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

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Word count

Abstract: 240 words; **Text:** 1518words; **Figures:** 1; **Tables:** 1.

Abstract

Introduction: Cognitive behavior therapy (CBT) is becoming the most commonly implemented and standard treatment for depression. Up to date, only a few number of studies have investigated the potentially anti-inflammatory effects of CBT for depression and results are inconsistent between studies. The current study aims to provide a comprehensive, systematic review of the treatment effects of CBT on inflammation of individuals with depression, and clarify the alterations of inflammatory cytokines pre- and post- CBT treatment by meta-analysis.

Methods and analysis: This study will be conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. Electronic databases (CENTRAL, MEDLINE, Web of Science, and PsycINFO) will be searched systematically using predetermined terms. Database searches will be supplemented by expert contact, reference and citation checking, and grey literature. Primary outcomes of interest will be validated measures of levels of inflammatory cytokines pre- and post- CBT treatment in individuals with depression. Hedges' g will be used to express the effect size (ES).

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

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

be disseminated through a peer-reviewed publication and inform the most up-to-date evidence of the roles of CBT treatment for depression.

Keywords: Depression; Cognitive Behavior Therapy; Inflammation; Cytokines; C-reactive protein

Article Summary

Strengths and limitations of this study

- This will be the first meta-analysis exploring the treatment effects of CBT on inflammation of individuals with depression.
- The results could provide the most up-to-date evidence to assist in shared decision making between patients, caregivers, and clinicians in treating the individuals with depression by using CBT.
- An insufficient amount of original researches is a possible limitation.
- Potential high heterogeneity may cause selection bias and also decrease the reliability of our results.

Introduction

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

Cognitive behavior therapy (CBT) is becoming the most commonly implemented and standard treatment for depression [11]. Briefly, CBT is a psychological intervention based on effecting behavioral changes through cognitive aspects. The individuals develop strategies for managing and preventing depressive symptoms by monitoring mood symptoms and utilizing a repertoire of coping skills to manage stress in CBT [12]. A meta-analysis found that there is no difference in treatment effects of CBT and second generation antidepressants, either alone or in combination[13]. Recent published literatures illustrated

that similar with antidepressant treatment, CBT may also contribute to reduction of chronic low-grade peripheral inflammation. However, the underlying biological processes of the CBT effects on depression are still very limited.

Up to date, only a few number of studies have investigated the potentially anti-inflammatory effects of CBT for depression and results are inconsistent between studies and the results were inconsistent. For example, some researches pointed out that IL-6 was decreased after CBT, while no significant changes were founded in other studies [14]. Additionally, whether the alterations of inflammatory cytokines associated with improvements in depression after CBT treatment is also not well established. So far it is worthy to conduct a systematic review and meta-analysis to summarize the most updated research results for the role of CBT treatment in inflammation of depression.

Aims and Objectives

The current study aims to provide a comprehensive, systematic review of the treatment effects of CBT on inflammation of individuals with depression, and clarify the alterations of inflammatory cytokines pre- and post- CBT treatment by meta-analysis. From the previous evidence, we hypothesized that some inflammatory cytokines, such as CRP, IL-6, TNF-α, may decrease after the CBT intervention.

Methods

Search Strategy

The systematic review and meta-analysis will be conducted and reported in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement [15]. **Figure 1** summarizes the study selection as a PRISMA flowchart. Electronic databases (CENTRAL, MEDLINE, EMBASE, and PsycINFO) will be searched systematically using predetermined terms. The keywords of our search strategy will be the key terms mapped to subject headings for (i) depression (major depressive disorder, depression, mood disorder, dysthymic disorder); (ii) CBT (psychotherapy, cognitive therapy, cognitive behavioral therapy); (iii) inflammatory cytokines (cytokine, interleukin, chemokine, interferons, tumor necrosis factor, as well as the specific inflammatory biomarkers). The search strategy of PubMed is shown in **Table 1**.

