

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)	Pros and cons of gastric bypass surgery in individuals with obesity and type 2 diabetes: nationwide, matched, observational cohort study
AUTHORS	Liakopoulos, Vasileios; Franzén, Stefan; Svensson, Ann-Marie; Miftaraj, Mervete; Ottosson, Johan; Näslund, Ingmar; Gudbjornsdottir, Soffia; Eliasson, Björn

VERSION 1 – REVIEW

REVIEWER	John Wentworth Walter and Eliza Hall Institute
REVIEW RETURNED	10-May-2018

GENERAL COMMENTS	<p>This is an important paper that provides further insight into the long-term health effects of RYGB surgery in people with type 2 diabetes. The methodology is sound and the prose is clear and concise.</p> <p>My only concern is that measured (eg age, income, BMI) and unmeasured (especially diabetes duration but also HbA1c, eGFR, retinopathy, albuminuria and engagement with the health system) baseline differences are likely to have affected mortality outcomes. I therefore do not agree with the statement in the abstract: "We confirmed lower risks of all-cause mortality (49%) and cardiovascular disease (34%)..." Less strong language would be appropriate. Is it possible to include the above mentioned missing data, even if they are far from complete?</p>
-------------------------	--

REVIEWER	Gema Frühbeck Clínica Univ. de Navarra, University of Navarra, CIBEROBN, ISCIII, Spain
REVIEW RETURNED	23-Jun-2018

GENERAL COMMENTS	<p>GENERAL COMMENTS</p> <p>The topic is interesting and relevant. Given the continuing obesity epidemic and the increasing number of patients undergoing bariatric surgery the topic is timely and has pragmatic clinical implications. The manuscript is clearly written making it easy to read.</p> <p>The manuscript will benefit from considering a couple of additional details just to round it off:</p> <p>1) Abstract: in the Conclusions section of the Abstract (page 4) the authors point out that "Long-term postoperative monitoring and support... should be provided to optimize the outcomes". However, it needs to be stressed that this is precisely a requirement of all</p>
-------------------------	--

	<p>bariatric/metabolic surgery guidelines [e.g. Position Statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). <i>Obes Surg.</i> 2016 Aug;26(8):1659-96.]. This point should be mentioned in the Discussion of the manuscript.</p> <p>2) Abstract: in this context, the authors also mentioned in the Conclusions section of the Abstract (page 4) "... , and possibly also better selection of patients... should be provided to optimize the outcomes". In the Discussion of the manuscript it would be important and worthwhile mentioning that currently eligibility and success criteria also point precisely to the need of more functional pre- and post-operative patient assessment [Frühbeck G. Bariatric and metabolic surgery: a shift in eligibility and success criteria. <i>Nat Rev Endocrinol.</i> 2015 Aug;11(8):465-77.].</p> <p>3) Research Design & Methods: were all bariatric surgery procedures performed via a minimally invasive laparoscopic approach or were some carried out via open surgery? Please indicate since it may relate to the post-surgical complications.</p> <p>4) Discussion (page 12, last paragraph): add a relevant reference related to the discussed topic, namely Spittal et al. Bariatric surgery: many benefits, but emerging risks. <i>Lancet Diabetes Endocrinol</i> 2018 Mar;6(3):161-3.</p> <p>5) References: add the above-mentioned references related to the discussed topic to provide a broader perspective of the topic.</p> <p>6) References: provide full details for references # 11, 16, 25, 28 and 33.</p> <p>MINOR COMMENTS Page 2, Participants paragraph: replace "27,5 kg/m2" by "27.5 kg/m2" (and apply throughout the manuscript). Page 6, parag. 1, line 5: add "as" before "long-term". Page 7, parag. 3, line 2: add "as" before "patients". Page 13, last parag., line 3: replace "systemic" by "systematic".</p>
--	--

REVIEWER	Ricardo Cohen Director, The Center for Obesity and Diabetes, Oswaldo Cruz Hospital, Sao Paulo,. Brazil
REVIEW RETURNED	26-Jun-2018

GENERAL COMMENTS	<p>This is an observational matched study performed in Swedish databases.</p> <p>However, the manuscript does not describe the follow up of the non operated group. There is no mention of any complications that any T2D obese patient undergo during its life with a chronic and progressive disease. Diagnosis of T2D was made during hospitalization, what is questionable.</p> <p>The authors do not inform if RYGB was performed laparoscopically or open. Any surgical technical detail was omitted, as if the peritoneal spaces were closed during the operation, what can avoid long term reoperations for internal hernias.</p> <p>Drugs for T2D treatment employed and glycemic control were not detailed. Hypoglycemia is a considerable side effect after insulin use.</p> <p>There are mentions on malnutrition and micronutrients deficiencies, but they were not defined.</p>
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: John Wentworth

Institution and Country: Walter and Eliza Hall Institute

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

This is an important paper that provides further insight into the long-term health effects of RYGB surgery in people with type 2 diabetes. The methodology is sound and the prose is clear and concise. My only concern is that measured (e.g. age, income, BMI) and unmeasured (especially diabetes duration but also HbA1c, eGFR, retinopathy, albuminuria and engagement with the health system) baseline differences are likely to have affected mortality outcomes. I therefore do not agree with the statement in the abstract: "We confirmed lower risks of all-cause mortality (49%) and cardiovascular disease (34%)..." Less strong language would be appropriate. Is it possible to include the above mentioned missing data, even if they are far from complete?

Response

Thank you very much for your appreciation of our paper and this comment.

We have now slightly revised the abstract: "The results agree with the previously suggested lower risks of all-cause mortality (49%) and cardiovascular disease (34%) ...".

