Author’s response to reviews

Title: Economic burden of moderate to severe Irritable Bowel Syndrome with Constipation in six European countries

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Reviewer reports:

Michael Camilleri (Reviewer 1):

This is an interesting multi-national study assessing healthcare costs in several European countries. The data are well documented in the manuscript and tables.

Dear reviewer, thank you for your valuable observations. We have done our best to address all your commentaries and made any required modifications accordingly.
The following comments are intended to strengthen the manuscript and acknowledge additional limitations

1. Biased sample: Study center recruitment in table 1 shows that most patients were attending specialist centers and only Germany and Spain had recruited participants from primary care. Therefore, this introduces referral bias in the sample studied. This needs to be acknowledged in the discussion.

Thank you for your comment. This has been added as a limitation in the Discussion section.

2. Comparison between health care utilization and costs between specialist care and primary care patients: though the sample size is small, it may be worth contrasting the results with the specialist care cohort in the SAME countries, that is Germany and Spain

We agree that this comparison would be interesting. However, the study was not designed to compare these two settings, and, as noted, the sample sizes are small to preclude clear conclusions. A future comparative study is anticipated.

3. You need to discuss the potential limitation introduced by the fact that the sample size required 90 per country and this was not achieved by several participating countries e.g. Sweden and France.

A sample size of 90 patients per country was calculated to produce a 95% CI equal to the sample mean ± ≤ 20% of the standard deviation of the direct costs associated with IBS-C. Not reaching this sample size weakens the accuracy of the 95%CI of mean direct costs in these two countries. However, we do not see this as a major limitation to the study results, as there has not been big deviations in these countries results when compared to those of the 90+ population countries.

4. Given the small sample size in Sweden, and the specialty care cohort there, it may be that the indirect costs in Sweden need to be downplayed as they may be reflective of the same secondary or tertiary care bias which may be more accessible to higher paid patients. This may be totally wrong....and if so, you need to discuss it.
You are correct. This is already commented in the discussion:

Sweden had the highest indirect costs at over €11,000 per year due to Sweden having the highest percentage of employed patients whose income was above the national average in this study, and one of the highest average gross incomes in Europe. The focus on work productivity and sick leave as an estimate of indirect cost is a limitation of this study as salaries and type of employment are variable between countries.

Additionally, the fact that indirect costs assessment was incomplete is included among the limitations:

The main limitations of this study were the incomplete assessment of indirect healthcare costs associated with work productivity and absenteeism […]

5. Some of the health care costs reflect utilization of tests. Do you have information on the types of test e.g. relatively expensive colonoscopy or CT imaging? If possible, how might these costs be reduced e.g. with biomarkers, such as stool DNA markers or blood to screen for colon cancer; with colonic transit and anorectal manometry to obtain more specific diagnosis than the exclusive symptom-based criteria for IBS-C, which do not define whether to treat rectal evacuation disorder or introduce more effective therapy earlier, and avoid emergency department attendance or even hospitalization.

Thank you for your observation. The utilization of procedures, investigations or tests over 12 months due to IBS-C is detailed in Table 4, including CT, colonoscopies, etc.

6. With regard to hospitalization, there is an opportunity to discuss the results of health care utilization for GI indications from the work of Peery A, Sandler R et al at University of North Carolina in USA. Those studies also show significant health care utilization and hospitalization costs due to constipation.
Thank you for your observation. We assume you refer to doi: 10.1053/j.gastro.2018.08.063. However, this study by Peery et al does not use a specific IBS-C or even constipation population, but all patients attended across US due to Gastrointestinal, Liver, and Pancreatic Diseases.

Further, the study does not detail data of patients hospitalized due to constipation. They are included under the term “Functional/motility disorders”, which includes: esophageal (eg, achalasia), gastric (eg, dyspepsia), and intestinal (eg, irritable bowel syndrome) functional/motility syndromes, as well as constipation and diarrhea.

Thus, we think both studies are not fully comparable and will refrain from making comparisons between them.

Francesco Torresan (Reviewer 2): Interesting study about direct and indirect costs related to moderate and severe IBS-C. The manuscript is well written and stresses the large impact of this condition on healthcare systems and society.

Dear reviewer, thank you for your valuable observations. We have tried to address all your commentaries and made required modifications accordingly.

2 issues should be discussed and addressed:

1. 525 patients diagnosed with IBS-C were included. During the last 6 months observation period many patients underwent diagnostic tests which could have modified the initial diagnosis. Did a subgroup of these patients have a different diagnosis after these tests or did you exclude them?

Thank you for your observation. I am afraid this was not studied and thus, we cannot answer this question. Patients were, accordingly, not excluded for this reason.
2. Patients were included both from primary or specialist care. Do you have subgroups of patients managed only by primary physician and only by specialists? It could be interesting to study if there is a cost saving in patients followed only by specialists

Thank you for your observation. The 87.4% of patients were included from specialist care, with France, Italy and UK including 100% of patients from specialist care. Thus, only Germany and Spain have patients both from primary and specialist care. Unfortunately, we have not analyzed their data separately. The study was not designed to compare these two settings and the sample sizes are too small to preclude clear conclusions. A future comparative study is anticipated.