Author’s response to reviews


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Author’s response to reviews:

Dear Prof Cheungpasitporn,

Thank you for providing the reviewers' comments for our recent Systematic Review Protocol entitled: “Evaluation of the effect of insulin sensitivity-enhancing lifestyle- and dietary-related adjuncts on antidepressant treatment response: Protocol for a systematic review and meta-analysis”. We are grateful for the observations of the reviewers and have provided below our responses to same.

We look forward to the decision of the Journal in the very near future.

Best regards,

Benedict K. Ryan, PhD.

Abstract:

* Line 45: I do not think the term "cohort" is appropriate in this context. Please adjust.

Response: This section has now been rephrased to read “in some depressed patients” - Line 44 (in the revised manuscript; see track changes)
* Lines 48 - 50: If I understood well, the objective of your review is "to evaluate the effectiveness of insulin sensitivity-enhancing lifestyle and dietary-related adjuncts in improving antidepressant treatment response". This is not what I understand when reading the last sentence of the "Background" section of the abstract. Please adjust.

Response: Understanding has been improved by restructuring the sentence (Lines 48-51).

* Lines 51 - 58: The way it is actually phrased, the "Methods/design" section of the abstract seems to mainly describe the objectives (from line 51 - 55) and not the actual methodology. Please adjust.

Response: This section has now been appropriately adjusted (Lines 55-60).

Background:

* General on the whole section: The "Background" section is quite long but repetitive and not convincing enough. I believe that the subject of this review is very pertinent, but the "Background" section doesn't really convince me of that. It includes too much information on associations between IR and depression/depression treatment response and is missing/lacking explanations of mechanisms may explain that IR is more prevalent in individuals with depression or vice-versa. Why might the presence of IR in individuals with depression impair response to common pharmacological treatments? This section also misses explanations on mechanisms linking the lifestyle adjuncts to IR and depression - you only briefly mention that the lifestyle adjuncts can help to improve both insulin sensitivity and depression symptoms (this should be discussed before the discussion section). Please 1) check for repetitions, 2) explain the link between IR and depression/depression treatment response, and 3) describe (or at least mention) most common mechanisms linking lifestyle adjuncts to IR and depression.

Response:

1) Repetitions have now been removed- e.g. Lines 179-180 (in the revised manuscript; see track changes)

2) The background now includes further explanation of the link between IR and depression/depression treatment response- Lines 123-137

3) The most common mechanisms linking lifestyle to IR and depression are now mentioned- Lines 137-142.

* Lines 69 - 73: In the DMS III and IV, chronic depression is a specifier of major depressive disorder and not a diagnosis by itself. The way it is phrased it leads to thinking that chronic depression is a diagnosis by itself, and the difference between persistent depressive disorder/dysthymia and chronic depression is not apparent. Please modify this passage to
improve understanding by the reader. I also suggest, once the variations in terminologies between DMS IV and V are explained, to stick to one term throughout the whole text.

Response:

- This section has now been adjusted, as recommended- Lines 74-80
- From this section forward, dysthymia (instead of PDD/dysthymia) is now used throughout the manuscript e.g. See Line 217

* Line 84: I don't think the term "cohort" is appropriate in this context. Please adjust.

Response:

Adjusted as requested- now Line 94.

* Line 100: Influenced/undermined - please choose one term (I believe "influenced" could be better in this context).

Response: Amended as suggested.

* Lines 127 - 129: "...with insomnia being more frequently reported". While this is true, depressions that are resistant to pharmacological treatment are more likely to be atypical. Individuals with atypical depression usually experience hypersomnia. In your discussion (lines 395 - 399). You explain some potential mechanisms linking sleep to depressive symptoms, and these mechanisms have mostly been suggested in contexts of sleep deprivation. I believe it could be pertinent to explain the possible effects of both insomnia and hypersomnia on depression pathophysiological pathways.

Response: This suggestion has now been effected in the discussion- Lines 483-488 (in the manuscript)

Objectives:

* The last paragraph of the "Background" section and the "Objectives" section are repetitive. In the "Objectives" section you are repeating your hypothesis and are stating what the main aim of the review is twice (first sentence (lines 147 - 149) and last sentence (lines 152 - 158)). As written in lines 147 - 149, the main aim of the review is, in my opinion, very clear. The last sentence of the paragraph is confusing. When you write "the effect of the insulin sensitivity-enhancing adjuncts (exercise; probiotics; ...), collectively, in improving depressive symptoms ...", the word collectively leads to thinking that you are looking for studies with interventions
including ALL the lifestyle-related adjuncts that you enumerate just before. Revising the last paragraph of the introduction and the "objectives" for clearness and conciseness (perhaps an "objectives" section isn't needed - the objectives could just be presented at the end of the "Background" section and the variables will be explained in the "Methodology" section.