Selection Criteria

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

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

Outcome Measures and Data Extraction

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

Statistical analysis

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

overestimate the effect size in small samples. According to the statistical power analysis for the behavioral sciences (2nd edition), the ES is judged using the values of 0.2, 0.5, and 0.8 for small, medium and large (Cohen, 1988). The heterogeneity across the studies will be evaluated by chi-square statistics and I-Squared (I^2) test. A value of $P<0.10$ or $I^2>50\%$ indicated that the heterogeneity of effect estimates within each group of studies was statistically significant [16], which shows that the percentage of the variability in effect estimates owes to heterogeneity rather than chance. Furtherly, the subgroup analysis and meta-regression will also be performed to investigate the source of the heterogeneity, and the potential influence of included characteristics of the studies on the pooled effect size. Sensitivity analysis was performed to strengthen the results and investigate whether any single study would have an effect on the heterogeneity of total measurements in each meta-analysis. Additionally, the positive and negative results may not be equally likely to get published, thus the funnel plot with Begg's test and Egger's test will be used for testing the publication bias. If publication bias will be found, then the trim and fill method would be used to both identify and correct the asymmetry of funnel plot. All two-tailed *p*-values < 0.05 will be defined as statistical significance. All the data analyses will be conducted using Stata (version 15.0, Stata Corp LP, College Station, TX, USA).

Patient and public involvement

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

Ethics and Dissemination

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

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

Discussion

Presentation of results and reporting

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

Potential resources of limitations

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

To the best of our knowledge, this will be the first meta-analysis exploring the treatment effects of CBT on inflammation of individuals with depression. From our findings herein, we can provide the most up-to-date evidence to assist in shared decision

making between patients, caregivers, and clinicians in treating the individuals with depression by using CBT and provide a foundation for future studies in this area.

Author contributors

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

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Competing interests

None declared.

Patient consent for publication

Not required.

Data statement

No applicable.

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Figure Legend

Figure 1. PRISMA flow diagram of study selection process.

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-1β"[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-1β"[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

