

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Weight loss surgery for obstructive sleep apnoea with obesity in adults: a systematic review and meta-analysis protocol
AUTHORS	Dong, Zhiyong; Hong, Brian Y; Yu, Ashley; Cathey, John; Shariful Islam, Sheikh Mohammed; Wang, Cunchuan

VERSION 1 – REVIEW

REVIEWER	Chris Turnbull Oxford University Hospitals NHS Foundation Trust
REVIEW RETURNED	20-Dec-2017

GENERAL COMMENTS	<p>This is a well written protocol addressing an important question of the safety and efficacy of weight loss surgery for obstructive sleep apnoea. The planned systemic review and meta-analysis should provide appropriate answers to this question. However, there are specific points I would like the authors to address:</p> <ol style="list-style-type: none">1. In the abstract and the introduction the authors state that OSA is the "source" of significant morbidity and mortality. The evidence that is available, and that they have quoted, is observational. This data shows an association between OSA and outcomes such as cardiovascular disease but does not show causation.2. This is not the first systematic review and meta-analysis to assess the efficacy of weight loss surgery (previous articles include PMID 25537297, 23299507, and 19486716). It is, to my knowledge, the first to address the safety of weight loss surgery in OSA. However, I am not sure if there will be sufficient data to assess this outcome.3. The authors refer to a comparison of upper airway surgery with weight loss surgery but I do not understand how this will help the authors with the main objectives.4. In the discussion of how weight loss surgery might lead to improvements in OSA the authors refer to reduced extra-luminal narrowing by weight loss surgery reducing neck circumference. Obesity could also contribute to OSA by abdominal/thoracic adiposity reducing FRC and reducing caudal traction on the pharynx leading to increased upper airway collapsibility, or via increased upper airway adiposity such as tongue fat. The authors include measurements of waist circumference and neck circumference and should therefore be able to assess for any changes in abdominal adiposity as well as extra-luminal neck fat.5. In the methods the authors state that they will only include RCTs and will exclude observational studies. In an earlier section authors state that they might include non-randomised control trials if RCT
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	data is lacking. Clarification as to whether non-randomised control studies will be included would be helpful.
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REVIEWER	Marta Drummond Centro Hospitalar São João, Porto, Portugal, Medicine Faculty Porto Portugal
REVIEW RETURNED	15-Feb-2018

GENERAL COMMENTS	<p>This manuscript is an intention to perform a metanalysis and systematic review comparing surgical procedures as different as bariatric surgery and other surgeries aiming to reduce respiratory events during sleep. This is a methodological error, the metanalysis should only include the several types of bariatric surgery or ORL surgeries or maxillo facial surgeries, etc. why comparing such different procedures with one another as they are used in different phenotypes of OSA patients?</p> <p>Both the abstract and the article are too long and repetitive and does not add to the scientific knowledge in this field. The english needs improvements. The objectives and methods are clearly pointed. It would be very intersting to see the results of a metanalysis comparing different bariatric surgery procedures.</p>
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REVIEWER	Verbraecken Johan Antwerp University Hospital and University of Antwerp, Belgium
REVIEW RETURNED	17-Feb-2018

GENERAL COMMENTS	<p>Dong et al have planned to perform a meta-analysis in weight-reduction surgery for obstructive sleep apnoea with obesity in adults. They have described their approach in the manuscript submitted. The paper is well written, and the protocol reports the objectives, methods (eligibility, search methods) is an adequate manner. Guidance is also given on assessment of risk of bias, heterogeneity, and finally, sensitivity analysis.</p> <p>The authors report that they will also include unpublished data (page 7/20 line 36). This is very unusual, and the authors should explain precisely what they mean.</p> <p>Minor comments:</p> <ul style="list-style-type: none"> - page 3/20 line 30: The primary outcomes that will be measured are ... - page 4/20: line 20: various types - page 5/20: line 45: diagnosis of OSA. After subsequent (...years), they ... - page 5/20: line 54: apnea-hypopnea index - page 7/20: line 33: assessed - page 8/20: line 44: measured - page 8/20: line 46: one month - page 12/20: line 20: ...obtained. That is, ... - page 12/20: line 44: RCTs, ... - page 13/20: line 7: heterogeneity, - page 14/20: line 14: "middle-aged patients" instead of "Adult patients" ? - page 15/20: line 1: currently, ... - page 15/20: line 17: required, ... - page 19/20: line 3: adjusted
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Comments:

Reviewer reports:

Reviewer #1 Chris Turnbull:

This is a well written protocol addressing an important question of the safety and efficacy of weight loss surgery for obstructive sleep apnoea. The planned systemic review and meta-analysis should provide appropriate answers to this question. However, there are specific points I would like the authors to address:

Authors' response: We thank you for reviewing our manuscript and for the valuable comments.