The methods used in this study were not identical to our previous publications (Eliasson B, Liakopoulos V, Franzen S, et al. Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study. *The Lancet Diabetes & Endocrinology*. 2015;3(11):847-5), which used more covariates and analyzed the importance of them (Liakopoulos V et al. Changes in risk factors and their contribution to reduction of mortality risk following gastric bypass surgery among obese individuals with type 2 diabetes: a nationwide, matched, observational cohort study. *BMJ Open Diabetes Res Care*. 2017;5(1)). Our motif was now to focus on a broad spectrum of causes for re-hospitalizations, and to ensure maximizing the number of persons in both groups. The reviewer's comment is of course very valid and we have now added an additional sentence in the paragraph on these limitations in the discussion.

Reviewer: 2

Reviewer Name: Gema Frühbeck

Institution and Country: Clínica Univ. de Navarra, University of Navarra, CIBEROBN, ISCIII, Spain

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

GENERAL COMMENTS

The topic is interesting and relevant. Given the continuing obesity epidemic and the increasing number of patients undergoing bariatric surgery the topic is timely and has pragmatic clinical implications. The manuscript is clearly written making it easy to read.

The manuscript will benefit from considering a couple of additional details just to round it off:

1) Abstract: in the Conclusions section of the Abstract (page 4) the authors point out that "Long-term postoperative monitoring and support... should be provided to optimize the outcomes". However, it needs to be stressed that this is precisely a requirement of all bariatric/metabolic surgery guidelines [e.g. Position Statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). *Obes Surg*. 2016 Aug;26(8):1659-96.]. This point should be mentioned in the Discussion of the manuscript.

Response

Thank you for your comment and the useful reference. We have now added a paragraph that emphasize these aspects of current guidelines of bariatric surgery.

2) Abstract: in this context, the authors also mentioned in the Conclusions section of the Abstract (page 4) "..., and possibly also better selection of patients... should be provided to optimize the outcomes". In the Discussion of the manuscript it would be important and worthwhile mentioning that currently eligibility and success criteria also point precisely to the need of more functional pre- and post-operative patient assessment [Frühbeck G. Bariatric and metabolic surgery: a shift in eligibility and success criteria. Nat Rev Endocrinol. 2015 Aug;11(8):465-77.].

Response

We completely agree. See the previous response.

3) Research Design & Methods: were all bariatric surgery procedures performed via a minimally invasive laparoscopic approach or were some carried out via open surgery? Please indicate since it may relate to the post-surgical complications.

Response

We studied patients that received primary gastric bypass (see flow chart in the supplementary material). 96.0% the procedures were performed laparoscopically, 1.7% were initially laparoscopic and converted to open surgery, and 2.3% primary open surgery. This information has now been added in the manuscript.

4) Discussion (page 12, last paragraph): add a relevant reference related to the discussed topic, namely Spittal et al. Bariatric surgery: many benefits, but emerging risks. Lancet Diabetes Endocrinol 2018 Mar;6(3):161-3.

Response

We added this reference as well as a sentence relevant to this topic.

5) References: add the above-mentioned references related to the discussed topic to provide a broader perspective of the topic.

Response

Thank you. We have now added all the proposed references.

6) References: provide full details for references # 11, 16, 25, 28 and 33.

Response

The list of references has been corrected.

MINOR COMMENTS

Page 2, Participants paragraph: replace "27,5 kg/m²" by "27.5 kg/m²" (and apply throughout the manuscript).

Page 6, parag. 1, line 5: add "as" before "long-term".

Page 7, parag. 3, line 2: add "as" before "patients".

Page 13, last parag., line 3: replace "systemic" by "systematic".

Response

Thank you. We have now corrected all of these points.

Reviewer 3

Reviewer Name: Ricardo Cohen

Institution and Country: Director, The Center for Obesity and Diabetes, Oswaldo Cruz Hospital, Sao Paulo,. Brazil

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

Please leave your comments for the authors below

This is an observational matched study performed in Swedish databases.

However, the manuscript does not describe the follow up of the non operated group. There is no mention of any complications that any T2D obese patient undergo during its life with a chronic and progressive disease. Diagnosis of T2D was made during hospitalization, what is questionable.

The authors do not inform if RYGB was performed laparoscopically or open. Any surgical technical detail was ommited, as if the peritoneal spaces were closed during the operation, what can avoid long term reoperations for internal hernias.

Drugs for T2D treatment employed and glycemic control were not detailed. Hypoglycemia is a considerable side effect after insulin use.

There are mentions on malnutrition and micronutrients deficiencies, but they were not defined.

Response

Thank you for these comments.

The aim of our study is to identify clinical benefits and postoperative adverse events both short- and long-term for patients with type 2 diabetes already diagnosed before the surgery, that received primary gastric bypass surgery, compared with patients that also had type 2 diabetes but did not receive surgical treatment. We used rehospitalizations due to many different diagnoses as outcome measures (including CVD and severe renal disease), and thus did not address microvascular complications not requiring new admissions in a hospital.

As pointed out in the response to Reviewer 2, 96.0% the procedures were performed laparoscopically, 1,7% were converted to open surgery and thus 2,3% open surgery. We have not addressed the roles of detailed surgical techniques, which we think is beyond the scope of this study, but have added this information and briefly discussed as a limitation.

The importance of other covariates and diabetes treatment has also been addressed in the discussion.

We used ICD codes (e.g., malnutrition and anemia) after re-hospitalizations as outcome measures.

VERSION 2 – REVIEW

REVIEWER	John Wentworth Royal Melbourne Hospital
REVIEW RETURNED	20-Aug-2018
GENERAL COMMENTS	No further concerns. Thank you.