274

275

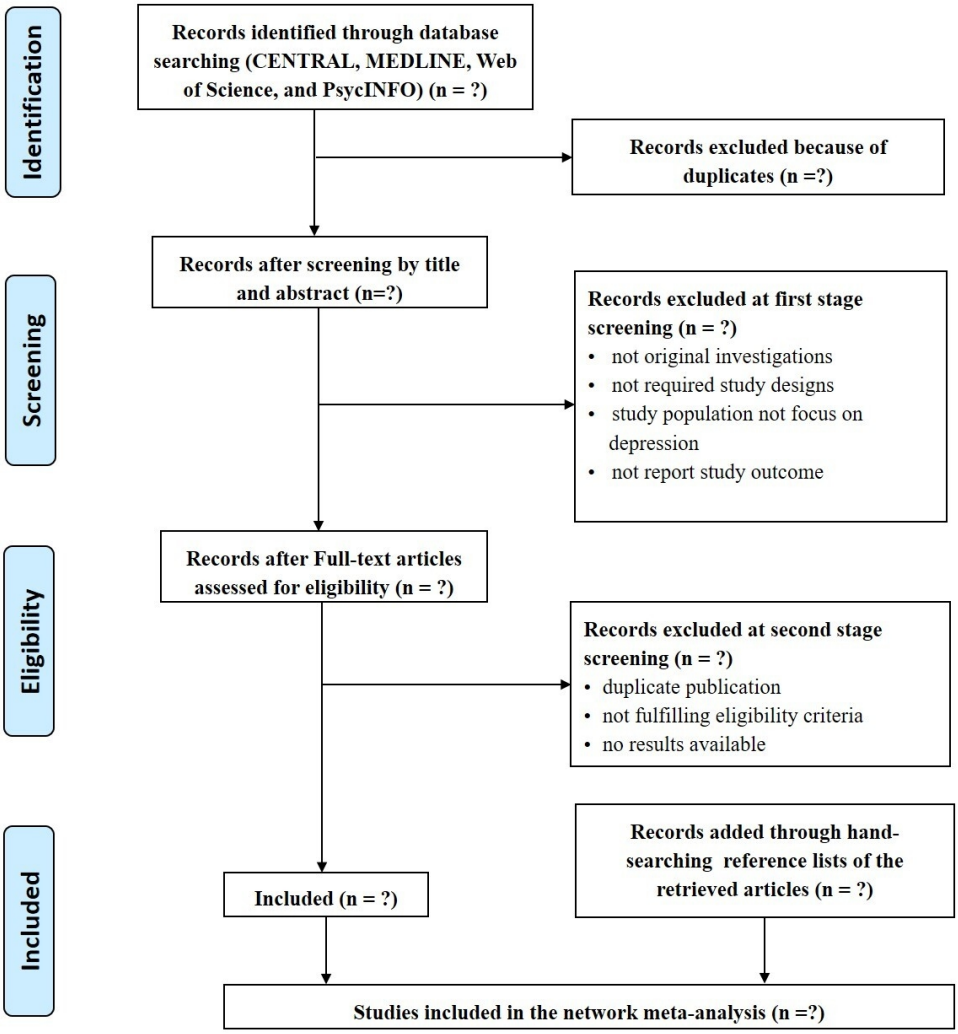

Figure 1. PRISMA flow diagram of study selection process.

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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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			
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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			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	7

		obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7-8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7-8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7-8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

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

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Strengths and limitations of this study

- This will be the first meta-analysis exploring the treatment effects of CBT on inflammation of individuals with depression.
- The results could provide the most up-to-date evidence to assist in shared decision making between patients, caregivers, and clinicians in treating the individuals with depression by using CBT.
- An insufficient amount of original researches is a possible limitation.
- Potential high heterogeneity may cause selection bias and also decrease the reliability of our results.

Introduction

Depression is a severe and the most prevalent form of mental illness that characterized by neurocognitive deficits and disability [1]. The disorder manifests in millions of individuals worldwide, and is a global health priority. The exploration of underlying mechanisms of depression are increasing over the past decades, none of them could clearly clarify the potential triggers of depression [2]. In recent years, the inflammatory processes are considered to be important contributors to depression. A systematic review and meta-analysis confirmed that a high proportion of depressed individuals showed signs of inflammation[3]. The potential bidirectional relationship of depression and inflammation were also clarified [4]. For instance, early infection and autoimmune diseases are highly associated with high risk of depressive disorders in adulthood [5]; evidence from preclinical and clinical researches reached a consistency that the concentrations of pro-inflammatory cytokines are significantly increases in individuals or animal models of depression [6]. The inflammatory cytokines as mediators of environmental and genetic factors that may contribute to the development of depression from a biological perspective[7]. A previous study suggested that inflammation may be involved in some certain medical conditions, and it may activate the pathogenesis of depression by interfering with the monoamine, glutamate, and neurotrophic system [8]. Dowlat et al. 's study reported that major depression leads to immune dysregulation and activation of the inflammatory response system [9]. In addition, a growing number of evidence indicated that inflammation is thought to be an active process, which can affect multiple aspects of central nervous system function, including neurotransmitter metabolism, neuroendocrine function and information processing, leading to behavioral changes in individuals with depression [10]. The results of

several meta-analyses have proved that depression is related to chronic low-grade inflammation, as manifested by higher concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), compared with healthy controls [11 12]. Above findings have facilitated the development of the inflammatory hypothesis of depression, predicting that inflammation plays a role in the formation, progression and perpetuation of depression.[13 14]. Cognitive behavior therapy (CBT) is becoming the most commonly implemented and standard treatment for depression [15]. Briefly, CBT is based on the premise that non-helpful faith and negative thoughts are the main causes of depression. The individuals develop strategies for managing and preventing depressive symptoms by monitoring mood symptoms and utilizing a repertoire of coping skills to manage stress in CBT [16]. A meta-analysis found that there is no difference in treatment effects of CBT and second generation antidepressants, either alone or in combination[17]. Recent published literatures illustrated that similar with antidepressant treatment, CBT may also contribute to reduction of chronic low-grade peripheral inflammation[18]. However, the underlying biological processes of the CBT effects on depression are still very limited.

