical conditions,
70 and it may activate the pathogenesis of depression by interfering with the monoamine,
71 glutamate, and neurotrophic system ⁸. Dowlat et al. 's study reported that major depression
72 leads to immune dysregulation and activation of the inflammatory response system ⁹. In
73 addition, a growing number of evidence indicated that inflammation is thought to be an
74 active process, which can affect multiple aspects of central nervous system function,
75 including neurotransmitter metabolism, neuroendocrine function and information
76 processing, leading to behavioral changes in individuals with depression ¹⁰. The results of

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2
3 77 several meta-analyses have proved that depression is related to chronic low-grade
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5 78 inflammation, as manifested by higher concentrations of C-reactive protein (CRP),
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7 79 interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), compared with healthy controls
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10 80 ^{11 12}. Above findings have facilitated the development of the inflammatory hypothesis of
11
12 81 depression, predicting that inflammation plays a role in the formation, progression and
13
14 82 perpetuation of depression.^{13 14}. Cognitive behavior therapy (CBT) is becoming the most
15
16 83 commonly implemented and standard treatment for depression ¹⁵. Briefly, CBT is based on
17
18 84 the premise that non-helpful faith and negative thoughts are the main causes of depression.
19
20 85 The individuals develop strategies for managing and preventing depressive symptoms by
21
22 86 monitoring mood symptoms and utilizing a repertoire of coping skills to manage stress in
23
24 87 CBT ¹⁶. A meta-analysis found that there is no difference in treatment effects of CBT and
25
26 88 second generation antidepressants, either alone or in combination¹⁷. Recent published
27
28 89 literatures illustrated that similar with antidepressant treatment, CBT may also contribute
29
30 90 to reduction of chronic low-grade peripheral inflammation¹⁸. However, the underlying
31
32 91 biological processes of the CBT effects on depression are still very limited.

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38 92 To date, only a few number of studies have investigated the potentially anti-inflammatory
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40 93 effects of CBT for depression and results are inconsistent between studies and the results
41
42 94 were inconsistent. For example, some researches pointed out that IL-6 was decreased after
43
44 95 CBT, while no significant changes were founded in other studies ¹⁹. Keri et al. (2014)
45
46 96 demonstrated that in adults with a first episode of depression, 16 weeks of CBT alone was
47
48 97 associated with a reduction in TLR-4 signaling, but no change in TLR-2 signaling, IL-6,
49
50 98 or CRP levels, which suggested that it took longer time or other mechanisms for them to
51
52 99 normalize ²⁰. Additionally, whether the alterations of inflammatory cytokines associated

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3 100 with improvements in depression after CBT treatment is also not well established. So far
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5 101 it is worthy to conduct a systematic review and meta-analysis to summarize the most
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8 102 updated research results for the role of CBT treatment in inflammation of depression.
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11 103

14 104 **Aims and Objectives**

16
17 105 The current study aims to provide a comprehensive, systematic review of the treatment
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19 106 effects of CBT on inflammation of individuals with depression, and clarify the alterations
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21 107 of inflammatory cytokines pre- and post- CBT treatment by meta-analysis. From the
22
23 108 previous evidence, we hypothesized that some inflammatory cytokines, such as CRP, IL-
24
25 109 6, TNF- α , may decrease after the CBT intervention.
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32 111 **Methods**

35 112 *Search Strategy*

37
38 113 The systematic review and meta-analysis will be conducted and reported in accordance
39
40 114 with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*
41
42 115 statement ²¹. **Figure 1** summarizes the study selection as a PRISMA flowchart. A
43
44 116 systematic search of predetermined terms will be conducted with electronic databases of
45
46
47 117 CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to July 2021. The
48
49 118 keywords of our search strategy will be the key terms mapped to subject headings for (i)
50
51 119 depression (major depressive disorder, depression, mood disorder, dysthymic disorder);
52
53
54 120 (ii) CBT (psychotherapy, cognitive therapy, cognitive behavioral therapy); (iii)

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3 121 inflammatory cytokines (cytokine, interleukin, chemokine, interferons, tumor necrosis
4
5 122 factor, as well as the specific inflammatory biomarkers). The search strategy of PubMed is
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8 123 shown in **Table 1**.

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10
11 124 *Selection Criteria*

12
13 125 The studies conducted the within-group comparisons of the peripheral levels of
14
15 126 cytokines and chemokines in participants with depression at baseline and after CBT will
16
17 127 be included in the current meta-analysis. Study eligibility for the inclusion will be assessed
18
19 128 by the approach of Population, Intervention, Comparison, Outcome and Study Design
20
21 129 (PICOS). Moreover, according to the quality assessment recommendation of Cochrane
22
23 130 Collaboration, we will use Newcastle-Ottawa Scale (NOS) to evaluate the quality of the
24
25 131 included literatures ²². Population: adult subjects (≥ 18 years old) meeting the major
26
27 132 depression diagnoses by the Diagnostic and Statistical Manual of Mental Disorders (DSM;
28
29 133 no restrictions on editions) or International Classification of Diseases and Related Health
30
31 134 Problems (ICD) criteria; Intervention and Comparison: assessed the results of
32
33 135 inflammatory cytokines (e.g., IL-6, CRP or IL-10) before and after CBT. Outcome:
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35 136 reported mean or median resting levels of inflammatory cytokines in saliva, blood, or urine
36
37 137 was reported before and at least once after starting CBT, or the effect size could be
38
39 138 calculated from the reported results. Study Design: random controlled trial (RCT), open-
40
41 139 label study, or longitudinal study with pre-test-post-test design. Exclusion criteria of the
42
43 140 studies will meet if they (1) did not focus on evaluating inflammatory cytokines levels on
44
45 141 depression; (2) only reported stimulated levels of cytokines; (3) were repetitive
46
47 142 publications from the same datasets by the same or different authors; (4) included
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49 143 participants who have been receiving pharmacological treatment in the past one month.
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144 *Outcome Measures and Data Extraction*

145 The outcome for this meta-analysis will be the changes of inflammatory cytokines pre-
146 and post- CBT treatment in individuals with depression, as measured by the standard mean
147 differences (SMDs) their concentrations. Paired investigators (Jiatong Xu and Haijing Ma)
148 will independently select the studies, reviewed the main reports and supplementary
149 materials, extracted the relevant information. All reference lists of the retrieved articles
150 will be reviewed to identify the potential studies. The following information will be
151 extracted from each study: first author, publication year, study design, country, geographic
152 location, age, sex, intervention, duration of intervention, whether it is a major depressive
153 episode (MDE), inflammatory biomarkers measured, type of sample specimen required for
154 test, sample detection method, sample size, the mean levels of subjects' inflammatory
155 cytokines and standard deviations (SDs) before and after CBT treatment.

