**Author’s response to reviews**

**Title:** Irritable bowel syndrome-like symptoms and health related quality of life two years after Roux-en-Y gastric bypass - a prospective cohort study

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BMC Gastroenterology

Dear Editor,

We appreciate the useful comments made by the peer reviewers and are grateful for the opportunity to submit a revised version of the manuscript BMGE-D-19-00262.

A general response to the comments made by the Reviewers is that, as defined in the introduction and commented in the discussion, this is not a study exploring causes of the gut symptoms defined. The study investigates to what extent IBS like symptoms are present in a defined prospective patient cohort. The study also aims to explore preoperative predictors of such symptoms. We believe that our findings are highly relevant to the physicians and health care providers who meet these patients as knowledge about abdominal symptoms after bariatric surgery is limited. The findings should also be of interest for patients opting for bariatric surgery, as what to expect and who may be at risk is explored.

Once more, we do apologize for the delayed response. Below we give a point-by-point response to the Reviewers’ comments. All changes are highlighted in the manuscript. We hope that the adjustments made to the manuscript and our responses address the comments adequately.
Comments from Yoav Mazor (Reviewer 1)
The authors should be applauded for their effort to assess complications of RYGB and their relation to quality of life measures.

We are happy that the reviewer find the topic interesting and appreciate the encouraging comment.

To apply the Rome III definition to patients following surgery, specifically intestinal surgery, requires additional care. We are grateful for these insightful reflections and agree that care is required. After the reviewer comments, we have chosen to use the nomenclature “IBS-like symptoms” instead of “IBS” postoperatively.

The main aim of our study as stated in the introduction was “...to study the change in the prevalence of IBS from before to two years after RYGB and to search for preoperative predictors of IBS after RYGB.” In the revised manuscript this reads “...to study the change in the prevalence of IBS-like symptoms from before to two years after RYGB and to search for preoperative predictors of these symptoms after RYGB” (page 5).

Despite the conceptual challenges, we believe this is an important topic to explore due to the scarcity of knowledge of abdominal symptoms and pain post RYGB in general. Focus on these symptoms during follow up consultations may benefit the patients in regard to abdominal discomfort and quality of life. The observed associations between quality of life and these symptoms also stress the relevance of our study.

As we used the Rome III criteria (without separate questions regarding pain and discomfort) we unfortunately cannot evaluate the prevalence of abdominal pain separately. However, the study by Chahal-Kummen et al., (which included a subset of the present patient cohort with a different set of questionnaires) could give an impression of the prevalence of abdominal pain: 11.9% of the patients reported abdominal pain before and 28.7% after RYGB. The study referred to as “accepted” in the original manuscript has been published and this is corrected in the reference list in the revised manuscript:


What was the prevalence of each of the Rome criteria (change in stool form, frequency and relation of pain to defecation) before and after surgery? We have chosen not to report these findings as we believe this will complicate our findings and the readability of the manuscript. Our aim has been to evaluate the presence of IBS-like symptoms and not to evaluate every sub-symptom explored in the Rome III questionnaire. We
are uncertain as to whether these details would improve our manuscript. If the Editors find them highly relevant we could add these.

How many patients were actually defined as IBS due to abdominal pain and change in defecation habits resulting from surgery?

Whether the changes observed of IBS-like symptoms were causally related to the surgical procedure or not is unfortunately unknown, and with the current study design we cannot answer this research question as stated in the limitation paragraph. Importantly, as we use the Rome III criteria we evaluate both pain and discomfort without differentiating between these measures.

What was the prevalence of other pain-related Rome diagnoses such as central-mediated (chronic functional) abdominal pain, dyspepsia or non-specific abdominal pain?

The prevalence of other pain-related Rome diagnoses was not a predefined aim and thus not evaluated in our study. The aim of the study was to explore the prevalence of IBS-like symptoms before and after RYGB.

What, if any, work up was performed for these problems (abdominal pain and change in stool habits)? Although no formal guidelines exist, in light of the above publications reasonable testing would include exclusion of surgical complications, celiac, lactose intolerance and biliary colic. How many patients were tested for these alternative diagnoses.

Evaluations of potential celiac disease and lactose intolerance was initiated at the discretion of the attending physician. A systematic diagnostic work-up, however, was not performed as part of the study. This is in line with the aims for the present study presented in the introduction.

Based on our clinical experience with patients reporting abdominal pain and symptoms post RYGB, a subset will remain without a clearly defined cause of their symptoms despite thorough diagnostic work-up. We have explored this issue in a previous study (Diagnosis and treatment of chronic abdominal pain 5 years after Roux-en-Y gastric bypass. Blom-Høgestøl IK, Stubhaug A, Kristinsson JA, Mala T. Surg Obes Relat Dis. 2018;14:1544-1551).

That diagnostic work-up was not performed systematically in all patients is stated in the original manuscript in the discussion, page 14 “However, participants fulfilling the Rome III criteria for IBS were not systematically examined for underlying pathophysiology of IBS-like symptoms. To what extent the altered physiology or other aspects of the surgical procedure itself contributed to the increase in bowel symptoms could not be answered by this study”.