To date, only a few number of studies have investigated the potentially anti-inflammatory effects of CBT for depression and results are inconsistent between studies and the results were inconsistent. For example, some researches pointed out that IL-6 was decreased after CBT, while no significant changes were founded in other studies [19]. Keri et al. (2014) demonstrated that in adults with a first episode of depression, 16 weeks of CBT alone was associated with a reduction in TLR-4 signaling, but no change in TLR-2 signaling, IL-6, or CRP levels, which suggested that it took longer time or other mechanisms for them to normalize [20]. Additionally, whether the alterations of inflammatory cytokines associated

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

Aims and Objectives

The current study aims to provide a comprehensive, systematic review of the treatment effects of CBT on inflammation of individuals with depression, and clarify the alterations of inflammatory cytokines pre- and post- CBT treatment by meta-analysis. From the previous evidence, we hypothesized that some inflammatory cytokines, such as CRP, IL-6, TNF-α, may decrease after the CBT intervention.

Methods

Search Strategy

The systematic review and meta-analysis will be conducted and reported in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement [21]. **Figure 1** summarizes the study selection as a PRISMA flowchart. A systematic search of predetermined terms will be conducted with electronic databases of CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to July 2021. The keywords of our search strategy will be the key terms mapped to subject headings for (i) depression (major depressive disorder, depression, mood disorder, dysthymic disorder); (ii) CBT (psychotherapy, cognitive therapy, cognitive behavioral therapy); (iii)

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

Selection Criteria

The studies conducted the within-group comparisons of the peripheral levels of cytokines and chemokines in participants with depression at baseline and after CBT will be included in the current meta-analysis. Study eligibility for the inclusion will be assessed by the approach of Population, Intervention, Comparison, Outcome and Study Design (PICOS). Moreover, according to the quality assessment recommendation of Cochrane Collaboration, we will use Newcastle-Ottawa Scale (NOS) to evaluate the quality of the included literatures [22]. Population: adult subjects (≥18 years old) meeting the major depression diagnoses by the Diagnostic and Statistical Manual of Mental Disorders (DSM; no restrictions on editions) or International Classification of Diseases and Related Health Problems (ICD) criteria; Intervention and Comparison: assessed the results of inflammatory cytokines (e.g., IL-6, CRP or IL-10) before and after CBT. Outcome: reported mean or median resting levels of inflammatory cytokines in saliva, blood, or urine was reported before and at least once after starting CBT, or the effect size could be calculated from the reported results. Study Design: random controlled trial (RCT), open-label study, or longitudinal study with pre-test-post-test design. Exclusion criteria of the studies will meet if they (1) did not focus on evaluating inflammatory cytokines levels on depression; (2) only reported stimulated levels of cytokines; (3) were repetitive publications from the same datasets by the same or different authors; (4) included participants who have been receiving pharmacological treatment in the past one month.

Outcome Measures and Data Extraction

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

Statistical analysis

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

p-value of 0.05 divided by the total number of outcomes [23]. The heterogeneity across the studies will be evaluated by chi-square statistics and I-Squared (I^2) test. A value of $P<0.10$ or $I^2>50\%$ indicated that the heterogeneity of effect estimates within each group of studies was statistically significant [24], which shows that the percentage of the variability in effect estimates owes to heterogeneity rather than chance. Furtherly, the subgroup analysis and meta-regression will also be performed to investigate the source of the heterogeneity, and the potential influence of included characteristics of the studies on the pooled effect size. Sensitivity analysis was performed to strengthen the results and investigate whether any single study would have an effect on the heterogeneity of total measurements in each meta-analysis. Additionally, the positive and negative results may not be equally likely to get published, thus the funnel plot with Begg's test and Egger's test will be used for testing the publication bias. If publication bias will be found, then the trim and fill method would be used to both identify and correct the asymmetry of funnel plot. All two-tailed *p*-values < 0.05 will be defined as statistical significance. All the data analyses will be conducted using Stata (version 15.0, Stata Corp LP, College Station, TX, USA).

