PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of non-pharmacological strategies in the management of type 2 diabetes in primary care: a protocol for a systematic review and network meta-analysis
AUTHORS	Leite, Renata GOF; Banzato, Luísa Rocco; Galendi, Julia SC; Mendes, Adriana L; Bolfi, Fernanda; Veroniki, Areti-Angeliki; Thabane, Lehana; Nunes-Nogueira, Vania dos Santos

VERSION 1 – REVIEW

REVIEWER	Siew Lim Monash University, Australia
REVIEW RETURNED	16-Oct-2019

GENERAL COMMENTS	Thank you for the opportunity to review this protocol paper on non pharmacological strategies in type 2 diabetes in primary care. This is an important topic, but there are several issues with the current manuscript, as described below. Firstly, could you please clarify how this systematic review is going to differ from the following from your group, as it seems like there is substantial conceptual overlap between the proposed protocol and the one below: Simões Corrêa Galendi J, Leite RGOF, Mendes AL, Nunes-Nogueira VDS. Effectiveness of strategies for nutritional therapy for patients with type 2 diabetes and/or hypertension in primary care: protocol of a systematic review of randomised controlled trials. BMJ Open. 2019 Sep 4;9(9):e030450. Overall the manuscript requires language support. The introduction needs restructuring to clearly present 1) the clinical importance of the issue, 2) current evidence on non pharmacological management of diabetes, in primary care setting or other setting, 3) the gap in the current literature. The literature review also did not include some key papers such as: • Franz MJ et al. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet. (2015) • Odgers-Jewell K et al. Effectiveness of group-based self-management education for individuals with Type 2 diabetes: a systematic review with meta-analyses and meta-regression. Diabet Med. (2017) The Registration Number section in page 4 is incomplete.

The Patient and Public Involvement section did not describe involvement of patients with type 2 diabetes.

It is unclear whether the non pharmacological strategies described should be implemented as standalone or adjunct to pharmacotherapy to be included in this review. For example, would an intervention of medication+lifestyle be included?

The use of NMA in meta-analysis to determine the effect of interventions is unconventional. Please provide a rationale on the benefit of choosing this approach over the conventional meta-analysis presenting pooled effect size with 95% confidence interval.

The section on transitivity on page 12 appears like moderator analysis that are usually assessed through meta-regression or subgroup analysis. Please explain the statistical approach chosen instead.

On page 14 line 46, it was stated that studies with imputed data will be excluded. You have mentioned earlier that intention-to-treat data are preferred when available. Please reconcile these differences.

REVIEWER	Rimke Vos
	Leiden University Medical Centre, the Netherlands
REVIEW RETURNED	19-Oct-2019

GENERAL COMMENTS	I read manuscript BMJOpen--2019-034481, a protocol aiming to evaluate the comparative effectiveness of nonpharmacological strategies in the management of T2DM in primary care or community settings by means of a systematic review and network analysis.
	I read the manuscript with pleasure. However, I have some comments, as listed below:
	Abstract:
	- The registration number is missing, this is also the case on page 7, row 39.
	Strength and limitations section:
	- I am not sure how familiar readers ar with the abbreviation NMA, I suggest to write out the abbreviation.
	- Statements are all quit general. May be the authors can include a statement indicating the strength of using a network meta-analysis over only a systematic review, instead of mentioning that this is the first paper doing so.
	Introduction:
	- The introduction is long, I would suggest to shorten the first more general part and emphasize earlier the gap in knowledge.
	- Row 36, suggestion to use young adults instead of young people.
	- NMA, introduce the abbreviation again in the main part of the protocol.
	Methods:

	- Page 7, row 34, should the word 'network' not be deleted since the 'N' of NMA stands for 'network'? - Page 8, row 11, abbreviation ADA and please include the definition cutoffs. - Page 9, row 50, suggestions to use setting instead of scenario - Page 9, row 60, what is the definition of secondary diabetes - Study section; why will four people independently review the title-abstracts. Will they all review all selected papers or will the authors make two duo's? - Why is the number of reviewers for data extraction two, and who will do this? Why are it not the same authors as for the selection of studies? - What if no consensus is reached, who will make the final decision, is there a fifths/ third author who will do this, who was not involved in the review process? - Page 12, why is medication adherence measured if the focus is on nonpharmacological interventions, I can imagen some reasons, but please explain. - Page 12, I would suggest to clearly indicate in the subtitle the description of the Network Meta-analysis (so use this term in the subtitle). - Can the authors explain a bit more what is meant with direct and indirect effect. - Page 14, please provide cutoffs for the subgroup analysis, e.g. mention the diabetes duration instead of longer time diabetes, and mention the number of complications instead of more complications. In other words give a clear definition of your subgroups.

