Response to Reviewer's Comments

Manuscript: Burden of Illness of Irritable Bowel Syndrome in China: A prospective study.

General Comment: First I would like to congratulate the authors on this study and paper. It is a relevant topic with interesting results, the paper is well written.

Response: We would like to thank the reviewer for the encouraging comment.

However, I do have a few comments.

Comment 1) The authors describe a potential bias regarding external validity in the limitation section due to the inclusion of patients via the Third Hospital of Dalian Medical University. This is a very important point and to my opinion should be discussed in more detail.

First of all, could the authors describe in the method section what kind of referral center this is, 2nd or 3rd? And furthermore, are any patients included via general practitioners. If not, this should be listed as a limitation. The authors extrapolate their results to the complete country by using the prevalence data from other studies. However, most IBS patients in all countries are not treated in second or third referral centers, but mostly stay at GP practices. Even more, many patients do not seek medical attentions at all. And therefore the costs of these patients are much lower compared to referred patients. Therefore, if the results of a second or third referral center are extrapolated to all IBS patients, it could be a relevant overestimation of the costs.

Could the authors comment on this and include this both in the method section (i.e. describe the type of patients) and in the discussion.

Response: The authors would like to thank the reviewer for the insightful comments. The Third Hospital of Dalian Medical University is a Level 3 hospital (i.e. the equivalent of tertiary hospital in western classification). In China, there is not yet an established and mandatory referral system, and patients are free to seek

treatments at whatever healthcare facilities. Due to the better facilities and availability of clinical expertise, most Chinese patients would prefer to seek treatment at Level 3 hospitals. This is causing extremely high caseloads and congestions at these hospitals, a phenomenon that the Chinese government is tackling. Hence, to recruit IBS patients at a Level 3 hospital would capture the typical cohort of patients who are seeking treatments for their conditions. Hence, the estimation of the cost of treatment would also be a close approximation of the typical treatment cost for the condition, and probably not a gross over-estimation.

We have added more details about this in the method section of the revised manuscript (page 2, paragraph 1, lines 4-10).

> ***Original:*** *Nil*
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> ***Revised:*** *The Third Hospital of Dalian Medical University is a level 3 comprehensive hospital (the equivalent of tertiary referral hospital in western countries), renowned for its management of cardiovascular and cerebrovascular diseases, metabolic diseases, gastrointestinal diseases and senile diseases. In China, patients have the freedom to choose the healthcare institution when seeking treatments. Due to the availability of advanced technology and experienced doctors, the level 3 comprehensive hospitals are usually their first choice.*

Comment 2) The authors include 105 patients. They describe in the limitation section a potential bias regarding the relative small number of subjects. Furthermore, all subjects are from the same region. We know that significant differences in lifestyle, demographics and costs (use and access to medical facilities) are present in all countries. China is particularly large with large differences between regions. Could the authors describe why they think that these 105 patients are representative of all patients from all regions of China? Or is this a relevant lamination?

Response: Indeed, China is a large country and there exists sometimes quite large variations in lifestyles, use and access to medical facilities like any large country. The question raised by the reviewer is certainly pertinent, but also a dilemma faced by researchers conducting studies in China considering the resource implication for capturing representative samples. Anyway, what would be

considered as an adequately representative sample for a country like China is somewhat difficult to define.

Like many other researchers, unfortunately, in our study, we were constrained by our resources and could only recruit subjects from one location. However, when considering the relatively lack of genetic difference, the rather standardized treatment for IBS, and the health seeking habit of the Chinese population, our cohort could be considered as typical of IBS sufferers in China if interpreted with some caution. We have mentioned this as one of the limitations of the study in the discussion of the revised manuscript (Page 17, paragraph 1, lines 5- 12 of the revised manuscript).

> ***Original:*** *Nil*
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> ***Revised:*** *Certainly, significant differences in lifestyle, demographics, use and access to medical facilities exist in all countries and sometimes even different regions in the same country. So there is the risk to extrapolate the results from our sample as representative of all patients from all regions of China. However, when considering the relatively lack of genetic difference, the rather standardized treatment for IBS, and the health seeking habit of the Chinese population, our cohort could be considered as typical of IBS sufferers in China if interpreted with some caution.*

Comment 3) In the method section authors describe an exclusion criterion to be 'previous hypnotherapy'. Why should these patient be excluded? If therapy is some how a bias, why not exclude all patients who have had or still have some kind of medical or non-pharmaceutical therapy?