Patient and public involvement

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

Ethics and Dissemination

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

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

Discussion

Presentation of results and reporting

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

Potential resources of limitations

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

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

Contributorship statement

Cao B, Xu JT and Ma HJ conceived the study and developed the search strategy. Cao B drafted the protocol and tested the search strategies in consultation with a librarian. Li RN, Ding L and Liu J provided advice on the protocol. All authors critically revised the protocol for methodological and intellectual content and have read and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Data statement

No applicable.

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Figure Legend

Figure 1. PRISMA flow diagram of study selection process.

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-1β"[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-1β"[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

322

323

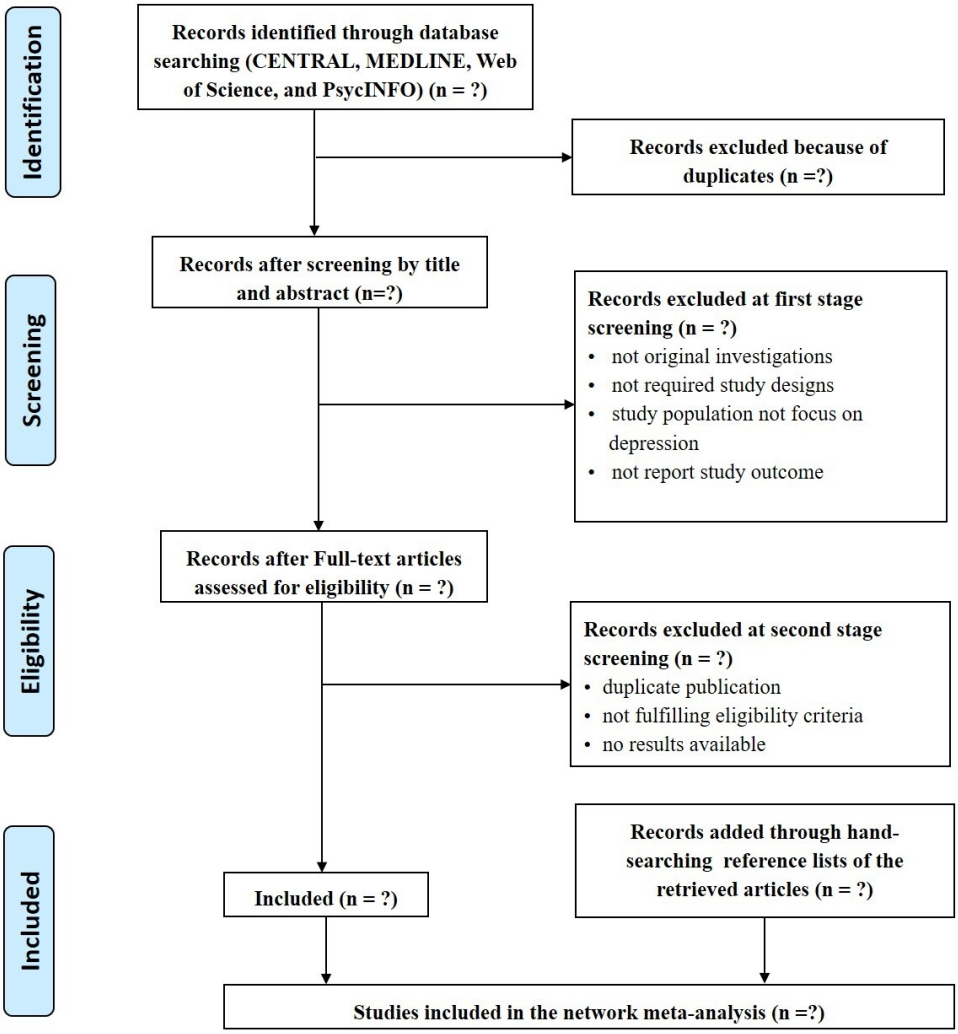

Figure 1. PRISMA flow diagram of study selection process.