REVIEWER	Sazlina Shariff Ghazali Universiti Putra Malaysia
REVIEW RETURNED	21-Oct-2019

GENERAL COMMENTS	Comments for Effectiveness of non-pharmacological strategies in management of type 2 diabetes in primary care: a protocol for a systematic review and network meta-analysis General comments • A comprehensive method section written by the authors • Require English language editing for this manuscript Abstract • Page 3, lines 44-50: The number of databases used for searches is not the same as those mentioned in the main text. Introduction • Page 7, lines 13-18: authors to provide the rationale of why network meta-analysis is needed in the context of management of T2DM • Page 7, lines 21-28: authors to provide explicit review questions using PICOS and the need to clearly state the outcomes of this review. One of the review questions would be as the one stated on page 16 line 39 Methods Eligibility criteria

<table>
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• Suggest rearranging the presentation of the eligibility criteria according to PICOS for better clarity

Definitions of intervention
• Page 8, line 27: What do the authors meant by this statement "to promote in diabetic patients a greater commitment to this condition" ?
• Page 9, line 24: suggest the secondary outcome "weight loss" to be changed to "anthropometric measurements"
• Page 9, line 37: what do the authors meant by these sentences: "The outcomes will be evaluated at 6, 12, and more than 12 months. For trials with outcomes within these time-points we will consider the closest time-point, and for those who had more than one time of outcome evaluation, we will consider the longest time-point."?
o Do you mean studies with outcomes that were evaluated in the selected studies at 6, 12 or more than 12 months will be included?

Data sources and search strategy
• Page 10, line 6:
o what do the authors meant by "4 search strategies created"? Does the authors mean "4 concepts created " for the search strategy?
o Suggest stating the total number of databases that search will be conducted.
• Page 10, line 13: The authors need to provide detail description of the intended index terms of the subject headings used for the searches. What are the keywords used and the combination intended to be used.
• Page 10, line 39: to provide citation to the software used.

Study selection
• Page 10: this section should include information on the criteria for selection of studies to be included in NMA

Data extraction
• Suggest presentation of the data items using the PICOS approach for better clarity
• Authors to clearly define all the outcomes to be extracted
• How will the authors extract data on interventions of the selected studies? Any checklist for this?

Discussion
• The review question on page 16 line 39 should be stated earlier before the objective/aim of this review.

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VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Thank you for your comments and suggestions that considerably improved the quality of our review protocol. All your suggestions were included in the revised manuscript, as presented below:

1. Firstly, could you please clarify how this systematic review is going to differ from the following from your group, as it seems like there is substantial conceptual overlap between the proposed protocol and the one below:
Response: This protocol differs from our previous published protocol because in the current systematic review, we will consider all non-pharmacological strategies for T2DM in primary care.

Additionally, here, we will perform a network meta-analysis combining direct and indirect comparisons of all strategies in a single model. In the previous protocol, only nutritional therapy has been evaluated in direct comparisons (only nutritional therapy versus usual care). We have included this explanation, in the methodology section (page 8, line 41)

2. Overall the manuscript requires language support.
Response: We have submitted the protocol to Editage for English editing. I have attached the certificate

3. The introduction needs restructuring to clearly present 1) the clinical importance of the issue, 2) current evidence on non-pharmacological management of diabetes, in primary care setting or other setting, 3) the gap in the current literature. The literature review also did not include some key papers such as: • Franz MJ et al. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet. (2015) • Odgers-Jewell K et al. Effectiveness of group-based self-management education for individuals with Type 2 diabetes: a systematic review with meta-analyses and meta-regression. Diabet Med. (2017)
Response: We have restructured all introduction and included the topics suggested, as well as the two references (introduction, page 4 (line 40) and 5 (line 3))

4. The Registration Number section in page 4 is incomplete.
Response: We have updated PROSPERO details (page 3 and 6)

5. The Patient and Public Involvement section did not describe involvement of patients with type 2 diabetes.
Response: We have included that a group of patients with type 2 diabetes during follow-up in a tertiary Brazilian healthcare also identified this study as a priority area for managing patients with T2DM in primary healthcare (page 6, line 56)

6. It is unclear whether the non pharmacological strategies described should be implemented as standalone or adjunct to pharmacotherapy to be included in this review. For example, would an intervention of medication+lifestyle be included?
Response: In order to clarify your important observation, we have included on page 7, line 37, the following paragraph:
"the strategies can be implemented as either standalone or adjunct to the pharmacotherapy of T2DM. Regarding adjunct treatment, both groups must have received similar drug treatment."

