PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does Cognitive Behavior Therapy Affect Peripheral Inflammation of Depression? A Protocol for the Systematic Review and Meta-analysis.
AUTHORS	Cao, Bing; Li, Ruonan; Ding, Ling; Xu, Jiatong; Ma, Haijing; Liu, Jie; Xue, Jian

VERSION 1 – REVIEW

REVIEWER	Christian Rück Karolinska Institutet, Department of Clinical Neuroscience
REVIEW RETURNED	17-Feb-2021

GENERAL COMMENTS	Thank you for letting me review this study protocol. I found it in general to be interesting and concise. I have a number of concerns and comments, listed here: 1. I think the authors should make the rational for the study clearer. Please be more specific with how depression in humans has been linked or not to the biomarkers of interest and how CBT would moderate those. 2. There are a lot of language issues. Examples include: Row 57 “is” is missing before “a global health priority” Row 59- This sentence needs clarification: 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. Please provide the evidence here. The sentence following that has language issues as well. Row 64: “The cytokines, considered as molecular signals of sickness,…” I think this is probably a error here, I am thinking the cytokines are not sickness signals? Please note that depression is typically referred to as a disorder. This section could benefit from some more detail, the pros and cons of the mentioned studies and what to make of them: Previous meta-analyses pointed out that pharmacological interventions could affect the levels of cytokines, for instance, Interleukin (IL)-6, C-reactive protein (CRP) . 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. Row 71: I do not think that there is a consensus that the change in behaviour is mediated via cognitive changes. Row 78: Please provide a reference. Row 83: it would be interesting to know more about why the results may differ. Aims: I am wondering, if you look at changes in cytokines before and after but do not use a control group, how do you know that the changes are related to CBT and not merely are a variation over

	time? Or will studies with control groups be used? How will you deal with multiple testing (multiple biomarkers)? I would recommend that you incorporate measures of study quality as well, in line with the quest for open science. Maybe the Newcastle-Ottawa Scale (NOS) would work.

REVIEWER	antoine yrondi CHU Toulouse, Psychiatry
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	This is an interesting protocol focusing on the influence of CBT on inflammation during depressive episode. However, some points should be improved. It would better whether authors used major depressive episode (MDE) instead of depression. Indeed, MDE is well defined unlike depression. Moreover, in the sentence “Recent published literatures illustrated that similar with antidepressant treatment, CBT may also contribute to reduction of chronic low-grade peripheral inflammation”, References are missing. In addition, authors should exclude all studies including patients with treatment that could have anti-inflammatory properties.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Christian Rück, Karolinska Institutet

Comments to the Author:

Thank you for letting me review this study protocol. I found it in general to be interesting and concise.

I have a number of concerns and comments, listed here:

1. I think the authors should make the rational for the study clearer. Please be more specific with how depression in humans has been linked or not to the biomarkers of interest and how CBT would moderate those.

Response: *We appreciate the thoughtful comment from the reviewer. According to reviewer’s suggestion, we have added more detailed description and evidence in the introduction section. The added sentences are as follows: “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."; "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." (Page 4, lines 69-77; Page 5, lines 96-100)

2. There are a lot of language issues. Examples include:

Row 57 "is" is missing before "a global health priority"

Response: *Thanks for the reviewers' comments and pointing out the grammatical errors. We have corrected the problems. Also, we have proofread the entire article carefully, edited and corrected some minor mistakes. We truly hope that these minor mistakes will not reduce your interest of the current article.*

Row 59- This sentence needs clarification: 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. Please provide the evidence here. The sentence following that has language issues as well.

Response: *According to the original literature, the sentence has been rephrased to "The inflammatory cytokines as mediators of environmental and genetic factors that may contribute to the development of depression from a biological perspective." (Page 4, lines 67-69)*

Row 64: "The cytokines, considered as molecular signals of sickness,…" I think this is probably a error here, I am thinking the cytokines are not sickness signals? Please note that depression is typically referred to as a disorder.

Response: *We have added the clarification and detailed evidence in the introduction section. The rephrased and added sentences are as follows: "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 patients showed signs of inflammation3. 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." (Page 4, lines 60-67)*

This section could benefit from some more detail, the pros and cons of the mentioned studies and what to make of them: Previous meta-analyses pointed out that pharmacological interventions could affect the levels of cytokines, for instance, Interleukin (IL)-6, C-reactive protein (CRP) . 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.