Although a major undertaking, future studies may systematically evaluate casual explanations for the findings observed. A challenge, however, will probably be that, in our experience, a substantial subset of patients will be reluctant to embark on the extensive evaluation that may be required. For some a diagnosis will not be established despite extensive evaluations. For these patients we still may not be sure if there could be a physiologic or organic substrate for their symptoms.

What medications were patients taking at follow up?

Unfortunately the use of medication was not included in our database. This could have added information relevant for interpretation of our findings. We have added a comment about this in the limitation paragraph (page 14).
“Reporting on the use of medication at the follow-up consultations may have added information relevant for interpretation of our findings, particularly medications affecting gastrointestinal function”.

What was the prevalence of the different subtypes of IBS? At baseline, 4/233 (1.7%) had IBS-C, 5/233 (2.1%) had IBS-D, 15/233 (6.4%) had IBS-M and 1/233 (0.4%) had IBS-U. At the two year control; 11/233 (4.7%) had IBS-C, 12/233 (5.2%) had IBS-D, 34/233 (14.6%) had IBS-M, 3/233 (1.3%) had IBS-Y and for 1/233 (0.4%) we did not have enough information for further subtyping. We think perhaps presenting these data will complicate the presentation of our findings without adding more substance to the interpretation of our results.

No discussion of the associating of high vitamin B1 with developing of IBS/pain/change in bowel?

We agree with the Reviewer and have commented on this finding in the revised manuscript. The association of high preoperative vitamin B1 levels with IBS after RYGB could be a statistical type 1 error. High vitamin B1 could also, as low LDL, be considered as a proxy for a healthy or a specific type of diet, but it is not obvious to us why this should dispose to IBS-like symptoms after bariatric surgery. We have added the following to the revised manuscript (page 12):

“ Unexpectedly, high levels of vitamin B1 before RYGB was an independent preoperative predictor of IBS-like symptoms two year post surgery. This finding could be a proxy indicating a specific diet used by these patients or it may be a statistical type 1 bias. The finding should be further explored in future studies”.

Comments from Cesare Cremon (Reviewer 2)

Did the authors exclude SIBO in their patients after RYGB by glucose breath testing or culture of jejunum aspirate for bacterial counts? Probably a high proportion of subjects suffer from this condition rather than IBS. If the authors did not evaluate this aspect I suggest to include this in discussion as a major limitation of the study.

We did not exclude small intestinal bacterial overgrowth (SIBO), but do agree that this is a relevant diagnosis in this context. As stated in the discussion the included patients “…were not systematically examined for underlying pathophysiology of IBS-like symptoms. To what extent the altered physiology or other aspects of the surgical procedure itself contributed to the increase in bowel symptoms could not be answered by this study”.

However, we do concur that when such symptoms occur evaluations should be made and recognized guidelines for diagnostic work should be available. SIBO may be particularly relevant in this regard. In the revised manuscript “IBS” is changed to “IBS-like symptoms” as suggested by the reviewer, that to some extent underlines that other causes than IBS may be involved.

We have also added to the limitation paragraph of the study (page 14);

“In particular evaluation of small intestinal bacterial overgrowth would be relevant in the evaluation of symptoms”

I suggest to prefer the term IBS-like symptoms rather than IBS.

We agree with the reviewer and have changed the wording throughout the manuscript. Consequently, the title of the manuscript also has been modified and now reads:
“Irritable bowel syndrome-like symptoms and health related quality of life two years after Roux-en-Y gastric bypass - a prospective cohort study”

By definition, IBS is a functional bowel disorder in which macroscopic organic causes are excluded. RYGB may perturb pain perception and alter gastrointestinal physiology, pathophysiological mechanisms involved in symptom generation in IBS.

We do agree that RYGB in particular may alter gastrointestinal physiology. However whether pain perception is altered as suggested remains to be explored. On the other side IBS-like symptoms in patients that have not undergone abdominal surgery may also be induced by altered physiology from use of medication, bacterial overgrowth and undiagnosed organic disease.

By changing the nomenclature from “IBS” to “IBS-like symptoms” we think we have addressed this comment. Furthermore, as already stated, the aim of the study was to explore the prevalence of such symptoms, not potential causes. This is also underlined by the change in nomenclature as stated.

It is well defined that factors triggering the onset or exacerbation of IBS symptoms include for example surgery. The study is lacking of a control group represented for example by subjects who underwent laparoscopic cholecystectomy. It is possible that laparoscopic abdominal surgery rather than RYGB is involved in new onset of IBS-like symptoms. I suggest to include a control group to assess the real prevalence of new IBS-like symptoms after RYGB.

We agree that a control group would have improved our study and the interpretation of our findings, particularly in regard to any causal relationships to the findings observed. However, it could be challenging to define what group would be reasonable to include as a control. Furthermore, as the aim of the study is not to explore potential causes of the findings observed this may render a control group less important. Unfortunately, we have no data from a control group available, and a new control group would take 2-3 years to include. We have added this to the limitations of the study (discussion).

“A control group consisting of patients undergoing other abdominal surgery could add information relevant to the interpretation of our findings” (Page 14).

Typos
Page 13, Line 39-44: These findings supports an association…. and highlights
Thank you for the thorough evaluation of the manuscript. This has been corrected in the revised version.