156 *Statistical analysis*

157 Only the inflammatory cytokines with sufficient numbers of studies (≥ 3) will be
158 performed the meta-analysis. Analyses will be performed for pre- and post-treatment of
159 CBT. The main analysis will be conducted with a random effects model. Forest plots will
160 be used to estimate the alteration of the levels of inflammatory cytokines pre- and post-
161 treatment CBT, which will be evaluated by SMD with a 95% confidence interval (CI). The
162 effect size (ES) are expressed as Hedges' g in order to adjusted for a potential bias wo
163 overestimate the effect size in small samples. According to the statistical power analysis
164 for the behavioral sciences (2nd edition), the ES is judged using the values of 0.2, 0.5, and
165 0.8 for small, medium and large (Cohen, 1988). In addition, we will conduct Bonferroni
166 adjustment for multiple testing in meta-analysis, which means we will produce a rejection

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3 167 p-value of 0.05 divided by the total number of outcomes ²³. The heterogeneity across the
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5 168 studies will be evaluated by chi-square statistics and I-Squared (I^2) test. A value of $P < 0.10$
6
7
8 169 or $I^2 > 50\%$ indicated that the heterogeneity of effect estimates within each group of studies
9
10 170 was statistically significant ²⁴, which shows that the percentage of the variability in effect
11
12 171 estimates owes to heterogeneity rather than chance. Furtherly, the subgroup analysis and
13
14 172 meta-regression will also be performed to investigate the source of the heterogeneity, and
15
16 173 the potential influence of included characteristics of the studies on the pooled effect size.
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18 174 Sensitivity analysis was performed to strengthen the results and investigate whether any
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20 175 single study would have an effect on the heterogeneity of total measurements in each meta-
21
22 176 analysis. Additionally, the positive and negative results may not be equally likely to get
23
24 177 published, thus the funnel plot with Begg's test and Egger's test will be used for testing the
25
26 178 publication bias. If publication bias will be found, then the trim and fill method would be
27
28 179 used to both identify and correct the asymmetry of funnel plot. All two-tailed p -values $<$
29
30 180 0.05 will be defined as statistical significance. All the data analyses will be conducted using
31
32 181 Stata (version 15.0, Stata Corp LP, College Station, TX, USA).

182 *Patient and public involvement*

183 Patients were not involved in the development of this systematic review protocol. The
184 data for this systematic review will be collected from previously published studies.

185 *Ethics and Dissemination*

186 Formal ethical approval is not required as primary data will not be collected with the
187 systematic review and meta-analysis. Data from previously published studies will be
188 retrieved and analyzed. This study including protocol development will run from October
189 2020 to October 2021. The results will be disseminated through a peer-reviewed

190 publication and inform the most up-to-date evidence of the roles of CBT treatment for
191 depression.

192

193 **Discussion**

194 *Presentation of results and reporting*

195 Our current systematic review and meta-analysis will provide a comprehensive
196 evidence for the treatment effects of CBT on inflammation of individuals with depression.
197 We will use the PRISMA guidelines and checklist in the publication process. The
198 quantitative data will be summarized and presented in tables, forest plots, and charts. The
199 alterations of inflammatory cytokines pre- and post- CBT treatment in individuals with
200 depression will be presented.

201 *Potential resources of limitations*

202 The current study is anticipated to have some limitations. Firstly, we might not find a
203 sufficient amount of original researches to perform the analyses. Secondly, the potential
204 high heterogeneity between studies in the exposure of interest and restriction to studies in
205 English language, which will lead to selection bias and also decrease the reliability of our
206 results.

207 To the best of our knowledge, this will be the first meta-analysis exploring the
208 treatment effects of CBT on inflammation of individuals with depression. From our
209 findings herein, we can provide the most up-to-date evidence to assist in shared decision
210 making between patients, caregivers, and clinicians in treating the individuals with
211 depression by using CBT and provide a foundation for future studies in this area.

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2
3 **212 Contributorship statement**
4

5 **213** Cao B, Xu JT and Ma HJ conceived the study and developed the search strategy. Cao
6
7 **214** B drafted the protocol and tested the search strategies in consultation with a librarian. Li
8
9 **215** RN, Ding L and Liu J provided advice on the protocol. All authors critically revised the
10
11 **216** protocol for methodological and intellectual content and have read and approved the final
12
13 **217** manuscript.
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21

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23
24 **221** which funds Cao B. The funding bodies had no part in either the study design, conduct,
25
26 **222** analysis or interpretation of this study.
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30 **223 Competing interests**
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32 **224** None declared.
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35 **225 Patient consent for publication**
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37 **226** Not required.
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40 **227 Data statement**
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42 **228** No applicable.
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229 **References**

- 230 1. Ang YS, Frontero N, Belleau E, et al. Disentangling vulnerability, state and trait features of
231 neurocognitive impairments in depression. *Brain* 2020 doi: 10.1093/brain/awaa314
232 [published Online First: 2020/11/12]
- 233 2. McIntosh AM, Hall LS, Zeng Y, et al. Genetic and Environmental Risk for Chronic Pain and the
234 Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-
235 Model Analysis. *PLoS Med* 2016;13(8):e1002090. doi: 10.1371/journal.pmed.1002090
236 [published Online First: 2016/08/17]
- 237 3. Osimo EF, Baxter LJ, Lewis G, et al. Prevalence of low-grade inflammation in depression: a
238 systematic review and meta-analysis of CRP levels. *Psychological medicine*
239 2019;49(12):1958-70. doi: 10.1017/S0033291719001454 [published Online First:
240 2019/07/02]
- 241 4. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and
242 Inflammation: Double Trouble. *Neuron* 2020;107(2):234-56. doi:
243 10.1016/j.neuron.2020.06.002 [published Online First: 2020/06/20]
- 244 5. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as
245 risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* 2013;70(8):812-20.
246 doi: 10.1001/jamapsychiatry.2013.1111 [published Online First: 2013/06/14]
- 247 6. Kim YK, Na KS, Myint AM, et al. The role of pro-inflammatory cytokines in neuroinflammation,
248 neurogenesis and the neuroendocrine system in major depression. *Progress in neuro-*
249 *psychopharmacology & biological psychiatry* 2016;64:277-84. doi:
250 10.1016/j.pnpbp.2015.06.008 [published Online First: 2015/06/27]
- 251 7. Song C, Wang H. Cytokines mediated inflammation and decreased neurogenesis in animal
252 models of depression. *Progress in neuro-psychopharmacology & biological psychiatry*
253 2011;35(3):760-8. doi: 10.1016/j.pnpbp.2010.06.020 [published Online First:
254 2010/07/06]
- 255 8. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a
256 literature review. *CNS Spectr* 2008;13(6):501-10. doi: 10.1017/s1092852900016734
257 [published Online First: 2008/06/24]
- 258 9. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major
259 depression. *Biol Psychiatry* 2010;67(5):446-57. doi: 10.1016/j.biopsych.2009.09.033
260 [published Online First: 2009/12/18]
- 261 10. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery.
262 *Brain Behav Immun* 2007;21(4):374-83. doi: 10.1016/j.bbi.2007.01.010 [published
263 Online First: 2007/03/16]
- 264 11. Kohler CA, Freitas TH, Stubbs B, et al. Peripheral Alterations in Cytokine and Chemokine
265 Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic
266 Review and Meta-Analysis. *Molecular neurobiology* 2018;55(5):4195-206. doi:
267 10.1007/s12035-017-0632-1 [published Online First: 2017/06/15]
- 268 12. Wiedlocha M, Marcinowicz P, Krupa R, et al. Effect of antidepressant treatment on
269 peripheral inflammation markers - A meta-analysis. *Progress in neuro-*
270 *psychopharmacology & biological psychiatry* 2018;80(Pt C):217-26. doi:
271 10.1016/j.pnpbp.2017.04.026 [published Online First: 2017/04/27]
- 272 13. Kohler-Forsberg O, C NL, Hjorthoj C, et al. Efficacy of anti-inflammatory treatment on major
273 depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta*