To my opinion non of the therapies should be listed as an exclusion criterion, as we are interested in the full IBS population, regardless their status of therapy.

Could the authors comment on this? If they agree, could they include the previously excluded patients based on hypnotherapy? If they do not agree, could provide valid arguments why hypnotherapy should be an exclusion criterion and include this explanation in the method section?

Response: The exclusion criterion was adapted and based on two published studies, (Hoekman DR, et al. "Annual Costs of Care for Pediatric Irritable Bowel Syndrome, Functional Abdominal Pain, and Functional Abdominal Pain Syndrome"J Pediatr. 2015 Nov;167(5):1103-8.e2. doi: 10.1016/j.jpeds.2015.07.058. Epub 2015 Aug 29 and Dekel R, et al. Abdominal Pain in Irritable Bowel Syndrome (IBS). In: Leonardo Kapural. Chronic Abdominal Pain: An Evidence-Based, Comprehensive Guide to Clinical Management. New York: Science+Business Media, 2015:59-67. doi:10.1007/978-1-4939-1992-5_6).

Currently, the most popular and frequently used treatment of IBS in China is base d on pharmacotherapy rather than psychological or psychiatric treatment. Further more, none of the patients participating in the study had been treated with previo us hypnotherapy, nor did we exclude any patient based on this criterion. To avoid the confusion, we have deleted the sentence in the method section.

Comment 4) The authors describe a specially designed questionnaire which they have used for the study. As the questionnaire is the instrument by which all results have been collected it is very important that this instrument is described in great detail, for the study to be reproducible.

Could the authors describe the questionnaire in more detail and provide the full list of questions as supplementary material to the article?

Furthermore, could they describe if the questionnaire is validated in some way?

Response: The questionnaire was adopted from a previous published study of economic burden for Parkinson's Disease (Zhao YJ, Tan LCS, Au WL, Seah SH, Lau PN, Luo N, Li SC, Wee HL. Economic Burden of Parkinson's disease in Singapore. *Eur J Neurol* 2011; 18(3): 519-26). We have provided more details about the questionnaire in the revised manuscript (Page 2, paragraph 1, line 13), and supply it as supplementary material for the article.

Original: *Nil*

Revised: ..... *a standardized questionnaire adopted from a published study,*[35]

Comment 5) In the method section the authors describe at some point patients below the age of 16 years. Does this study include adults as well as pediatric patients, and if yes, why?

Response: The authors would like to thank the reviewer pointing this out. As mentioned in our previous response, the criterion was adapted and based on two published literatures. Since, we did not include pediatric patients in our current study, we have therefore made the amendment in the revised manuscript.

Comment 6) In the method section I read a somewhat remarkable sentence: "As IBS-related death was very rare,..." This sentence indicates that although rare, IBS related death occurs sometimes. IBS is per definition benign and not lethal, therefore the sentence should be formulated differently.

Response: The reason for mentioning mortality related to IBS is based on the fact that productivity loss due to pre-mature mortality due to a disease is an important component in economic consideration. We were trying to provide a reason to support our omission of this component in our study. We have amended the sentence as suggested by the reviewer in the revised manuscript (Page 7, paragraph 3, lines 1-2 of revised manuscript).

> ***Original:*** *As IBS-related death was very rare,*[42] *productivity loss related to early death was not considered in this study.*[43]
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> ***Revised:*** *In this study, due to the nature of the disease being studied, productivity loss due to premature mortality was not included.*

Comment 7) I agree to include a subtype analysis in the paper. However, the number of patients per subtypes are really small. This is in particular true for the

IBS-M subtype (n=9). Extrapolating this data to China is risky. This is very clearly be noted in the paper and the data should be interpreted with care.

Response: We appreciate the valuable comment and have amended the manuscript to reflect this in the discussion (page 17, paragraph 2, lines 1-8 of revised manuscript).

Original: *Nil*

Revised: *See Response to Comment 9.*

Comment 8) In Table 1, 42% of patients are described as retired. How does this impact the data regarding work related costs?

This should be described in the text.