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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		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			

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Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	7

		obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7-8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7-8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7-8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048162.R2
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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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Does Cognitive Behavior Therapy Affect Peripheral Inflammation of Depression? A Protocol for the Systematic Review and Meta-analysis.

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Word count

Abstract: 247 words; **Text:** 1806 words; **Figures:** 1; **Tables:** 1.

Abstract

Introduction: Cognitive behavior therapy (CBT) is becoming the most commonly implemented and standard treatment for depression. Up to date, only a few numbers of 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

Methods and analysis: This study will be conducted in accordance with the *Preferred 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).

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

Ethics and Dissemination: Formal ethical approval is not required by the National Ethical 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

depression will be disseminated through a peer-reviewed publication and inform the most up-to-date evidence of the roles of CBT treatment for depression.

Keywords: Depression; Cognitive Behavior Therapy; Inflammation; Cytokines; C-reactive protein

Article Summary

Strengths and limitations of this study

- This will be the first meta-analysis exploring the association between CBT and changes of peripheral inflammation of individuals with depression.
- The results could provide the most up-to-date evidence to assist in shared decision making between patients, caregivers, and clinicians in treating the individuals with depression by using CBT.
- An insufficient number of original researches is a possible limitation.
- Potential high heterogeneity may cause selection bias and also decrease the reliability of our results.

Introduction

Depression is a severe and the most prevalent form of mental illness that characterized by neurocognitive deficits and disability [1]. The disorder manifests in millions of individuals worldwide, and is a global health priority. The exploration of underlying mechanisms of depression are increasing over the past decades, none of them could clearly clarify the potential triggers of depression [2]. In recent years, the inflammatory processes are considered to be important contributors to depression. A systematic review and meta-analysis confirmed that a high proportion of depressed individuals showed signs of inflammation[3]. The potential bidirectional relationship of depression and inflammation were also clarified [4]. For instance, early infection and autoimmune diseases are highly associated with high risk of depressive disorders in adulthood [5]; evidence from preclinical and clinical researches reached a consistency that the concentrations of peripheral pro-inflammatory cytokines significantly increase in individuals or animal models of depression [6]. The inflammatory cytokines are mediators of environmental and genetic factors that may contribute to the development of depression from a biological perspective[7]. A previous study suggested that inflammation may be involved in some certain medical conditions, and it may activate the pathogenesis of depression by interfering with the monoamine, glutamate, and neurotrophic system [8]. Dowlat et al. 's study reported that major depression leads to immune dysregulation and activation of the inflammatory response system [9]. In addition, a growing body of evidence indicated that inflammation is thought to be an active process. The inflammatory process can affect multiple aspects of central nervous system function, and leads to behavioral changes in individuals with depression [10]. The results of several meta-analyses have proved that depression is related

to chronic low-grade inflammation. It is manifested by higher concentrations of peripheral C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), compared with healthy controls [11 12]. Above findings have facilitated the development of the inflammatory hypothesis of depression, and have also predicted that inflammation plays a role in the formation, progression and perpetuation of depression.[13 14]. Cognitive behavior therapy (CBT) is becoming the most commonly implemented and standard treatment for depression [15]. Briefly, CBT is based on the premise that false beliefs and negative thoughts are the main causes of depression. The individuals develop strategies for managing and preventing depressive symptoms by monitoring mood symptoms and utilizing a repertoire of coping skills to manage stress in CBT [16]. A meta-analysis found that there is no difference in treatment effects of CBT and second-generation antidepressants, either alone or in combination[17]. Recent published literatures illustrated that similar with antidepressant treatment, CBT may also contribute to reduction of chronic low-grade peripheral inflammation[18]. However, the underlying biological processes of the CBT effects on depression are still very limited.