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3 274 *psychiatrica Scandinavica* 2019;139(5):404-19. doi: 10.1111/acps.13016 [published
4 275 Online First: 2019/03/06]
5 276 14. Husain MI, Strawbridge R, Stokes PR, et al. Anti-inflammatory treatments for mood
6 277 disorders: Systematic review and meta-analysis. *Journal of psychopharmacology*
7 278 (Oxford, England) 2017;31(9):1137-48. doi: 10.1177/0269881117725711 [published
8 279 Online First: 2017/09/01]
9 280 15. Lopez MA, Basco MA. Effectiveness of cognitive behavioral therapy in public mental health:
10 281 comparison to treatment as usual for treatment-resistant depression. *Adm Policy Ment*
11 282 *Health* 2015;42(1):87-98. doi: 10.1007/s10488-014-0546-4 [published Online First:
12 283 2014/04/03]
13 284 16. Pearlstein JG, Staudenmaier PJ, West AE, et al. Immune response to stress induction as a
14 285 predictor of cognitive-behavioral therapy outcomes in adolescent mood disorders: A
15 286 pilot study. *J Psychiatr Res* 2020;120:56-63. doi: 10.1016/j.jpsychires.2019.10.012
16 287 [published Online First: 2019/10/22]
17 288 17. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second
18 289 generation antidepressants and cognitive behavioral therapies in initial treatment of
19 290 major depressive disorder: systematic review and meta-analysis. *BMJ* 2015;351:h6019.
20 291 doi: 10.1136/bmj.h6019 [published Online First: 2015/12/10]
21 292 18. Lopresti AL. Cognitive behaviour therapy and inflammation: A systematic review of its
22 293 relationship and the potential implications for the treatment of depression. *Aust N Z J*
23 294 *Psychiatry* 2017;51(6):565-82. doi: 10.1177/0004867417701996 [published Online First:
24 295 2017/04/07]
25 296 19. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and
26 297 therapeutic implications. *Neuroscience* 2013;246:199-229. doi:
27 298 10.1016/j.neuroscience.2013.04.060 [published Online First: 2013/05/07]
28 299 20. Keri S, Szabo C, Kelemen O. Expression of Toll-Like Receptors in peripheral blood
29 300 mononuclear cells and response to cognitive-behavioral therapy in major depressive
30 301 disorder. *Brain Behav Immun* 2014;40:235-43. doi: 10.1016/j.bbi.2014.03.020
31 302 [published Online First: 2014/04/15]
32 303 21. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
33 304 meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097. doi:
34 305 10.1371/journal.pmed.1000097
35 306 22. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors'
36 307 assessments. *BMC Med Res Methodol* 2014;14:45. doi: 10.1186/1471-2288-14-45
37 308 23. Ng A, Tam WW, Zhang MW, et al. IL-1beta, IL-6, TNF- alpha and CRP in Elderly Patients with
38 309 Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. *Sci Rep*
39 310 2018;8(1):12050. doi: 10.1038/s41598-018-30487-6 [published Online First:
40 311 2018/08/15]
41 312 24. Cao B, Wang DF, Xu MY, et al. Lower folate levels in schizophrenia: A meta-analysis.
42 313 *Psychiatry Res* 2016;245:1-7. doi: 10.1016/j.psychres.2016.03.003

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316 **Figure Legend**

317 **Figure 1.** PRISMA flow diagram of study selection process.

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Table 1. Search strategy for PubMed

Search number	Query
#1	"major depression"[Title/Abstract] OR "major depressive disorder"[Title/Abstract] OR "depressive symptom*"[Title/Abstract] OR "symptom, depressive"[Title/Abstract] OR "depress*"[Title/Abstract] OR "dysphor*"[Title/Abstract] OR "dysthym*"[Title/Abstract] OR "adjustment disorder*"[Title/Abstract] OR "mood disorder*"[Title/Abstract] OR "affective disorder"[Title/Abstract] OR "affective disorders"[Title/Abstract] OR "emotional depression*"[Title/Abstract]
#2	"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh] OR "Depressive Disorder, Major"[Mesh]
#3	#1 OR #2
#4	"Cognitive Behavioral Therapy"[Mesh]
#5	"behavioral therapies, cognitive"[Title/Abstract] OR "behavioral therapy, cognitive"[Title/Abstract] OR "cognitive behavioral Therap*"[Title/Abstract] OR "cognitive behavior therap*"[Title/Abstract] OR "cognitive psychotherap*"[Title/Abstract] OR "behavior modification"[Title/Abstract] OR "behavior therap*"[Title/Abstract] OR "cognitive therap*" [Title/Abstract] OR "psychotherapy*" [Title/Abstract]
#6	#4 OR #5
#7	"Cytokines"[Mesh] OR "Chemokines"[Mesh] OR "Interleukins"[Mesh]
#8	"cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "chemokine*" [Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR "interferon"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "IFN"[Title/Abstract] OR "TNF"[Title/Abstract] OR "CRP"[Title/Abstract] OR "IL-1 β "[Title/Abstract] OR "IL-2"[Title/Abstract] OR "IL-4"[Title/Abstract] OR "IL-6"[Title/Abstract] OR "IL-8"[Title/Abstract] OR "IL-10"[Title/Abstract] OR "IL-12"[Title/Abstract] OR "IL-18"[Title/Abstract] OR "TGF- β "[Title/Abstract] OR "IFN- γ "[Title/Abstract]) OR ("cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "chemokine*" [Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR "interferon"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "IFN"[Title/Abstract] OR "TNF"[Title/Abstract] OR "CRP"[Title/Abstract] OR "IL-1 β "[Title/Abstract] OR "IL-2"[Title/Abstract] OR "IL-4"[Title/Abstract] OR "IL-6"[Title/Abstract] OR "IL-8"[Title/Abstract] OR "IL-10"[Title/Abstract] OR "IL-12"[Title/Abstract] OR "IL-18"[Title/Abstract] OR "TGF- β "[Title/Abstract] OR "IFN- γ "[Title/Abstract])
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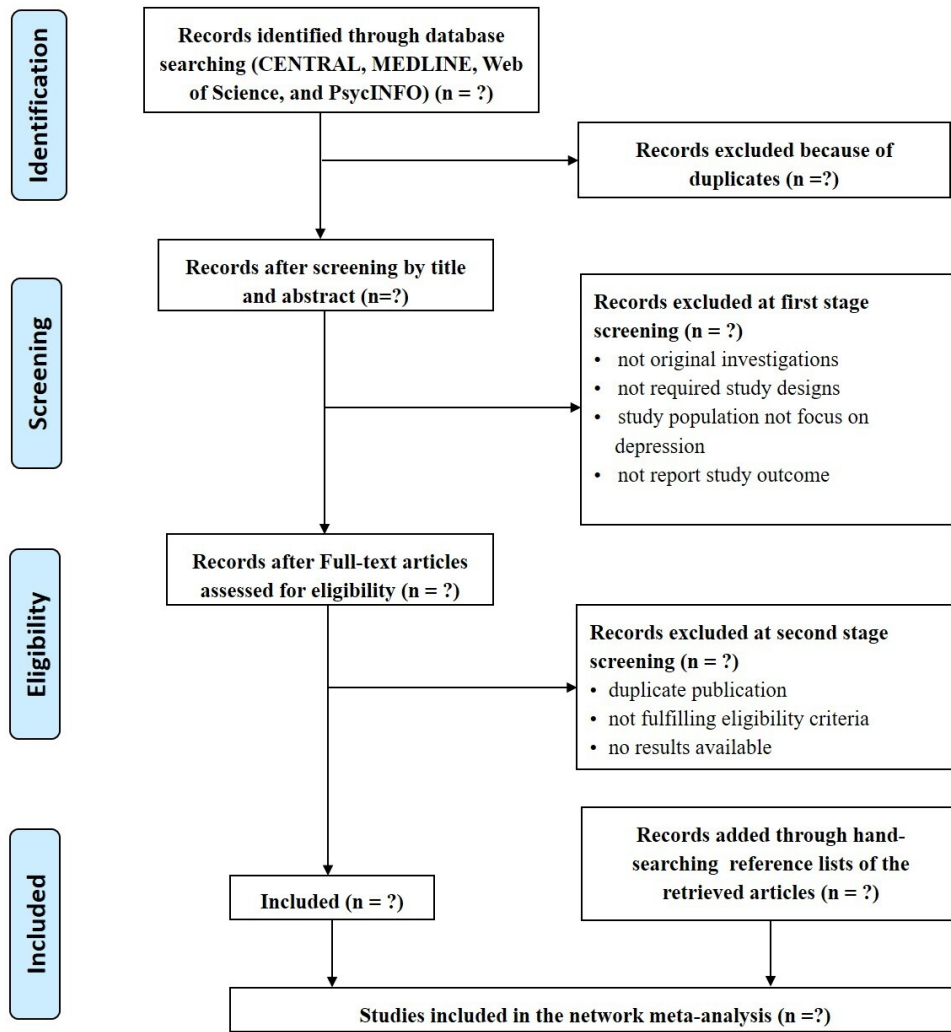


