PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative long-term effectiveness and safety of primary bariatric surgeries in treating type 2 diabetes mellitus in adults: a protocol for systematic review and network meta-analysis of randomized controlled trials
AUTHORS	Ding, Li; Zhuo, Chuanjun; Fan, Yuxin; Zhang, Yalan; Li, Hui; Qi, Dongwang; Tang, Shaofang; Cui, Jingqiu; He, Qing; liu, ming

VERSION 1 - REVIEW

REVIEWER	Jøran Hjelmesæth Morbid Obesity Center, Vestfold Hospital Trust, Tønsberg, and University of Oslo, Norway
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	Li Ding and coauthors have written an excellent manuscript describing a protocol for a systematic review and network metaanalysis of randomized controlled trials regarding long-term effectiveness and safety of primary bariatric surgeries in treating type 2 diabetes mellitus in adults. This reviewer has only a few comments and questions. 1. It is discussable whether 3-years can be regarded as “long-term”, some would argue that < 1 year is short-term, 1-4 years medium-term, and 5 years or more “long-term”? 2. However, probably very few really long-term studies are available for analysis, and even a lower treshold of 3 years might result in very few rcts to include in the analysis? 3. The scientific language might be difficult to understand for clinicians/surgeons, and some central terms and sentences could have been explained in more common words, at least once. See for example page 3 lines 30-40. 4. Regarding Strengths and limitations (page 4), the sentence “….innovative scoring system ….” seems abstract and should be more precisely explained. 5. Page 8, line 48, “6%” is incorrect, do you mean “< 6%” (less than 6%), or “6% and below”? 6. Page 8, line 56, “6.5%” is incorrect, do you mean “< 6.5%” (less than 6.5%)? 7. Page 10, bullet point 2 weight loss: Most journals advocate to include total body weight loss percent (TBW%) as more appropriate than “excess weight loss”, or at least TBW% should be included in addition to EWL. Further, baseline BMI and body weight should be included (not only follow-up). Finally, an increasing number of studies include measurements of fat mass and fat free mass (BIA and/or DXA) which might be of great interest to understand the possible mediating effects of reduced fat mass on the primary (diabetes) and secondary (lipids, blood pressure) outcomes.

REVIEWER	Jennifer Donnan Memorial University of Newfoundland, Canada
REVIEW RETURNED	14-Feb-2019

GENERAL COMMENTS	The purpose of this study was to assess the examine the remission rates for type 2 diabetes in patient who undergo bariatric surgery. Overall, this was a very well designed study with robust methods and thorough analysis plans. Specific Comments: 1. While I see the benefit of conducting this study when reviewed in isolation, I am not sure how much will be added to the existing literature given the very recent publication of an NMA (Kodama, 2018) asking the same research question. That said, I recognize the uniqueness of narrowing the study question to only include longer durations of follow-up and there is a high likelihood that new RCTs will be published in the interim. So this may be able to provide a new perspective on this question. 2. My knowledge of bariatric surgery, at least in Canada, is that the biggest barrier is the limited number of surgeries conducting, severely limiting access. There are more people willing to accept the barriers that you have identified on page 18, lines 46-51 then there are available surgery slots. In Canada it is an excess demand/limit supply issue. 3. For the comparators included. It might be worth including the possibility of a no treatment comparator. It is reasonable to think that a group of patients with obesity (with or without diabetes) may be randomized to bariatric surgery or no active therapy. 4. Some very minor grammatical error to correct. For example: a. Page 4, line 14: Clinical, should be clinically b. Page 4, line 51: comparing should be compared

VERSION 1 – AUTHOR RESPONSE

Response 1: Response to Professor Hjelmesæth

Thank you for your enlightening comments to our manuscript. Here are our responses to your comments.

Comment 1. It is discussable whether 3-years can be regarded as “long-term”, some would argue that < 1 year is short-term, 1-4 years medium-term, and 5 years or more “long-term”?

Response 1. We completely agree that 5 years or more would be more proper for the term “long-term”. In fact, we agonized over the choices both for the threshold of 3 years vs. 5 years, and for the wording of long-term vs. mid-term vs. mid- to long-term, once we had agreed upon the threshold of 3 years. As you pointed out in your 2nd comment, it is highly likely that a higher threshold of 5 years may result in too few RCTs, especially in the arms of relatively new procedures, precluding meta-analysis. However, we indeed are very curious about the comparative long-term effectiveness and safety of primary bariatric surgeries in treating type 2 diabetes mellitus, we would like to work for it. We will collect two sets of data from both time points, 3 years and 5 years, if applicable, from the studies included, while the inclusion threshold of 3 year remain unchanged. We have revised the manuscript accordingly (page 8, lines 12-15 [in the clean version of the revised manuscript], page 32,

lines 19-23 [in the track change version of the revised manuscript]) under the section eligibility criteria – study designs, as well as corresponding items in “Supplementary Material 2 Preliminary Screening Questionts and Data Extraction Form (Revised)” (page 56, attrition, page 59-76 outcome data). Thank you again for your comment!

Comment 2. However, probably very few really long-term studies are available for analysis, and even a lower treshold of 3 years might result in very few rcts to include in the analysis?

Response 2. We concur. There is no way to tell for sure since we have not proceeded with screening of preliminary search results without consolidating the protocol with you. We will systemically review the literature, and see if we can get data with sufficient homogeneity for meta-analysis. We will keep track of ongoing studies, and update the systemic review at least every 2 years.