7. The use of NMA in meta-analysis to determine the effect of interventions is unconventional. Please provide a rationale on the benefit of choosing this approach over the conventional meta-analysis presenting pooled effect size with 95% confidence interval. Response: In order to clarify your important question, in the paper, on page 6 we have added the following paragraphs:
"NMA combines direct and indirect evidence; therefore, the relative effectiveness of two non-pharmacological strategies can be estimated even if studies that directly compared them did not exist. Denoting nutritional therapy, social support, and usual care as non-pharmacological strategies A, B, and C, respectively, an indirect comparison (AB) can be obtained by subtracting the meta-analytic estimates of all studies of nutritional therapy versus usual care (AC) from the estimate of all studies of social support versus usual care (BC).
Traditional meta-analyses are limited to the comparisons of two groups, failing to generate a complete picture of the effectiveness of non-pharmacological treatments for T2DM. In the current review, since there are more than 10 strategies of interest and for most there are no trials involving a direct comparison, the NMA was selected a substitute of the traditional meta-analysis."

8. The section on transitivity on page 12 appears like moderator analysis that are usually assessed through meta-regression or subgroup analysis. Please explain the statistical approach chosen instead.

Response: Transitivity is defined as the conceptual manifestation of consistency. We will assess whether there are possible effect modifiers vary considerably across treatment comparisons in the network, and if this is the case, we will use meta-regression or subgroup analysis to explore this further.

9. On page 14 line 46, it was stated that studies with imputed data will be excluded. You have mentioned earlier that intention-to-treat data are preferred when available. Please reconcile these differences.
Response: Thank you for this comment. We have updated this paragraph accordingly (page 14, line 32)

Referee 2
Thank you very much for your comments and suggestions that absolutely improved the quality of our review. All your suggestions were included in the revised manuscript, as you can see below:
1. Abstract: - The registration number is missing, this is also the case on page 7, row 39.
Response: We have included this registration number (page 3 and 6).
2. Strength and limitations section: - I am not sure how familiar readers are with the abbreviation NMA, I suggest to write out the abbreviation.
Response: We have written this out the abbreviation (page 3, line 34)

3. Statements are all quit general. May be the authors can include a statement indicating the strength of using a network meta-analysis over only a systematic review, instead of mentioning that this is the first paper doing so.
Response: We have included two statements indicating the strength of network meta-analysis
4. Introduction: - The introduction is long, I would suggest to shorten the first more general part and emphasize earlier the gap in knowledge.
Response: We have rewritten the introduction

5. Row 36, suggestion to use young adults instead of young people. - NMA, introduce the abbreviation again in the main part of the protocol.
Response: We have rewritten the introduction and removed this paragraph

6. Methods: - Page 7, row 34, should the word 'network' not be deleted since the 'N' of NMA stands for 'network'?
Response: We have rewritten this phrase

7. Page 8, row 11, abbreviation ADA and please include the definition cutoffs.
Response: We have rewritten this phrase and included the cutoffs (page 7, line 37)

8. Page 9, row 50, suggestions to use setting instead of scenario
Response: We have changed this word (page 9, line 27)

9. Page 9, row 60, what is the definition of secondary diabetes
Response: We have defined as being due to drugs or chronic disease (page 9, line 37)

10. Study section; why will four people independently review the title-abstracts. Will they all review all selected papers or will the authors make two duo's? - Why is the number of reviewers for data extraction two, and who will do this? Why are it not the same authors as for the selection of studies?
Response: Thank you for important question, we will select in four because we imagine that after searching in the literature, we will find out a big amount of studies. In order to avoid mistakes in the selection process we will work in pairs and independently, according to the standard Cochrane recommendation for systematic reviews.

11. What if no consensus is reached, who will make the final decision, is there a fifths hird author who will do this, who was not involved in the review process?
Response: We have rewritten this phrase (page 10, line 38)

12. Page12, why is medication adherence measured if the focus is on nonpharmacological interventions, I can imagen some reasons, but please explain.
Response: We have chosen to evaluate medication adherence as an outcome because many patients are with the diabetes in uncontrol status because they do not take the pharmacological treatment properly. Due to that some strategies have as objective to improve the patient compliance to the drug treatment, for example diabetes self-management education and support (DSMES). However, after your observation, we have discussed this measurement and concluded that as transitivity across treatment comparisons, medication adherence is not applicable, and removed it from this section.

13. Page 12, I would suggest to clearly indicate in the subtitle the description of the Network Meta-analysis (so use this term in the subtitle).
Response: We have indicated Network Mata-analysis in the subtitle (page 12)

14. Can the authors explain a bit more what is meant with direct and indirect effect.
Response: We have explained on page 6 (the two first paragraphs of methodology) direct and indirect effect on network meta-analysis.