Figure 1. PRISMA flow diagram of study selection process.

100x106mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

Reporting Item			Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			

1	#4	If the protocol represents an amendment of a previously completed or	NA
2		published protocol, identify as such and list changes; otherwise, state	
3		plan for documenting important protocol amendments	
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6	Support		
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8	Sources	#5a Indicate sources of financial or other support for the review	10
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10	Sponsor	#5b Provide name for the review funder and / or sponsor	10
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12	Role of sponsor or	#5c Describe roles of funder(s), sponsor(s), and / or institution(s), if any,	10
13	funder	in developing the protocol	
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17	Introduction		
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19	Rationale	#6 Describe the rationale for the review in the context of what is already	4-5
20		known	
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22	Objectives	#7 Provide an explicit statement of the question(s) the review will	5
23		address with reference to participants, interventions, comparators, and	
24		outcomes (PICO)	
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28	Methods		
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30	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design, setting,	6-7
31		time frame) and report characteristics (such as years considered,	
32		language, publication status) to be used as criteria for eligibility for	
33		the review	
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35	Information sources	#9 Describe all intended information sources (such as electronic	6-7
36		databases, contact with study authors, trial registers or other grey	
37		literature sources) with planned dates of coverage	
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39	Search strategy	#10 Present draft of search strategy to be used for at least one electronic	6-7
40		database, including planned limits, such that it could be repeated	
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42	Study records - data	#11a Describe the mechanism(s) that will be used to manage records and	7
43	management	data throughout the review	
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45	Study records -	#11b State the process that will be used for selecting studies (such as two	7
46	selection process	independent reviewers) through each phase of the review (that is,	
47		screening, eligibility and inclusion in meta-analysis)	
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49	Study records - data	#11c Describe planned method of extracting data from reports (such as	7
50	collection process	piloting forms, done independently, in duplicate), any processes for	
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3	Data items	#12 List and define all variables for which data will be sought (such as	7
4		PICO items, funding sources), any pre-planned data assumptions and	
5		simplifications	
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8	Outcomes and	#13 List and define all outcomes for which data will be sought, including	7
9	prioritization	prioritization of main and additional outcomes, with rationale	
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12	Risk of bias in	#14 Describe anticipated methods for assessing risk of bias of individual	8
13	individual studies	studies, including whether this will be done at the outcome or study	
14		level, or both; state how this information will be used in data synthesis	
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17	Data synthesis	#15a Describe criteria under which study data will be quantitatively	7-8
18		synthesised	
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21	Data synthesis	#15b If data are appropriate for quantitative synthesis, describe planned	7-8
22		summary measures, methods of handling data and methods of	
23		combining data from studies, including any planned exploration of	
24		consistency (such as I ² , Kendall's τ)	
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28	Data synthesis	#15c Describe any proposed additional analyses (such as sensitivity or	7-8
29		subgroup analyses, meta-regression)	
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31	Data synthesis	#15d If quantitative synthesis is not appropriate, describe the type of	NA
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35	Meta-bias(es)	#16 Specify any planned assessment of meta-bias(es) (such as publication	8
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39	Confidence in	#17 Describe how the strength of the body of evidence will be assessed	8
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BMJ Open

Does Cognitive Behavior Therapy Affect Peripheral Inflammation of Depression? A Protocol for the Systematic Review and Meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-048162.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Sep-2021
Complete List of Authors:	Cao, Bing; Southwest University, Li, Ruonan; Southwest University Ding, Ling; Jiangjin Central Hospital of Chongqing, Pharmacy Department Xu, Jiatong; Southwest University Ma, Haijing; Southwest University Liu, Jie; Jiangjin Central Hospital of Chongqing, Pharmacy Department Xue, Jian; Zunyi Medical and Pharmaceutical College, Health Management Department
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health
Keywords:	Depression & mood disorders < PSYCHIATRY, CLINICAL PHYSIOLOGY, IMMUNOLOGY, MENTAL HEALTH

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3 **1 Does Cognitive Behavior Therapy Affect Peripheral Inflammation of Depression? A**
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37 **Word count**

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39 **Abstract:** 247 words; **Text:** 1806 words; **Figures:** 1; **Tables:** 1.
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6 **18 Introduction:** Cognitive behavior therapy (CBT) is becoming the most commonly
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studies have investigated the potential relationship between CBT and the change of
inflammatory biomarkers in individuals of depression. And the results are inconsistent
among studies. The current study aims to provide a comprehensive, systematic review of
the association between CBT and changes of peripheral inflammation of individuals with
depression, and clarify the alterations of inflammatory cytokines pre- and post- CBT
treatment by meta-analysis. anti-inflammatory

26 **26 Methods and analysis:** This study will be conducted in accordance with the *Preferred*
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Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A
systematic search of predetermined terms will be conducted with electronic databases of
CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to July 2021. Database
searches will be supplemented by expert contact, reference and citation checking, and grey
literature. Primary outcomes of interest will be validated measures for levels of
inflammatory cytokines pre- and post- CBT treatment in individuals with depression.
Hedges' g will be used to represent the effect size (ES).

34 **34 Systematic review registration:** The protocol of current meta-analysis has been registered
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at the Open Science Framework [<https://doi.org/10.17605/osf.io/tr9yh>].