Response: *We appreciate the thoughtful comment from the reviewer. We have rephrased the sentences to "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.". Moreover, we also added more detailed information in the introduction section. (Page 5, lines 70-83)*

Row 71: I do not think that there is a consensus that the change in behaviour is mediated via cognitive changes.

Response: *Based on a careful review of the literature of the relavant studies, we have rephrased the sentence to "Briefly, CBT is based on the premise that non-helpful faith and negative thoughts are the main causes of depression." (Page 5, lines 84-85)*

Row 78: Please provide a reference.

Response: *We have added a related reference.*

Reference:

Lopresti AL. Cognitive behaviour therapy and inflammation: A systematic review of its relationship and the potential implications for the treatment of depression. Aust N Z J Psychiatry 2017;51(6):565-82. doi: 10.1177/0004867417701996 [published Online First: 2017/04/07]

Row 83: it would be interesting to know more about why the results may differ.

Response: *We have added a sample of different results. "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 ." (Page 5, lines 96-100)*

Aims: I am wondering, if you look at changes in cytokines before and after but do not use a control group, how do you know that the changes are related to CBT and not merely are a variation over time? Or will studies with control groups be used?

Response: *We appreciate for reviewer's thoughtful question. As mentioned in our introduction section, several pervious systematic reviews and meta-analyses has analyzed the differences of cytokines between depression and healthy controls. Thus, our meta-analysis will not included healthy controls. We know the reviewer's concern that our results may only reflect the changes over time, rather than the effect of CBT intervention. However, it is not easy to include a parallel treatment group as a control group when compare with the results of CBT. Because different studies of CBT intervention might have control group with different antidepressants, and some researches did not set such a control group. In the new version of manuscript, we added a exclusion criteria to exclude the participants who have been receiving pharmacological treatment in the past one month. In addition, in*

the discussion section of the formal article, we will cite the results of changes in cytokines before and after antidepressants, which will also assist the interpretation of our results.

How will you deal with multiple testing (multiple biomarkers)?

Response: *We have added the statistic analysis. After searching the literature, we think the Bonferroni adjustment should be performed to deal with multiple testing. Thus, we added the description of multiple testing in the method section, " We will conduct the 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." (Pages 8-9, lines 166-168)*

Reference:

Ng A, Tam WW, Zhang MW, et al. IL-1beta, IL-6, TNF- alpha and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep 2018;8(1):12050. doi: 10.1038/s41598-018-30487-6 [published Online First: 2018/08/15]

I would recommend that you incorporate measures of study quality as well, in line with the quest for open science. Maybe the Newcastle-Ottawa Scale (NOS) would work.

Response: *Thanks for reviewers suggestion, we have added the description of quality assessment, "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". (Page 7, lines 130-132)*

Reviewer: 2

Dr. antoine yrondi, CHU Toulouse

Comments to the Author:

This is an interesting protocol focusing on the influence of CBT on inflammation during depressive episode. However, some points should be improved.

It would better whether authors used major depressive episode (MDE) instead of depression. Indeed, MDE is well defined unlike depression.

Response: *We truly agree with reviewer's comments that it would better to use major depressive episode (MDE) instead of depression in the inclusion criteria. However, after preliminary literature search, We think that if we use major depressive episodes (MDE) instead of depression, then a large number of studies will not meet our inclusion criteria. According to reviewer's comment, our alternative solution is to use a subgroup analysis to surmise the groups of MDE or not. We have added "whether it is a major depressive episode (MDE)" as one of variables that should be extracted. (Page 8, lines 153-154)*

Moreover, in the sentence "Recent published literatures illustrated that similar with antidepressant treatment, CBT may also contribute to reduction of chronic low-grade peripheral inflammation", References are missing.

Response: *We have added the reference of mentioned sentence.*

Reference:

Lopresti AL. Cognitive behaviour therapy and inflammation: A systematic review of its relationship and the potential implications for the treatment of depression. Aust N Z J Psychiatry 2017;51(6):565-82. doi: 10.1177/0004867417701996 [published Online First: 2017/04/07]

In addition, authors should exclude all studies including patients with treatment that could have anti-inflammatory properties.

Response: *We have added an exclusion criteria in the methods section. Exclusion criteria of the studies will meet if they(4) included participants who have been receiving pharmacological treatment in the past one month. (Page 7, lines 143-144)*