Point to point:

1. In the abstract and the introduction the authors state that OSA is the "source" of significant morbidity and mortality. The evidence that is available, and that they have quoted, is observational. This data shows an association between OSA and outcomes such as cardiovascular disease but does not show causation.

Authors' response:

We agree, and we have rewritten the first paragraph of our introduction to address this comment. It has also been edited again by our native English-speaking coauthor.

2. This is not the first systematic review and meta-analysis to assess the efficacy of weight loss surgery (previous articles include PMID 25537297, 23299507, and 19486716). It is, to my knowledge, the first to address the safety of weight loss surgery in OSA. However, I am not sure if there will be sufficient data to assess this outcome.

Authors' response:

Thank you for your comment. Yes; it is the first study to address the safety of weight loss surgery in OSA. During a preliminary search, we have identified five RCTs that met inclusion criteria. We believe there will be insufficient data to assess this outcome. In that case, we will include nonrandomized controlled trials or cohort studies.

3. The authors refer to a comparison of upper airway surgery with weight loss surgery but I do not understand how this will help the authors with the main objectives.

Authors' response:

You are right. We have rewritten the types of interventions in our method section to remove this comparison.

4. In the discussion of how weight loss surgery might lead to improvements in OSA the authors refer to reduced extra-luminal narrowing by weight loss surgery reducing neck circumference. Obesity could also contribute to OSA by abdominal/thoracic adiposity reducing FRC and reducing caudal traction on the pharynx leading to increased upper airway collapsibility, or via increased upper airway adiposity such as tongue fat. The authors include measurements of waist circumference and neck circumference and should therefore be able to assess for any changes in abdominal adiposity as well as extra-luminal neck fat.

Authors' response:

Thank you for your comments. We have added this point to our discussion.

5. In the methods the authors state that they will only include RCTs and will exclude observational studies. In an earlier section authors state that they might include non-randomised control trials if RCT data is lacking. Clarification as to whether non-randomised control studies will be included would be helpful.

Authors' response:

Thank you for identifying this discrepancy. We have edited our methods section to clarify.

Reviewer #2: Marta Drummond

This manuscript is an intention to perform a meta-analysis and systematic review comparing surgical procedures as different as bariatric surgery and other surgeries aiming to reduce respiratory events during sleep. This is a methodological error, the meta-analysis should only include the several types of bariatric surgery or ORL surgeries or maxillo facial surgeries, etc. why comparing such different procedures with one another as they are used in different phenotypes of OSA patients?

Both the abstract and the article are too long and repetitive and does not add to the scientific knowledge in this field. The English needs improvements. The objectives and methods are clearly pointed. It would be very interesting to see the results of a meta-analysis comparing different bariatric surgery procedures.

Authors' response: Thank you for the valuable suggestions and feedback.

Point to point:

1. We agree that the study should only include the several types of bariatric surgery. We rewrote the types of intervention in methods, and deleted some types of surgery for OSA.
2. Our native English-speaking coauthor has edited the manuscript and added more recent citations on the epidemiology.
3. Thank you for the suggestion. Some of our coauthors are native English speakers and they will review and check the final version again to make sure the English is acceptable.

Reviewer #3: Verbraecken Johan

Dong et al have planned to perform a meta-analysis in weight-reduction surgery for obstructive sleep apnoea with obesity in adults. They have described their approach in the manuscript submitted. The paper is well written, and the protocol reports the objectives, methods (eligibility, search methods) in an adequate manner. Guidance is also given on assessment of risk of bias, heterogeneity, and finally, sensitivity analysis.

The authors report that they will also include unpublished data (page 7/20 line 36). This is very unusual, and the authors should explain precisely what they mean.

Authors' response: Thank you kindly for the comments and valuable suggestions.

Point to point:

Yes, it is a little confusing. We agree that the unpublished data should be explained.

We have elaborated in the methods section on how we plan to include unpublished data in our study.