36 **36 Ethics and Dissemination:** Formal ethical approval is not required by the National Ethical
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Review Board in China as primary data will not be collected. The results alterations of
peripheral inflammatory cytokines pre- and post- CBT treatment in individuals with

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3 39 depression will be disseminated through a peer-reviewed publication and inform the most
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5 40 up-to-date evidence of the roles of CBT treatment for depression.
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10 42 **Keywords:** Depression; Cognitive Behavior Therapy; Inflammation; Cytokines; C-
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16 17 18 45 **Article Summary**

19 20 46 *Strengths and limitations of this study*

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23 47 • This will be the first meta-analysis exploring the association between CBT and changes
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25 48 of peripheral inflammation of individuals with depression.
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28 49 • The results could provide the most up-to-date evidence to assist in shared decision
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30 50 making between patients, caregivers, and clinicians in treating the individuals with
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32 51 depression by using CBT.
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35 52 • An insufficient number of original researches is a possible limitation.
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37 53 • Potential high heterogeneity may cause selection bias and also decrease the reliability
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39 54 of our results.
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56 **Introduction**

57 Depression is a severe and the most prevalent form of mental illness that characterized by
58 neurocognitive deficits and disability ¹. The disorder manifests in millions of individuals
59 worldwide, and is a global health priority. The exploration of underlying mechanisms of
60 depression are increasing over the past decades, none of them could clearly clarify the
61 potential triggers of depression ². In recent years, the inflammatory processes are
62 considered to be important contributors to depression. A systematic review and meta-
63 analysis confirmed that a high proportion of depressed individuals showed signs of
64 inflammation³. The potential bidirectional relationship of depression and inflammation
65 were also clarified ⁴. For instance, early infection and autoimmune diseases are highly
66 associated with high risk of depressive disorders in adulthood ⁵; evidence from preclinical
67 and clinical researches reached a consistency that the concentrations of peripheral pro-
68 inflammatory cytokines significantly increase in individuals or animal models of
69 depression ⁶. The inflammatory cytokines are mediators of environmental and genetic
70 factors that may contribute to the development of depression from a biological perspective⁷.
71 A previous study suggested that inflammation may be involved in some certain medical
72 conditions, and it may activate the pathogenesis of depression by interfering with the
73 monoamine, glutamate, and neurotrophic system ⁸. Dowlat et al. 's study reported that
74 major depression leads to immune dysregulation and activation of the inflammatory
75 response system ⁹. In addition, a growing body of evidence indicated that inflammation is
76 thought to be an active process. The inflammatory process can affect multiple aspects of
77 central nervous system function, and leads to behavioral changes in individuals with
78 depression ¹⁰. The results of several meta-analyses have proved that depression is related

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3 79 to chronic low-grade inflammation. It is manifested by higher concentrations of peripheral
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5 80 C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α),
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8 81 compared with healthy controls^{11 12}. Above findings have facilitated the development of
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10 82 the inflammatory hypothesis of depression, and have also predicted that inflammation
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12 83 plays a role in the formation, progression and perpetuation of depression.^{13 14}. Cognitive
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14 84 behavior therapy (CBT) is becoming the most commonly implemented and standard
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16 85 treatment for depression¹⁵. Briefly, CBT is based on the premise that false beliefs and
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18 86 negative thoughts are the main causes of depression. The individuals develop strategies for
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20 87 managing and preventing depressive symptoms by monitoring mood symptoms and
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22 88 utilizing a repertoire of coping skills to manage stress in CBT¹⁶. A meta-analysis found
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24 89 that there is no difference in treatment effects of CBT and second-generation
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26 90 antidepressants, either alone or in combination¹⁷. Recent published literatures illustrated
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28 91 that similar with antidepressant treatment, CBT may also contribute to reduction of chronic
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30 92 low-grade peripheral inflammation¹⁸. However, the underlying biological processes of the
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32 93 CBT effects on depression are still very limited.

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38 94 To date, only a few numbers of studies have investigated the potentially anti-inflammatory
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40 95 effects of CBT for depression. Results are inconsistent among studies. For example, some
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42 96 researches pointed out that peripheral IL-6 was decreased after CBT, while no significant
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44 97 changes were founded in other studies¹⁹. Keri et al. (2014) reported that in adults with a
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46 98 first episode of depression, 16 weeks of CBT alone was associated with a reduction in
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48 99 TLR-4 signaling, but no change in TLR-2 signaling, IL-6, or CRP levels. This study
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50 100 suggested that it took longer time or other mechanisms for them to normalize²⁰.
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52 101 Additionally, whether the alterations of inflammatory cytokines associated with
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3 102 improvements in depression after CBT treatment is also not well established. So far it is
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5 103 worthy to conduct a systematic review and meta-analysis to summarize the most updated
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8 104 research results for the role of CBT treatment in inflammation of depression.
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12 13 14 106 **Aims and Objectives**

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17 107 The current study aims to provide a comprehensive, systematic review of the
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19 108 association between CBT and inflammation of individuals with depression, and clarify the
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21 109 alterations of inflammatory cytokines pre- and post- CBT treatment by meta-analysis.
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24 110 From the previous evidence, we hypothesized that some inflammatory cytokines, such as
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26 111 CRP, IL-6, TNF- α , may decrease after the CBT intervention.
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30 31 32 113 **Methods**

33 34 35 114 *Search Strategy*

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38 115 The systematic review and meta-analysis will be conducted and reported in accordance
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40 116 with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*
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42 117 statement²¹. **Figure 1** summarizes the study selection as a PRISMA flowchart. A
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45 118 systematic search of predetermined terms will be conducted with electronic databases of
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47 119 CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to July 2021. The
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49 120 keywords of our search strategy will be the key terms mapped to subject headings for (i)
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51 121 depression (major depressive disorder, depression, mood disorder, dysthymic disorder);
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54 122 (ii) CBT (psychotherapy, cognitive therapy, cognitive behavioral therapy); (iii)

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11 126 *Selection Criteria*

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13 127 The studies conducting the within-group comparisons of the peripheral levels of
14
15 128 cytokines and chemokines in participants with depression at baseline and after CBT will
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17
18 129 be included in the current meta-analysis. Study eligibility for the inclusion criteria will be
19
20 130 assessed by the approach of Population, Intervention, Comparison, Outcome and Study
21
22 131 Design (PICOS). Moreover, according to the quality assessment recommendation of
23
24 132 Cochrane Collaboration, we will use Newcastle-Ottawa Scale (NOS) to evaluate the
25
26 133 quality of the included literatures²². Population: adult subjects (≥ 18 years old) meeting the
27
28 134 major depression diagnoses by the Diagnostic and Statistical Manual of Mental Disorders
29
30 135 (DSM; no restrictions on editions) or International Classification of Diseases and Related
31
32 136 Health Problems (ICD) criteria; Intervention and Comparison: assessed the results of
33
34 137 peripheral inflammatory cytokines (e.g., IL-6, CRP or IL-10) before and after CBT.
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36 138 Outcome: reported mean or median resting levels of inflammatory cytokines in saliva,
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38 139 blood, or urine was reported before and at least once after starting CBT, or the effect size
39
40 140 (ES) could be calculated from the reported results. Study Design: random controlled trial
41
42 141 (RCT), open-label study, or longitudinal study with pre-test-post-test design. Exclusion
43
44 142 criteria of the studies will meet if they (1) did not focus on evaluating inflammatory
45
46 143 cytokines levels on depression; (2) only reported stimulated levels of cytokines; (3) were
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48 144 repetitive publications from the same datasets by the same or different authors; (4) included
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50 145 participants who have been receiving pharmacological treatment in the past one month.
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146 *Outcome Measures and Data Extraction*

147 The outcome for this meta-analysis will be the changes of inflammatory cytokines pre-
148 and post- CBT treatment in individuals with depression, which were measured by the
149 standard mean differences (SMDs) their concentrations. Paired investigators (Jiatong Xu
150 and Haijing Ma) will independently select the studies, reviewed the main reports and
151 supplementary materials, extracted the relevant information. All reference lists of the
152 retrieved articles will be reviewed to identify the potential studies. The following
153 information will be extracted from each study: first author, publication year, study design,
154 country, geographic location, age, sex, intervention, duration of intervention, whether it is
155 a major depressive episode (MDE), inflammatory biomarkers measured, type of sample
156 specimen required for test, sample detection method, sample size, the mean levels of
157 subjects' peripheral inflammatory cytokines and standard deviations (SDs) before and after
158 CBT treatment.