To date, only a few numbers of studies have investigated the potentially anti-inflammatory effects of CBT for depression. Results are inconsistent among studies. For example, some researches pointed out that peripheral IL-6 was decreased after CBT, while no significant changes were founded in other studies [19]. Keri et al. (2014) reported that in adults with a first episode of depression, 16 weeks of CBT alone was associated with a reduction in TLR-4 signaling, but no change in TLR-2 signaling, IL-6, or CRP levels. This study suggested that it took longer time or other mechanisms for them to normalize [20]. Additionally, whether the alterations of inflammatory cytokines associated with

improvements in depression after CBT treatment is also not well established. So far it is worthy to conduct a systematic review and meta-analysis to summarize the most updated research results for the role of CBT treatment in inflammation of depression.

Aims and Objectives

The current study aims to provide a comprehensive, systematic review of the association between CBT and inflammation of individuals with depression, and clarify the alterations of inflammatory cytokines pre- and post- CBT treatment by meta-analysis. From the previous evidence, we hypothesized that some inflammatory cytokines, such as CRP, IL-6, TNF-α, may decrease after the CBT intervention.

Methods

Search Strategy

The systematic review and meta-analysis will be conducted and reported in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement [21]. **Figure 1** summarizes the study selection as a PRISMA flowchart. A systematic search of predetermined terms will be conducted with electronic databases of CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to July 2021. The keywords of our search strategy will be the key terms mapped to subject headings for (i) depression (major depressive disorder, depression, mood disorder, dysthymic disorder); (ii) CBT (psychotherapy, cognitive therapy, cognitive behavioral therapy); (iii)

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

Selection Criteria

The studies conducting the within-group comparisons of the peripheral levels of cytokines and chemokines in participants with depression at baseline and after CBT will be included in the current meta-analysis. Study eligibility for the inclusion criteria will be assessed by the approach of Population, Intervention, Comparison, Outcome and Study Design (PICOS). Moreover, according to the quality assessment recommendation of Cochrane Collaboration, we will use Newcastle-Ottawa Scale (NOS) to evaluate the quality of the included literatures [22]. Population: adult subjects (≥18 years old) meeting the major depression diagnoses by the Diagnostic and Statistical Manual of Mental Disorders (DSM; no restrictions on editions) or International Classification of Diseases and Related Health Problems (ICD) criteria; Intervention and Comparison: assessed the results of peripheral inflammatory cytokines (e.g., IL-6, CRP or IL-10) before and after CBT. Outcome: reported mean or median resting levels of inflammatory cytokines in saliva, blood, or urine was reported before and at least once after starting CBT, or the effect size (ES) could be calculated from the reported results. Study Design: random controlled trial (RCT), open-label study, or longitudinal study with pre-test-post-test design. Exclusion criteria of the studies will meet if they (1) did not focus on evaluating inflammatory cytokines levels on depression; (2) only reported stimulated levels of cytokines; (3) were repetitive publications from the same datasets by the same or different authors; (4) included participants who have been receiving pharmacological treatment in the past one month.

Outcome Measures and Data Extraction

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

Statistical analysis

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

testing in meta-analysis, which means we will produce a rejection p-value of 0.05 divided by the total number of outcomes [23]. The heterogeneity across the studies will be evaluated by chi-square statistics and I-Squared (I^2) test. A value of $P<0.10$ or $I^2>50\%$ indicated that the heterogeneity of effect estimates within each group of studies was statistically significant [24], and it also shows that the percentage of the variability in effect estimates owes to heterogeneity rather than chance. Furtherly, the subgroup analysis and meta-regression will also be performed to investigate the source of the heterogeneity, and the potential influence of included characteristics of the studies on the pooled effect size. Sensitivity analysis was performed to strengthen the results and investigate whether any single study would have an effect on the heterogeneity of total measurements in each meta-analysis. Additionally, the positive and negative results may not be equally likely to get published, thus the funnel plot with Begg's test and Egger's test will be used for testing the publication bias. If publication bias will be found, then the trim and fill method would be used to both identify and correct the asymmetry of funnel plot. All two-tailed *p*-values < 0.05 will be defined as statistical significance. All the data analyses will be conducted using Stata (version 15.0, Stata Corp LP, College Station, TX, USA).

Patient and public involvement

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

Ethics and Dissemination

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

2020 to October 2021. The results will be disseminated through a peer-reviewed publication and inform the most up-to-date evidence of the roles of CBT treatment for depression.