Response:

This adjustment has been made as recommended. The ‘’objectives’’ section has been removed (Lines 186-198) and now the objectives are more clearly presented at the end of the background section (Lines 182-185)

Methodology:

* Lines 171 - 172: Please include an explanation (ideally a physiological one in relation to the outcome measures) for your choice of including studies with an intervention duration of 4 weeks or more.

The explanation for this is now included (Lines 226-228).

* Lines 173 - 195: At the beginning of the section describing the intervention types, you state that all types of lifestyle and dietary-related intervention having the potential to influence IR will be considered. However, as presented in lines 173 - 195, you seem to only include 5 types of interventions. No rationale was included as to why you chose physical activity, vitamin D, zinc, probiotics and hygienic-dietary recommendations, and do not include other interventions. For example, the Mediterranean diet (*you actually mention the healthy/Mediterranean diet in the "Background" section (line 120) but not in the methodology), omega-3 polyunsaturated fatty acids, monounsaturated fatty acids, as well as magnesium also appear to impact both mood and insulin sensitivity. Therefore, if you decided to focus on the 5 selected "types" of interventions for some specific reasons, please explain why. If not, you should include all types of lifestyle-related interventions and therefore make the necessary changes throughout the manuscript (i.e., in the methodology section, but also background and discussion where you mention these specific intervention types). Since a healthy diet and physical activity are part of the hygienic dietary recommendation***, why wouldn't you also include (if any) interventions including only sleep hygiene and only light exposure? These do not have to be done altogether to have an influence on IR and depression symptoms.

Response:

For completion, we have now included magnesium, omega-3 polyunsaturated fatty acids and monounsaturated fatty acids. We have also changed the word ‘all’ to ‘specified’ at the beginning of the intervention section (Line 223). The relevant sections (Abstract- Line 46, Background- Lines 149-163, Methodology- Lines 244-245; 255-259; 308-309, Discussions- Lines 444-445;
Healthy/Mediterranean diet mentioned in the background is actually included in the methodology, under the umbrella of ‘hygienic-dietary recommendations’ which is defined as the use of either the combination of the stated lifestyle and dietary-related adjuncts or any of them singly/individually used (Lines 47-48; 251-252, 447). Therefore, studies where any of these has been used as a stand-alone adjunct will also be included.

*** Shouldn't it be lifestyle "hygienic" recommendation rather than "dietary"?

Response:

The term ‘hygienic-dietary recommendations’ was taken from the study of Garcia-Toro et al. [64] which was identified from our preliminary search. We believe that the use of ‘dietary’ is appropriate in this context as it emphasizes to the reader that lifestyle interventions may potentially include interventions relating to diet, and/or other non-dietary lifestyle factors.

* Lines 196 - 201: Please include a brief explanation as to why you will only consider lithium and no other agents used as mood stabilizers for studies including bipolar depression.

Response:

While lithium is a commonly used mood stabilizer in the treatment of bipolar depression we acknowledge that other mood stabilisers are also potential treatment options. Recognising therefore the validity of these comments, we have now decided to consider all conventionally used mood stabilizers. See Lines 264-265.

* Lines 237: The search in electronic databases should be updated - the period of time between December 31st, 2017 and the future submission for publication of your systematic review is too long in my opinion. The date should be changed accordingly in the protocol.

Response:

This manuscript was submitted in February, 2018 and we had anticipated a journal response by Q1 2018. On this basis we had chosen a “cut-off” date of December 31st 2017. The journal response was however received in November 2018.

In recognition of the significant time-lapse which has occurred, we have decided to change the date to include publications up to 30th November, 2018. See Line 303.
The depression type (unipolar vs. bipolar), as well as the type of medication used (antidepressant vs. antidepressant + mood stabilizer), are also possible sources of heterogeneity and subgroup analyses for these variables might be necessary.

Response:

These recommendations have now been incorporated- Lines 424-427.

Discussion:

* To be adjusted according to changes made in the introduction. Perhaps, this section could include more on the scientific and clinical impact of the systematic review.