159 *Statistical analysis*

160 Only the inflammatory cytokines with sufficient numbers of studies (≥ 3) will be
161 performed the meta-analysis. Analyses will be performed for pre- and post-treatment of
162 CBT. The main analysis will be conducted with a random effects model. Forest plots will
163 be used to estimate the alteration of the levels of inflammatory cytokines pre- and post-
164 treatment CBT, which will be evaluated by SMD with a 95% confidence interval (CI). The
165 ES is represented as Hedges' g in order to adjusted for a potential bias wo overestimate the
166 ES in small samples. According to the statistical power analysis for the behavioral sciences
167 (2nd edition), the ES is judged using the values of 0.2, 0.5, and 0.8 for small, medium and
168 large (Cohen, 1988). In addition, we will conduct Bonferroni adjustment for multiple

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3 169 testing in meta-analysis, which means we will produce a rejection p-value of 0.05 divided
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5 170 by the total number of outcomes²³. The heterogeneity across the studies will be evaluated
6
7 171 by chi-square statistics and I-Squared (I^2) test. A value of $P < 0.10$ or $I^2 > 50\%$ indicated that
8
9 172 the heterogeneity of effect estimates within each group of studies was statistically
10
11 173 significant²⁴, and it also shows that the percentage of the variability in effect estimates
12
13 174 owes to heterogeneity rather than chance. Furtherly, the subgroup analysis and meta-
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15 175 regression will also be performed to investigate the source of the heterogeneity, and the
16
17 176 potential influence of included characteristics of the studies on the pooled effect size.
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19 177 Sensitivity analysis was performed to strengthen the results and investigate whether any
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21 178 single study would have an effect on the heterogeneity of total measurements in each meta-
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23 179 analysis. Additionally, the positive and negative results may not be equally likely to get
24
25 180 published, thus the funnel plot with Begg's test and Egger's test will be used for testing the
26
27 181 publication bias. If publication bias will be found, then the trim and fill method would be
28
29 182 used to both identify and correct the asymmetry of funnel plot. All two-tailed p -values $<$
30
31 183 0.05 will be defined as statistical significance. All the data analyses will be conducted using
32
33 184 Stata (version 15.0, Stata Corp LP, College Station, TX, USA).

34 35 36 37 38 39 40 41 185 *Patient and public involvement*

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43 186 Patients were not involved in the development of this systematic review protocol. The
44
45 187 data for this systematic review will be collected from previously published studies.

46 47 48 49 188 *Ethics and Dissemination*

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51 189 Formal ethical approval is not required, as primary data will not be collected with the
52
53 190 systematic review and meta-analysis. Data from previously published studies will be
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55 191 retrieved and analyzed. This study including protocol development will run from October

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3 192 2020 to October 2021. The results will be disseminated through a peer-reviewed
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5 193 publication and inform the most up-to-date evidence of the roles of CBT treatment for
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7 194 depression.
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12 13 14 196 **Discussion**

15 16 17 197 *Presentation of results and reporting*

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19 198 Our current systematic review and meta-analysis will provide comprehensive evidence
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21 199 for the association between CBT and inflammation of individuals with depression. We will
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23 200 use the PRISMA guidelines and checklist in the publication process. The quantitative data
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25 201 will be summarized and presented in tables, forest plots, and charts. The alterations of
26
27 202 inflammatory cytokines pre- and post- CBT treatment in individuals with depression will
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29 203 be presented.
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33 204 *Potential resources of limitations*

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36 205 The current study is anticipated to have some limitations. Firstly, we might not find a
37
38 206 sufficient number of original researches to perform the analyses. Secondly, the potential
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40 207 high heterogeneity between studies in the exposure of interest and restriction to studies in
41
42 208 English language will lead to selection bias and also decrease the reliability of our results.
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46 209 To the best of our knowledge, this will be the first meta-analysis exploring the
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48 210 association between CBT and peripheral inflammation of individuals with depression.
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50 211 From our findings herein, we can provide the most up-to-date evidence to assist in shared
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52 212 decision making between patients, caregivers, and clinicians in treating the individuals with
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54 213 depression by using CBT and provide a foundation for future studies in this area.
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3 214 **Contributorship statement**
4

5 215 Cao B, Xu JT and Ma HJ conceived the study and developed the search strategy. Cao
6
7 216 B drafted the protocol and tested the search strategies in consultation with a librarian. Li
8
9 217 RN, Ding L, Liu J and Xue J provided advice on the protocol. All authors critically revised
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11 218 the protocol for methodological and intellectual content and have read and approved the
12
13 219 final manuscript.
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21

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27
28 225 of Zunyi Science and Technology Bureau [grant numbers (2020)22];. The funding bodies
29
30 226 had no part in either the study design, conduct, analysis or interpretation of this study.
31
32
33

34 227 **Competing interests**
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36 228 None declared.
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39 229 **Patient consent for publication**
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41 230 Not required.
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45 231 **Data statement**
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47 232 No applicable.
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233 **References**

