Point-by-point response to reviewers

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors:

The manuscript entitled "Patients' perspectives on smoking and inflammatory bowel disease: an online survey in collaboration with European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA)" is an observational European study assessing patients' perception on smoking. Main strengths of the study are the multi-countries responses and the relative large number of responses. The main issue of the survey is that it replicated the results of previous smaller studies; thus the novelty of the results is questionable.

- **We thank Reviewer #1 for her/his comment. We agree that there are not very new findings in this study but it seems informative with some update educational value.**

Main concerns, beyond novelty
1. How the translations of the questionnaire to the different languages have been assessed and validated

- **Translations were made by translators that EFCCA has previously worked with. They were proofread by native speakers from EFCCA's member associations and revised, if necessary. PMI did final checks and revisions on the translations in order to have a double validation before the survey was launched. This has been specified in the main text (please see page 6).**

2. What was the response rate of the questionnaire? I understand that this is a difficult task but i propose the following to get an estimate: a. The site administrator can measure the clicks of the form and this number will be the denominator.; b. Calculate the number of the participating country societies' members and divide the number of your responses by this number

- **Thank you for your question. This survey enrolled 1180 IBD patients speaking nine different languages. However, 130 patients only selected their language and did not answer the first question (i.e. if they have ever smoked or consumed an alternative nicotine product). This group of patients was excluded, and we considered 1050 patients as participants. We specified this in the main text (please see page 8).**
- **We did not calculate the response rate according to the number of the participating country societies' members because national associations were encouraged to promote the survey online by providing their members with an online link but did not send an email to each member to inform them about this survey. We added an explanation in the main text (please see page 7), as follows: "National associations were encouraged to promote the survey online by providing their members with an online link on their website. Information on this survey was also displayed in posters and flyers at the clinic of each participating investigator."**

3. How did you secure GDPR issues

- **Thank you for your comment. We specified it in the main text, as follows (please see page 7): "Data was collected anonymously online, and participation was entirely optional. Since it was an anonymous survey, there was no data or user tracking. EFCCA strictly follows the General Data Protection Regulation (GDPR)**

and does not own the data that was transferred in a secured way to the biostatistician."

Minor concern

1. Abstract. Provide a structured form and delete the last sentence

- **Thank you for your comment. This has been done.**

2. Introduction. Please delete the 1st and the 4th paragraph; they do not add value in the manuscript

- **Thank you for your comment. These paragraphs have been deleted.**

3. Table 1. How many subjects are included. Different numbers in the title (1050) age (796), other variables (798)

- **Thank you for your question. As we write in the very first section of the results section: "This survey enrolled 1050 IBD patients speaking nine different languages. The most represented countries were Italy (20.3%), Finland (13.9%) and Portugal (13.9%). Among them, 807 (76.9%) patients declared to have ever smoked or consumed an alternative nicotine product and proceeded to complete the rest of the questionnaire". The survey had a hierarchical structure, meaning that only patients who answered to certain items could answer to other following questions. For this reason, the denominator for certain questions is different. In few cases, the patient did not answer, and this can result in a missing value.**

4. Delete table 2, since it overlaps with table 3.

- **Thank you for your suggestion. We agree with Reviewer #1 and have now deleted the old Table 2.**

5. Table 3 is too long. Please split it in more tables according to the assessed outcome

- **Thank you for your suggestion. We have now split the old Table 3 into three different tables. Please, note that, since we have removed the old Table 2, the three new tables are denominated Tables 2, 3 and 4.**

6. Figure 1 is not a figure. Name it supplemental document

- **Thank you for your comment. This has been done.**

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This survey of IBD patients, assessed the knowledge of patients with IBD regarding the impact of any type of nicotine-containing products in both CD and UC. The study is of importance and interest

- **We thank Reviewer #2 for her/his comment.**

However, the following needs to be clarified:

Methods 1. How were the patients chosen? Were the questionnaire sent to all patients with IBD on record?

- **Thank you for your comment. We added an explanation in the main text (please see pages 6 and 7), as follows: "National associations were encouraged to promote the survey online by providing their members with an online link on their website.**

Information on this survey was also displayed in posters and flyers at the clinic of each participating investigator."