Response: The impact of this regarding work related costs has been described in the revised manuscript (page 6, paragraph 1, lines 2-3 of revised manuscript).

Original: Nil

Revised: *For patients who were retirees, their indirect costs were calculated by family caregivers' lost workdays; and for patients who were employed, …….*

Comment 9) In table 7, the authors describe a significant difference (p = 0.031). This differences is mostly based on the IBS-M subtype. This subtype is only 9 patients and the SD is quite broad. Therefore hard conclusion based on this result is to my opinion invalid.

Furthermore, the statics are performed by ANOVA? Was there any correction for multiple testing?

Response: We agree that due to the small sample size, the conclusion that patients with IBS-M subtype have a significant difference may be risky.

However, based on clinical experience, patients with IBS-M are more difficult to treat. Other published studies also supported clinical difference in the various IBS-subtypes, with patients with IBS-M subtype posing more difficulties in the

management. (Kibune et al. Irritable bowel syndrome subtypes: Clinical and psychological features, body mass index and comorbidities. Rev Esp Enferm Dig. 2016;108(2):59-64. PMID: 26838486 DOI: 10.17235/reed.2015.3979/2015; Eriksson EM, et al. Irritable bowel syndrome subtypes differ in body awareness: psychological symptoms and biochemical stress markers. World J Gastroenterol. 2008;14(31):4889-96. PMID: 18756596 doi:10.3748/wjg.14.4889; Heitkemper M, et al. Subtypes of Irritable Bowel Syndrome Based on Abdominal Pain/Discomfort Severity and Bowel Pattern. Dig Dis Sci. 2011;56(7):2050-8. PMID: 21290181 DOI: 10.1007/s10620-011-1567-4). Hence, there is a good chance that the difference observed would be valid. Nevertheless, due to the relatively limited sample size, our observation will need confirmation with larger studies in future. We have added this in the discussion in the revised manuscript (page 17, paragraph 2, lines 1-8 of revised manuscript).

We have also changed the conclusion accordingly in the revised manuscript (page 17, paragraph 4, lines 6-7 of the revised manuscript).

Regarding the statistical analyses, the tests were performed by ANOVA and bias adjusted.

> **Original:** *Nil*
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> **Revised:** *Finally, due to the small sample size in our study, the conclusion that patients with IBS-M subtype have a significant difference may also be risky. However, based on clinical experience, patients with IBS-M are more difficult to treat. Other published studies also supported clinical difference in the various IBS-subtypes, with patients with IBS-M subtype posing more difficulties in the management.*[68-70] *Hence, there is a good chance that the difference observed would be valid. Nevertheless, due to the relatively limited sample size, our observation will need confirmation with larger studies in future.*

> **Original:** *Among the subtypes, IBS-M patients have the greatest economic burden.*

Revised: *Among the subtypes, IBS-M patients appear to have the greatest economic burden but would need further confirmation.*

Comment 10) In the discussion section the authors discuss differences in duration of IBS between the current study and pervious studies. I think this part should not be included as the 'duration of symptoms' is based on the moment of inclusion in the study and the culture or habit of referral to the hospital of IBS patients. If secondary referral is more common practice a study that targets these patients will find shorter duration compared to countries of regions were referral is more conservative. Therefore, a potential differences in disease duration is just a surrogate marker of time to referral.

Response: Surely we agree that the duration of symptoms at assessment would be affected by the culture and habit of referral. However, due to the uniqueness of the Chinese health care system, our study sample may resemble both IBS in primary care and specialist care in western countries. To provide information about the duration of symptoms would allow other researchers better assessment of comparative management cost. Therefore, we have retained the part in the original but have amended the discussion according to the comment by the reviewer to reflect that the difference between our study and overseas studies may be affected the referral system and habit (Page 13, paragraph 3, lines 3-6 of revised manuscript).

Original: *Nil*

Revised: *However, this difference would need to be interpreted with caution as it may be caused by the difference in referral systems as well as health seeking habits across different countries.*

Comment 11) The study focuses on the economic impact of IBS. Therefore the title of the manuscript should be changed to "The Economic Burden of Irritable Bowel Syndrome in China".

Response: We are happy to change the title to "The Economic Burden of Irritable Bowel Syndrome in China" as suggested by the reviewer.