- 234 1. Ang YS, Frontero N, Belleau E, et al. Disentangling vulnerability, state and trait features of
235 neurocognitive impairments in depression. *Brain* 2020 doi: 10.1093/brain/awaa314
236 [published Online First: 2020/11/12]
- 237 2. McIntosh AM, Hall LS, Zeng Y, et al. Genetic and Environmental Risk for Chronic Pain and the
238 Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-
239 Model Analysis. *PLoS Med* 2016;13(8):e1002090. doi: 10.1371/journal.pmed.1002090
240 [published Online First: 2016/08/17]
- 241 3. Osimo EF, Baxter LJ, Lewis G, et al. Prevalence of low-grade inflammation in depression: a
242 systematic review and meta-analysis of CRP levels. *Psychological medicine*
243 2019;49(12):1958-70. doi: 10.1017/S0033291719001454 [published Online First:
244 2019/07/02]
- 245 4. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and
246 Inflammation: Double Trouble. *Neuron* 2020;107(2):234-56. doi:
247 10.1016/j.neuron.2020.06.002 [published Online First: 2020/06/20]
- 248 5. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as
249 risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* 2013;70(8):812-20.
250 doi: 10.1001/jamapsychiatry.2013.1111 [published Online First: 2013/06/14]
- 251 6. Kim YK, Na KS, Myint AM, et al. The role of pro-inflammatory cytokines in neuroinflammation,
252 neurogenesis and the neuroendocrine system in major depression. *Progress in neuro-*
253 *psychopharmacology & biological psychiatry* 2016;64:277-84. doi:
254 10.1016/j.pnpbp.2015.06.008 [published Online First: 2015/06/27]
- 255 7. Song C, Wang H. Cytokines mediated inflammation and decreased neurogenesis in animal
256 models of depression. *Progress in neuro-psychopharmacology & biological psychiatry*
257 2011;35(3):760-8. doi: 10.1016/j.pnpbp.2010.06.020 [published Online First:
258 2010/07/06]
- 259 8. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a
260 literature review. *CNS Spectr* 2008;13(6):501-10. doi: 10.1017/s1092852900016734
261 [published Online First: 2008/06/24]
- 262 9. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major
263 depression. *Biol Psychiatry* 2010;67(5):446-57. doi: 10.1016/j.biopsych.2009.09.033
264 [published Online First: 2009/12/18]
- 265 10. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery.
266 *Brain Behav Immun* 2007;21(4):374-83. doi: 10.1016/j.bbi.2007.01.010 [published
267 Online First: 2007/03/16]
- 268 11. Kohler CA, Freitas TH, Stubbs B, et al. Peripheral Alterations in Cytokine and Chemokine
269 Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic
270 Review and Meta-Analysis. *Molecular neurobiology* 2018;55(5):4195-206. doi:
271 10.1007/s12035-017-0632-1 [published Online First: 2017/06/15]
- 272 12. Wiedlocha M, Marcinowicz P, Krupa R, et al. Effect of antidepressant treatment on
273 peripheral inflammation markers - A meta-analysis. *Progress in neuro-*
274 *psychopharmacology & biological psychiatry* 2018;80(Pt C):217-26. doi:
275 10.1016/j.pnpbp.2017.04.026 [published Online First: 2017/04/27]
- 276 13. Kohler-Forsberg O, C NL, Hjorthoj C, et al. Efficacy of anti-inflammatory treatment on major
277 depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta*

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2
3 278 *psychiatrica Scandinavica* 2019;139(5):404-19. doi: 10.1111/acps.13016 [published
4 279 Online First: 2019/03/06]
5 280 14. Husain MI, Strawbridge R, Stokes PR, et al. Anti-inflammatory treatments for mood
6 281 disorders: Systematic review and meta-analysis. *Journal of psychopharmacology*
7 282 (Oxford, England) 2017;31(9):1137-48. doi: 10.1177/0269881117725711 [published
8 283 Online First: 2017/09/01]
9 284 15. Lopez MA, Basco MA. Effectiveness of cognitive behavioral therapy in public mental health:
10 285 comparison to treatment as usual for treatment-resistant depression. *Adm Policy Ment*
11 286 *Health* 2015;42(1):87-98. doi: 10.1007/s10488-014-0546-4 [published Online First:
12 287 2014/04/03]
13 288 16. Pearlstein JG, Staudenmaier PJ, West AE, et al. Immune response to stress induction as a
14 289 predictor of cognitive-behavioral therapy outcomes in adolescent mood disorders: A
15 290 pilot study. *J Psychiatr Res* 2020;120:56-63. doi: 10.1016/j.jpsychires.2019.10.012
16 291 [published Online First: 2019/10/22]
17 292 17. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second
18 293 generation antidepressants and cognitive behavioral therapies in initial treatment of
19 294 major depressive disorder: systematic review and meta-analysis. *BMJ* 2015;351:h6019.
20 295 doi: 10.1136/bmj.h6019 [published Online First: 2015/12/10]
21 296 18. Lopresti AL. Cognitive behaviour therapy and inflammation: A systematic review of its
22 297 relationship and the potential implications for the treatment of depression. *Aust N Z J*
23 298 *Psychiatry* 2017;51(6):565-82. doi: 10.1177/0004867417701996 [published Online First:
24 299 2017/04/07]
25 300 19. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and
26 301 therapeutic implications. *Neuroscience* 2013;246:199-229. doi:
27 302 10.1016/j.neuroscience.2013.04.060 [published Online First: 2013/05/07]
28 303 20. Keri S, Szabo C, Kelemen O. Expression of Toll-Like Receptors in peripheral blood
29 304 mononuclear cells and response to cognitive-behavioral therapy in major depressive
30 305 disorder. *Brain Behav Immun* 2014;40:235-43. doi: 10.1016/j.bbi.2014.03.020
31 306 [published Online First: 2014/04/15]
32 307 21. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
33 308 meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097. doi:
34 309 10.1371/journal.pmed.1000097
35 310 22. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors'
36 311 assessments. *BMC Med Res Methodol* 2014;14:45. doi: 10.1186/1471-2288-14-45
37 312 23. Ng A, Tam WW, Zhang MW, et al. IL-1beta, IL-6, TNF- alpha and CRP in Elderly Patients with
38 313 Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. *Sci Rep*
39 314 2018;8(1):12050. doi: 10.1038/s41598-018-30487-6 [published Online First:
40 315 2018/08/15]
41 316 24. Cao B, Wang DF, Xu MY, et al. Lower folate levels in schizophrenia: A meta-analysis.
42 317 *Psychiatry Res* 2016;245:1-7. doi: 10.1016/j.psychres.2016.03.003

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320 **Figure Legend**

321 **Figure 1.** PRISMA flow diagram of study selection process.

322

For peer review only

323

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Table 1. Search strategy for PubMed

Search number	Query
#1	"major depression"[Title/Abstract] OR "major depressive disorder"[Title/Abstract] OR "depressive symptom*"[Title/Abstract] OR "symptom, depressive"[Title/Abstract] OR "depress*" [Title/Abstract] OR "dysphor*" [Title/Abstract] OR "dysthym*"[Title/Abstract] OR "adjustment disorder*"[Title/Abstract] OR "mood disorder*"[Title/Abstract] OR "affective disorder"[Title/Abstract] OR "affective disorders"[Title/Abstract] OR "emotional depression*"[Title/Abstract]
#2	"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh] OR "Depressive Disorder, Major"[Mesh]
#3	#1 OR #2
#4	"Cognitive Behavioral Therapy"[Mesh]
#5	"behavioral therapies, cognitive"[Title/Abstract] OR "behavioral therapy, cognitive"[Title/Abstract] OR "cognitive behavioral Therap*"[Title/Abstract] OR "cognitive behavior therap*"[Title/Abstract] OR "cognitive psychotherap*"[Title/Abstract] OR "behavior modification" [Title/Abstract] OR "behavior therap*"[Title/Abstract] OR "cognitive therap*" [Title/Abstract] OR "psychotherapy*" [Title/Abstract]
#6	#4 OR #5
#7	"Cytokines"[Mesh] OR "Chemokines"[Mesh] OR "Interleukins"[Mesh]
#8	"cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "chemokine*" [Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR "interferon"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "IFN"[Title/Abstract] OR "TNF"[Title/Abstract] OR "CRP" [Title/Abstract] OR "IL-1 β "[Title/Abstract] OR " IL-2"[Title/Abstract] OR "IL-4"[Title/Abstract] OR "IL-6"[Title/Abstract] OR "IL-8"[Title/Abstract] OR "IL-10"[Title/Abstract] OR "IL-12"[Title/Abstract] OR "IL-18"[Title/Abstract] OR "TGF- β "[Title/Abstract] OR "IFN- γ "[Title/Abstract]) OR ("cytokine*" [Title/Abstract] OR "interleukin*" [Title/Abstract] OR "chemokine*" [Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR "interferon"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "IFN"[Title/Abstract] OR "TNF"[Title/Abstract] OR "CRP" [Title/Abstract] OR "IL-1 β "[Title/Abstract] OR " IL-2"[Title/Abstract] OR "IL-4"[Title/Abstract] OR "IL-6"[Title/Abstract] OR "IL-8"[Title/Abstract] OR "IL-10"[Title/Abstract] OR "IL-12"[Title/Abstract] OR "IL-18"[Title/Abstract] OR "TGF- β "[Title/Abstract] OR "IFN- γ "[Title/Abstract])
#9	#7 OR #8
#10	#3 AND #6 AND #9

