Author’s response to reviews

Title: Probiotics for glycemic control in patients with type 2 diabetes mellitus: protocol for a systematic review

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Author’s response to reviews:

Dear Editor,

We would like to thank you and the reviewers for the kind suggestions. Please find our point-by-point responses below:

Reviewer #1: Thank you for sending me the article "Probiotics for glycemic control in patients with type 2 diabetes mellitus: protocol for a systematic review" for peer review. The authors make a great effort to justify their SR-MA, given the existence of recent SR, but emphasize the appearance of new clinical trials in recent years, and also interestingly add the comparison of the time of treatment with probiotics (long and short time). The protocol for the SR is very well written. It is noted that the authors have experience in the development of this research methodology. I believe that the form of presentation of the condition and intervention are clear for what they are looking for.

Response: We would like to thank you the reviewer for the time and effort reviewing our work and thank you for the compliment.

Reviewer #1: The objective is clear and coherent. I am concerned with the outcomes used in Health services outcomes: are you sure you have data from the clinical trials to extract this information? I recommend reviewing and considering them only if the information is feasible.
Response: Thank you for your kind suggestion. We considered that the health services outcomes are important factors for the guideline implementation and would like to include them. We are aware that these particular outcomes might not be available in the literature but their inclusion in our protocol would be a formal documentation of their existence.

Reviewer #1: The methodology to develop the search is clear and includes a broad search in the main databases and they hope to access clinical trial records and references of the identified articles. The assessment of the risk of bias with the Cochrane tool is clear. In addition, they innovate with the use of Covidence as a suitable software to use in SR. It is fantastic how they propose the evaluation of bias reporting. I ask you please include it clearly in the article. Almost that in a separate table where they show the reader their findings. It is likely that some of the articles do not even have records of their protocols. In case of identifying them, this should also be mentioned.

Response: Thank you so much for the compliments and suggestions. We will integrate them in our work.

Reviewer #1: I recommend improving the description of quality assessment with the GRADE tool, it is important to mention the domains of evaluation and the possible results of it. They adequately propose the evaluation of clinical and statistical heterogeneity; the justification of the MA and the sensitivity analyzes.

Response: Thank you for your suggestions. Regarding the GRADE tool, we have rewritten to “We plan to use the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence [51] for the primary outcomes (i.e. mean change in fasting blood glucose (mg/dL) from the baseline; mean change in glycosylated hemoglobin (%) from the baseline). We will use the five GRADE considerations (i.e. risk of bias, imprecision, inconsistency, indirectness and publication bias) and grade each outcome as follows [51]:

• High quality defined as we are very confident that the true effect lies close to that of the estimate of the effect.

• Moderate quality defined as we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

• Low quality defined as our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
• Very low quality defined as we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.”. In page 11-12, line 223-237.

Reviewer #1: I’m not sure if they overlooked it and did not want to annex it, but I cannot find the discussion of the article. Strongly recommending the inclusion of the discussion. It is a fundamental section for a publication. Also, in diabetes mellitus, it is necessary to mention the implications that the results may have. What has happened to the results of the other SRs published? has clinical practice varied with the results of these MA? In short, they have a large number of topics around the use of probiotics in type 2 diabetes that can be approached to the fullest in the discussion section.

Response: We have mentioned the discussion in page 5, line 91-107 in the “Mechanisms through which probiotics may improve glucose homeostasis” section and “Why it is important to do this review” section. We will add the dedicated Discussion section in the completed paper.

Reviewer #1: In conclusion, the article is very well conceived and written. However, as a reviewer I consider that it is necessary to include a discussion section to be accepted. For that reason my response to the editor is a major revision

Response: Thank you again for the compliments and suggestions. We are pleased to know that our protocol is satisfactory.

Reviewer #2: Thanks for inviting me to review this manuscript. In this protocol, authors aim to conduct a systematic review of randomised controlled trials that evaluated the effectiveness and safety of probiotics for glycaemic control in patients with T2DM. Overall, this is well written and devised protocol which adhered to the international standards of conducting systematic reviews (i.e. Cochrane). Few issues might help improving this protocol.

Response: We would like to thank you the reviewer for the time and effort reviewing our work and thank you for the compliment.

Reviewer #2: Introduction Page 5; lines 74-76: I would support these statements with evidence generated form systematic review and metanalysis.

Response: We agreed with the reviewer. However, since we would like to mention the data from the most recent year, unfortunately, to our best knowledge, there is no recent evidence generated systematic review and meta-analysis. We do hope that there will be one soon.
Reviewer #2: Authors mentioned that there are few systematic reviews which have synthesised data relevant to this question. I would expect more details about these reviews and why a new review is needed (e.g. this review has been conducted few years ago https://www.ncbi.nlm.nih.gov/pubmed/26899960).

Response: The review by Sun J and Buys NJ is a meta-analysis of randomised placebo-controlled trials that evaluated the effect of probiotics on glucose and glycemic factors in diabetes and its associated risk factors. Its result suggested that probiotics may be used as an important dietary supplement in reducing blood glucose in diabetes. However, their literature searches did not seem to be comprehensive (i.e. language, publication status, and date restrictions as well as inadequate search strategies). Therefore, there were short in the number of records identified through database searching (n= 546). In addition, the trials included had a short treatment duration period.

Reviewer #2: Methods Type of participants - authors should justify their decision to include people with prediabetes as this may varied widely between trials.

Response: We have rewritten to “We will include RCTs of participants of 18 years or older, of any sex, race/ethnicity, diagnosed with prediabetes (diagnosis as defined by the individual trial) or T2DM (diagnosis as defined by the individual trial).” in page 6, line 121-123.

Reviewer #2: Type of interventions - it would be great to briefly outline the differences between probiotics, prebiotics, and symbiotic.

Response: Thank you for your suggestion, regarding the probiotics, we have mentioned in page 4-5, line 78-90: Description of the intervention section. Regarding the prebiotics and symbiotic, we have rewritten to “We will include RCTs that the interventions are probiotics or synbiotics, which are defined as probiotics plus prebiotics (non-digestible food ingredients), of any type (i.e. fermented foods, functional foods and dietary supplements)…” in page 7, line 127-129.

Reviewer #2: Type of outcome measures - authors should explicitly articulate the short-term vs. long-term outcome measurements because the authors in the first sentences of this paragraph were talking about the duration of treatment with probiotics, which might not correlate with the timing of the outcomes.
Response: Thank you so much for your suggestion. The follow-up period was considered as a part of treatment duration and we decided to choose the outcome measurement at the longest follow-up time point, not at the end of the intervention.

Reviewer #2: I wonder if the authors have any plans to ask primary study authors specifically for data regarding the adverse events (since this is not commonly reported in the publications).

Response: Yes, we plan to ask primary study authors for incomplete or unclear information (as mentioned in page 9, line 189-191).

We hope that our responses are satisfactory. Should there is any comments or suggestions, please do not hesitate to let me know. Thank you very much for your kind consideration.

Best Regards,
Assist. Prof. Dr. Krit Pongpirul, MD, MPH, PhD.
On behalf of the authors