Response:

The recommended adjustments have now been made- Lines 444-447; 459-466; 476-480; 509-512.

Reviewer #2: Jeremiah et al present a protocol for the systematic review and meta-analysis on the 'Evaluation of the effect of insulin sensitivity-enhancing lifestyle- and dietary-related adjuncts on antidepressant treatment response'.

Overall it is a very interesting and well written protocol to evaluate the non-pharmacological treatments to help enhance the traditional treatment response to depression, which is a global epidemic affecting both rich and poor nations alike.

Minor points in the article which need clarification include, the following,

A. Any reason the authors have not registered the protocol with PROSPERO or Cochrane collaboration.?

Registration will help maintain transparency in the systematic review process, to assist in minimizing the risk of bias and help to reduce unnecessary duplication of the reviews.

Response:

We decided that publication of the protocol would achieve similar objectives as registering with PROSPERO and hence did not deem registration with PROSPERO as necessary. Taking account of these comments, we will endeavor to register with PROSPERO any future Systematic Reviews we will undertake.
B. Methods/design

- A comment on the language of the articles to be considered in the study is ideal. E.g. English language only vs English and others etc.

Response:
This has now been included- Lines 303-304.

- Under 'search strategy', does authors have any search constraints to describe or disclose?

Response:
No.

- Any type of publications or studies being excluded from the search?

Response:
No, apart from those that do not fit our inclusion criteria.

-On line '336-337', authors wrote, 'Where required study data is incomplete, or clarifications are needed, authors of the studies will be contacted during the study selection and data extraction process'.

Can they elaborate how and how many times they plan on contacting the authors of the included studies for this information?

Response:
This information is now stated in the protocol (Line 404).

Reviewer #3: This is very well written protocol. It is also important question to perform systematic review.

Response:
Thank you very much for taking your time to review this manuscript and for your favourable comments.
Reviewer #4: 1. The sentences need to be restructured to be made more simple and clear.

For eg: Background can be written as: depression is the leading cause of disability worldwide and is known to be associated with insulin resistance. Many studies have assessed the effect of exercise, vitamin D supplementation, zinc supplementation, probiotics and hygienic-dietary factors individually on antidepressant treatment response. Despite the established insulin sensitivity enhancing potential of these factors, no systematic review has collectively analyzed their antidepressant effect with regards to insulin sensitivity.

Response:

This has now been completed, as suggested- Lines 50-51

2. Others sentences that need to rewritten include: 51-54, 70-73, 74-79, 141-145 etc

Response:

All the sentences in question have now been restructured as appropriate- Lines 55-60, 74-80, 81-89, and 178-182.

3. Under Methods/Design- Types of studies mention: this systematic review will only include RCTs. This review is looking at RCTs for patients having depression also.

Response:

This section has now been reframed to capture the types of studies of interest- Lines 203-205.

4. After types of studies do inclusion criteria, then exclusion criteria and then interventions

Response:

Completed as requested. See Lines 206-266.

5. Treatment resistance is defined as failure to attain remission with at least two trials of adequate doses and duration of standard medications. What is the adequate dose and duration? In the inclusion or exclusion criteria you have not mentioned what medications participants are taking and how long to see if they are treatment resistant. The only criteria mentioned is that participants should have a diagnosis of MDD/PDD. If you are including people who got started on meds recently, then you cannot claim treatment resistance but just that there is improvement of insulin sensitivity in depression by the factors mentioned above.

Response:
Our systematic review is seeking to evaluate the effect of insulin sensitivity-enhancing lifestyle and dietary related adjuncts on antidepressant treatment response in patients with a clinical diagnosis of depression. It does not specifically focus on patients with treatment resistant depression, but rather seeks to establish whether interventions with known insulin sensitizing potential can potentiate the efficacy of antidepressant agents.

There is some debate in the literature regarding the precise definition of treatment resistant depression. In the manuscript we have employed the commonly used definition of treatment resistant depression. Treatment resistant depression refers to the situation where the depressed patient does not respond to adequate doses of two different antidepressants taken for a sufficient duration of time. An adequate dose of antidepressant means the licenced/approved dose of antidepressant for that particular agent while duration of treatment is usually taken to mean at least 4 weeks.

The antidepressant classes were stated in Lines 196-201 in the first manuscript, now Lines 260-266 in the revised manuscript.