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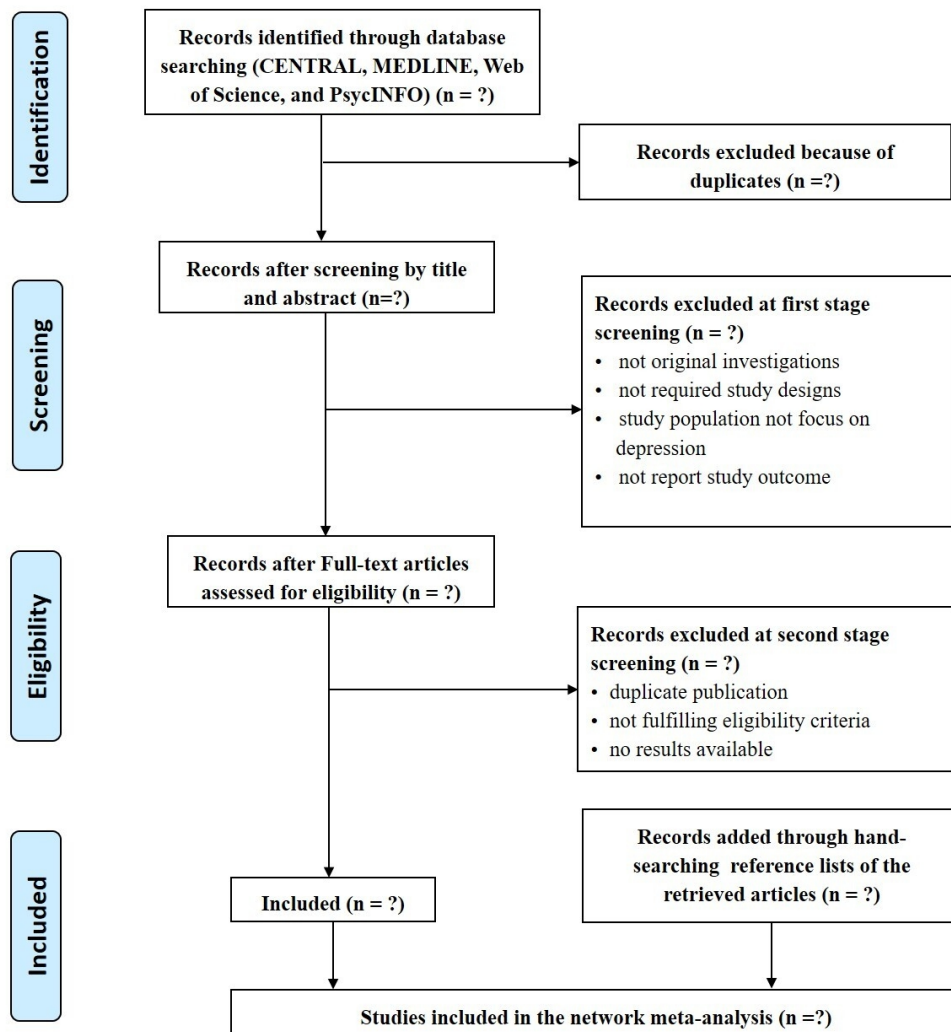


Figure 1. PRISMA flow diagram of study selection process.

100x106mm (300 x 300 DPI)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

Reporting Item			Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			

1		#4	If the protocol represents an amendment of a previously completed or	NA
2			published protocol, identify as such and list changes; otherwise, state	
3			plan for documenting important protocol amendments	
4				
5				
6	Support			
7				
8	Sources	#5a	Indicate sources of financial or other support for the review	10
9				
10	Sponsor	#5b	Provide name for the review funder and / or sponsor	10
11				
12	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any,	10
13	funder		in developing the protocol	
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16				
17	Introduction			
18				
19	Rationale	#6	Describe the rationale for the review in the context of what is already	4-5
20			known	
21				
22	Objectives	#7	Provide an explicit statement of the question(s) the review will	5
23			address with reference to participants, interventions, comparators, and	
24			outcomes (PICO)	
25				
26				
27				
28	Methods			
29				
30	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting,	6-7
31			time frame) and report characteristics (such as years considered,	
32			language, publication status) to be used as criteria for eligibility for	
33			the review	
34				
35	Information sources	#9	Describe all intended information sources (such as electronic	6-7
36			databases, contact with study authors, trial registers or other grey	
37			literature sources) with planned dates of coverage	
38				
39	Search strategy	#10	Present draft of search strategy to be used for at least one electronic	6-7
40			database, including planned limits, such that it could be repeated	
41				
42	Study records - data	#11a	Describe the mechanism(s) that will be used to manage records and	7
43	management		data throughout the review	
44				
45	Study records -	#11b	State the process that will be used for selecting studies (such as two	7
46	selection process		independent reviewers) through each phase of the review (that is,	
47			screening, eligibility and inclusion in meta-analysis)	
48				
49	Study records - data	#11c	Describe planned method of extracting data from reports (such as	7
50	collection process		piloting forms, done independently, in duplicate), any processes for	
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		obtaining and confirming data from investigators	
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3	Data items	#12 List and define all variables for which data will be sought (such as	7
4		PICO items, funding sources), any pre-planned data assumptions and	
5		simplifications	
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7			
8	Outcomes and	#13 List and define all outcomes for which data will be sought, including	7
9	prioritization	prioritization of main and additional outcomes, with rationale	
10			
11	Risk of bias in	#14 Describe anticipated methods for assessing risk of bias of individual	8
12	individual studies	studies, including whether this will be done at the outcome or study	
13		level, or both; state how this information will be used in data synthesis	
14			
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17	Data synthesis	#15a Describe criteria under which study data will be quantitatively	7-8
18		synthesised	
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21	Data synthesis	#15b If data are appropriate for quantitative synthesis, describe planned	7-8
22		summary measures, methods of handling data and methods of	
23		combining data from studies, including any planned exploration of	
24		consistency (such as I ² , Kendall's τ)	
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28	Data synthesis	#15c Describe any proposed additional analyses (such as sensitivity or	7-8
29		subgroup analyses, meta-regression)	
30			
31	Data synthesis	#15d If quantitative synthesis is not appropriate, describe the type of	NA
32		summary planned	
33			
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35	Meta-bias(es)	#16 Specify any planned assessment of meta-bias(es) (such as publication	8
36		bias across studies, selective reporting within studies)	
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39	Confidence in	#17 Describe how the strength of the body of evidence will be assessed	8
40	cumulative	(such as GRADE)	
41	evidence		
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