Comment 3. The scientific language might be difficult to understand for clinicians/surgeons, and some central terms and sentences could have been explained in more common words, at least once. See for example page 3 lines 30-40.

Response 3. Thank you very much for your great suggestion! We have revised the manuscript (page 3 lines 27-34, and page 12 lines 53-56[in the clean version of the revised manuscript], page 28, lines 27-34, and page 37 lines 4-7 [in the track change version of the revised manuscript]).

Comment 4. Regarding Strengths and limitations (page 4), the sentence “….innovative scoring system ….” seems abstract and should be more precisely explained.

Response 4. Thank you very much for your comment! We revised the sentence as “This protocol proposes a cumulative score based approach for integral assessment of safety of bariatric surgeries.” (page 4 lines 22-25[in the clean version of the revised manuscript], page 28, lines 22-25 [in the track change version of the revised manuscript])

Comment 5. Page 8, line 48, “6%” is incorrect, do you mean “< 6%” (less than 6%), or “6% and below”?

Response 5. Thank you very much for pointing it out. We have revised manuscript accordingly (page 8, line 46 [in the clean version of the revised manuscript], page 32, line 54 [in the track change version of the revised manuscript]).

Comment 6. Page 8, line 56, “6.5%” is incorrect, do you mean “< 6.5%” (less than 6.5%)?

Response 6. Thank you very much for pointing it out. We have revised manuscript accordingly (page 8, line 54 [in the clean version of the revised manuscript], page 33, lines 4 [in the track change version of the revised manuscript]).

Comment 7. Page 10, bullet point 2 weight loss: Most journals advocate to include total body weight loss percent (TBW%) as more appropriate than “excess weight loss”, or at least TBW% should be included in addition to EWL. Further, baseline BMI and body weight should be included (not only follow-up). Finally, an increasing number of studies include measurements of fat mass and fat free mass (BIA and/or DXA) which might be of great interest to understand the possible mediating effects of reduced fat mass on the primary (diabetes) and secondary (lipids, blood pressure) outcomes.

Response 7. We really appreciate your great comments. The manuscript has been revised accordingly (page 10 lines 14-20 [in the clean version of the revised manuscript], page 34, lines 22-28 [in the track change version of the revised manuscript]).

Response 2: Response to Professor Donnan

Thank you for your enlightening comments. Here are our responses to your comments.

Comment 1. While I see the benefit of conducting this study when reviewed in isolation, I am not sure how much will be added to the existing literature given the very recent publication of an NMA (Kodama, 2018) asking the same research question. That said, I recognize the uniqueness of narrowing the study question to only include longer durations of follow-up and there is a high likelihood that new RCTs will be published in the interim. So this may be able to provide a new perspective on this question.

Response 1. Thank you very much for your comment, and for finding merits in our proposal!

Comment 2. My knowledge of bariatric surgery, at least in Canada, is that the biggest barrier is the limited number of surgeries conducting, severely limiting access. There are more people willing to accept the barriers that you have identified on page 18, lines 46-51 then there are available surgery slots. In Canada it is an excess demand/limit supply issue.

Response 2. Thank you very much for your comment! It's a truly good point. The manuscript has been revised accordingly (page 18, line 54 [in the clean version of the revised manuscript], page 43, line 4 [in the track change version of the revised manuscript]).

Comment 3. For the comparators included. It might be worth including the possibility of a no treatment comparator. It is reasonable to think that a group of patients with obesity (with or without diabetes) may be randomized to bariatric surgery or no active therapy.

Response 3. Thank you very much for your comment! We have revised the manuscript for further clarification (page 7, line 53-56, [in the clean version of the revised manuscript], page 31, line 58 to page 32 line 4[in the track change version of the revised manuscript], under the section Eligibility Criteria - Comparators). We agree that patients with obesity (with or without diabetes) may be randomized to no active therapy. The rationale that we did not include a no treatment comparator was that we were focusing on patients with type 2 diabetes mellitus, so we assumed that the patients would at least receive usual care, with or without non-surgical interventions. As of potential bias and heterogeneity introduced by life-style interventions as control or during the follow-up period of bariatric surgeries, we would test the robustness of the findings by subgroup analysis whether adopting intensive life-style intervention as control or during the follow-up period of bariatric surgeries in the same effective arm.

4. Some very minor grammatical error to correct. For example:

Comment 4a. Page 4, line 14: Clinical, should be clinically

Response 4a. Thank you for pointing it out! The manuscript has been revised accordingly (page 4, line 14, as well as page 9, line 45 [in the clean version of the revised manuscript], page 28, lines 14 as well as Page 33, line 54 [in the track change version of the revised manuscript]).

Comment 4b. Page 4, line 51: comparing should be compared

Response 4b. Thank you for your comment! The manuscript has been revised accordingly (page 4, line 45 [in the clean version of the revised manuscript], page 28, lines 51 [in the track change version of the revised manuscript]

VERSION 2 – REVIEW

REVIEWER	Jøran Hjelmesæth Morbid Obesity Center Vestfold Hospital Trust Tønsberg and University of Oslo, Oslo NORWAY
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	The authors have responded well to my comments, and they changed the manuscript accordingly.

REVIEWER	Jennifer Donnan Memorial University of Newfoundland
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	Thank you for allowing me to review the revision to this manuscript. I have not further comments to add, the minor comments from my first review were addressed. Good luck with conducting this review, I look forward to seeing the results when they are published.