Minor comments:

- page 3/20 line 30: The primary outcomes that will be measured are ...
- page 4/20: line 20: various types
- page 5/20: line 45: diagnosis of OSA. After subsequent (...years), they ...
- page 5/20: line 54: apnea-hypopnea index
- page 7/20: line 33: assessed
- page 8/20: line 44: measured
- page 8/20: line 46: one month
- page 12/20: line 20: ...obtained. That is, ...
- page 12/20: line 44: RCTs, ...
- page 13/20: line 7: heterogeneity,
- page 14/20: line 14: "middle-aged patients" instead of "Adult patients" ?
- page 15/20: line 1: currently, ...
- page 15/20: line 17: required, ...
- page 19/20: line 3: adjusted

Authors' response: Thank you for the carefully identified comments.

We have made changes to address these comments accordingly. Finally, we would like to thank you again for taking the time to critically revise our manuscript. We believe that addressing the comments and incorporating the suggestions will substantially improve our paper.

VERSION 2 – REVIEW

REVIEWER	Verbraecken Johan Antwerp University Hospital and University of Antwerp, Belgium
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	No remarks.
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REVIEWER	Chris Turnbull Oxford University Hospitals NHS Foundation Trust
REVIEW RETURNED	27-Mar-2018

GENERAL COMMENTS	<p>This revised manuscript is much improved and the authors have taken into account comments from previous reviews. I have only a few minor suggestions:</p> <p>Page 3 Line 38-39: apnoeas and hypopnoeas are not caused by intermittent hypoxia, rather intermittent hypoxia and the other physiological processes listed are consequences of apnoeas and hypopnoeas.</p> <p>Page 3 Line 45-46: I'm not sure what the authors mean by apnea-hypertension and would ask for clarification as to whether this represents daytime hypertension in OSA or acute intermittent blood pressure surges overnight following arousal in OSA.</p> <p>Page 4 Line 26: typo, should read 'weight' not 'eight'</p> <p>Page 4 Line 34: typo, please remove the extra space after gastrectomy before the comma</p> <p>Page 6 Line 42: It is not clear whether the primary outcome will be the change in AHI from before to after weight loss surgery and ask the authors to clarify this.</p> <p>Page 12 Line 44: The authors discuss the association between BMI and OSA risk reported as a mean difference. However, BMI is not a dichotomous variable and OSA 'risk' is not a continuous variable. I assume they are referring to the difference in AHI between individuals who are obese and those who are non-obese, but this is not clear. I would ask the authors to clarify this point.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer #3 Verbraecken Johan:

Please state any competing interests or state 'None declared': None declared

Authors' response: We thank you for reviewing our manuscript and for the valuable comments. We have stated none declared for any competing interests. See page 33.

Reviewer #1: Chris Turnbull

Please state any competing interests or state 'None declared': None declared

Authors' response: Thank you, we have included as suggested.

This revised manuscript is much improved and the authors have taken into account comments from previous reviews.

Authors' response: We thank you for reviewing our manuscript and for the valuable comments.

Page 3 Line 38-39: apnoeas and hypopnoeas are not caused by intermittent hypoxia, rather intermittent hypoxia and the other physiological processes listed are consequences of apnoeas and hypopnoeas.

Authors' response: Thank you! We have made changes in the revised paper as suggested.

Page 3 Line 45-46: I'm not sure what the authors mean by apnea-hypertension and would ask for clarification as to whether this represents daytime hypertension in OSA or acute intermittent blood pressure surges overnight following arousal in OSA.

Authors' response: Thank you for the valuable suggestion. It represents both daytime and acute hypertension at night. In the revised paper, we have corrected the sentence.

Page 4 Line 26: typo, should read 'weight' not 'eight'

Authors' response: We have made the changes as suggested

Page 4 Line 34: typo, please remove the extra space after gastrectomy before the comma

Authors' response: we have made the change. Thank you!

Page 6 Line 42: It is not clear whether the primary outcome will be the change in AHI from before to after weight loss surgery and ask the authors to clarify this.

Authors' response: yes, the primary outcome will be the change in AHI from before to after weight loss surgery.

Page 12 Line 44: The authors discuss the association between BMI and OSA risk reported as a mean difference. However, BMI is not a dichotomous variable and OSA 'risk' is not a continuous variable. I assume they are referring to the difference in AHI between individuals who are obese and those who are non-obese, but this is not clear. I would ask the authors to clarify this point.

Authors' response: Thank you for the carefully identified comments. Yes, we were referring to difference in AHI between individuals who are obese and those who are non-obese.

We have made changes to address these comments accordingly.

Finally, we would like to thank you again for taking the time to critically revise our manuscript. We believe that addressing the comments and incorporating the suggestions will substantially improve our paper.