Discussion

Presentation of results and reporting

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

Potential resources of limitations

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

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

Contributorship statement

Cao B, Xu JT and Ma HJ conceived the study and developed the search strategy. Cao B drafted the protocol and tested the search strategies in consultation with a librarian. Li RN, Ding L, Liu J and Xue J provided advice on the protocol. All authors critically revised the protocol for methodological and intellectual content and have read and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Data statement

No applicable.

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Figure Legend

Figure 1. PRISMA flow diagram of study selection process.

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-1β"[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-1β"[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

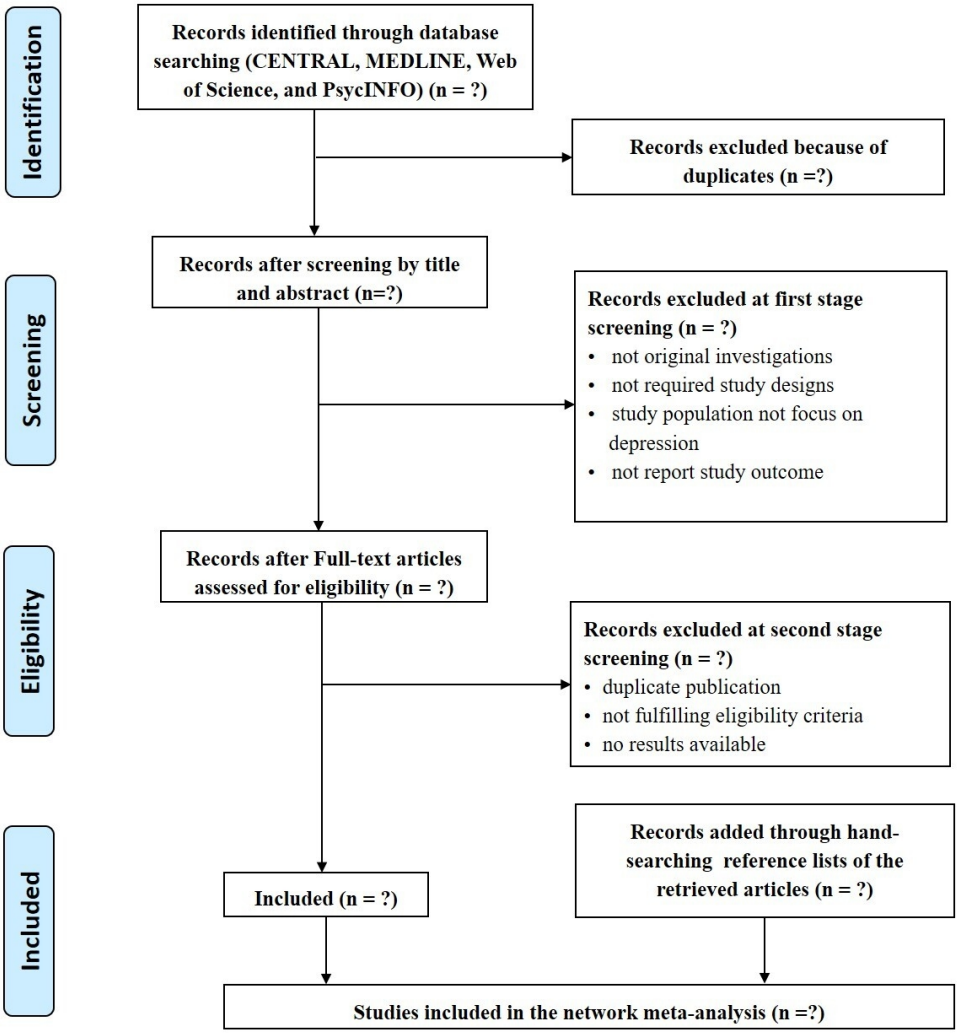

Figure 1. PRISMA flow diagram of study selection process.

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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		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			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	7

		obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7-8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7-8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7-8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8