15. Page 14, please provide cutoffs for the subgroup analysis, e.g. mention the diabetes duration instead of longer time diabetes, and mention the number of complications instead of more complications. In other words give a clear definition of your subgroups.
Response: We have provided the definition that we will use in our subgroup evaluations (page 13, line 50)

Referee 3
Thank you very much for your comments and suggestions that absolutely improved the quality of our review. All your suggestions were included in the revised manuscript, as you can see below:

General comments
1. A comprehensive method section written by the authors. Require English language editing for this manuscript
Response: English language was edited by Editage. We have attached the certificate.
2. Abstract • Page 3, lines 44-50: The number of databases used for searches is not the same as those mentioned in the main text.
Response: In the reviewed manuscript we fixed the number of databases in the abstract section
3. Introduction • Page 7, lines 13-18: authors to provide the rationale of why network meta-analysis is needed in the context of management of T2DM
Response: We have rewritten the introduction, and in the last and next-to-last paragraph we provided the rationale of why network meta-analysis is needed. In addition, on methods section we have explained why NMA was chosen instead of traditional meta-analysis
4. Page 7, lines 21-28: authors to provide explicit review questions using PICOS and the need to clearly state the outcomes of this review. One of the review questions would be as the one stated on page 16 line 39
Response: We have provided two explicit review questions in the next-to-last paragraph of introduction (page 5, line 33).

Methods
5. Eligibility criteria • Suggest rearranging the presentation of the eligibility criteria according to PICOS for better clarity
Response: We have rearranged the presentation of eligibility criteria according to PICOT (page 7, line 9)

6. Definitions of intervention • Page 8, line 27: What do the authors meant by this statement "to promote in diabetic patients a greater commitment to this condition" Response: Thank you for this remark. We have removed this phrase. The objective of the intervention is diabetes control.

7. Page 9, line 24: suggest the secondary outcome "weight loss" to be changed to "anthropometric measurements"
Response: We have changed this (page 8, line 59)

8. Page 9, line 37: what do the authors meant by these sentences: "The outcomes will be evaluated at 6, 12, and more than 12 months. For trials with outcomes within these time-points we will consider the closest time-point, and for those who had more than one time of outcome evaluation, we will consider the longest time- point."? o Do you mean studies with outcomes that were evaluated in the selected studies at 6, 12 or more than 12 months will be included?
Response: In order to clarify the time evaluation, we have changed the paragraph as (page 9, line 16):
"We will include only studies with follow up greater than 6 months. The outcomes will be evaluated at 6 to 12 months and greater than 12 months. For trials that had more than one time of outcome evaluation, we will consider the longest time point."

9. Data sources and search strategy • Page 10, line 6: o what do the authors meant by "4 search strategies created"? Does the authors mean "4 concepts created " for the search strategy? o Suggest stating the total number of databases that search will be conducted.
Response: We have corrected this information (page 9, line 45)

10. Page 10, line 13: The authors need to provide detail description of the intended index terms of the subject headings used for the searches. What are the keywords used and the combination intended to be used.
Response: We have used the following index terms and their synonyms: Diabetes Mellitus, Type 2; Primary Health Care; and Community Health Planning (page 9, line 54)

11. Page 10, line 39: to provide citation to the software used.
Response: We have provided the software (Stata, page 12, line 36)

12. Study selection • Page 10: this section should include information on the criteria for selection of studies to be included in NMA
Response: We have corrected this paragraph: "Four reviewers independently will perform in pairs the assessment of titles and abstracts (RGOFL, LRB, JSCG, VSNN), and the studies potentially eligible for inclusion in the review will be selected for full-text reading and subsequently assessed for adequacy to the proposed PICOT." Page 10, line 31

13. Data extraction • Suggest presentation of the data items using the PICOS approach for better clarity • Authors to clearly define all the outcomes to be extracted. How will the authors extract data on interventions of the selected studies? Any checklist for this?
Response: We have rewritten the paragraph in the reviewed manuscript:
"For each selected trial, the same four reviewers will use in pairs and independently an extraction form to record the year of publication, number of patients included, duration of follow-up, information

regarding the inclusion and exclusion criteria, type of intervention (frequency, descriptions, durations), baseline data (average age, gender, weight, BMI and WC, glycemic control prior to the study, duration of T2DM, medications in use), and all reported outcome measures (in all time points)." Page 10, line 47

14. Discussion • The review question on page 16 line 39 should be stated earlier before the objective/aim of this review.
Response: We have moved the question to the introduction section (page 5, line 32)

VERSION 2 – REVIEW

REVIEWER	RC Vos LUMC, the Netherlands
REVIEW RETURNED	05-Dec-2019

GENERAL COMMENTS	The authors handled I my raised questions.

REVIEWER	Sazlina Shariff Ghazali Universiti Putra Malaysia
REVIEW RETURNED	06-Dec-2019

GENERAL COMMENTS	The authors have addressed all the comments made earlier