2. How many countries were chosen. Explain the discrepency in language - were more patients chosen from some countries?

- **As said in the main text (please see page 6), the survey was made available in English, French, German, Spanish, Portuguese, Italian, Greek, Finnish and Slovenian.**
- **We cannot explain the discrepancy in languages because national associations were encouraged to promote the survey online by providing their members with an online link on their website, and information on this survey was also displayed in posters and flyers at the clinic of each participating investigator. The survey was closed after having enrolled more than 1000 participants, whatever their nationality. We specified this in the main text (please see page 7).**

Results 1. Explain the large difference in the gender ratio

- **We cannot fully explain the large difference in the gender ratio because the survey was closed after having enrolled more than 1000 participants, whatever their gender. We specified this in the main text (please see page 7). Were females more motivated than males to complete the questionnaire? We do not have enough data to conclude.**

Table Recommend that the tables be shorten to reflect the most important data

- **Thank you for your suggestion. We agree that in particular Table 2 contains too many information. As suggested by Reviewer #1, we have now excluded the old Table 2, as Tables 2 and 3 were overlapping on many questions and we have split the old Table 3 into more tables to improve clarity, as it was deemed too long.**

Reviewer #3:

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors:
Introduction: The association of smoking with CD is not totally consistent. See for example: Reif et al. American Journal of Gastroenterology 95: 479-483, 2000.

- **We agree and cited this article in the introduction as follows (please see page 4): "Thus, smoking habits are much more frequent in CD patients than in UC patients, except in Jewish patients in Israel in whom the stronger genetic tendency in CD may contribute to this discrepancy."**

Methods: In which language was the questionnaire prepared? Who did the translations and cross-translations?

- **As said in the main text (please see page 6), the survey was made available in English, French, German, Spanish, Portuguese, Italian, Greek, Finnish and Slovenian. Translations were made by translators that EFCCA has previously worked with. They were proofread by native speakers from EFCCA's member associations and revised, if necessary. PMI did final checks and revisions on the translations in order to have a double validation before the survey was launched. This has been specified in the main text (please see page 6).**

Was there any procedure to confirm medical data supplied by the patients?

- **Thank you for your question. Unfortunately there was no procedure to confirm medical data supplied by the patients. We specified this in the main text (please see page 8) as well as in the title of Table 1 and Table S1. However, this is not a major limitation because none of the analysis**

Page 5: multiple categorial options, change to categorical.

- **Thank you for your comment. This has been changed.**

Results: How many patients refused to complete the questionnaire? Were some questionnaires completed only partially? If so, how was this handled?

- **Thank you for your questions. The number of initial records in the database was 1180. However, 130 patients only selected their language, did not answer the first question (i.e. if they have ever smoked or consumed an alternative nicotine product) and did not enter their demographic details. This group of patients was excluded, and we considered 1050 patients as participants.**
- **The survey had a hierarchical structure, meaning that only patients who answered to certain items could answer to other following questions. For this reason, the denominator for several questions is different. In some cases, the patient did not answer and this can result in a missing value. We have transparently declared in our tables the denominator we have used to calculate the proportion of patients giving certain answers. We hope to have sufficiently clarified the doubts of the reviewer.**

"performed any intestinal surgery" - better to say "has undergone surgery"

- **Thank you for your comment. This has been changed.**

"marijuana" Can this be equated with smoking nicotine?

- **Thank you for your comment. For more rigor, we changed the term "alternative nicotine product" for "alternative smoking product".**

"Namely, 79.2% of smoking CD patients perceived their habit significantly of moderately worsened disease activity, while only 34.0% of smoking UC" This is poor English.

- **Thank you for your comment. We modified the sentence as follows: "More than three-quarters (79.2%) of CD patients perceived that smoking significantly or moderately worsened disease activity versus 34.0% of UC patients."**

"Among patients having ever smoked cigarettes, 31.7% did not discuss the effect of smoking on disease activity" This is not clear. Is it possible that the physicians did not raise the subject with their patients?

- **Thank you for your question. We agree that this was not clear and modified the sentence accordingly, as follows (please see page 10): "Among patients having ever smoked cigarettes, 31.7% did not receive any information from their physician on the effect of smoking on disease activity, while 45.4% of them received the information that smoking is detrimental to disease activity." This is why we conclude in our discussion that education on smoking is probably insufficiently considered for the management of our patients (please see page 18).**

Table 1. Participants' characteristics. It is preferable to separate all the data by diagnosis.

- **Thank you for your suggestion. Since Table 1 represents the description of all the IBD patients' characteristics, we have preferred to keep it simple as it is. In order to satisfy the reviewer's request, we have now added a supplementary table (please see supplementary Table S1) with the information contained in table 1 reported for patients with CD and UC. We have also included in the supplementary table the appropriate statistical tests to assess the difference in patients' characteristics by diagnosis, and have cited this new table in the results section, page 7.**

Table 2 and Table 3. Why is Table 2 not showing CD and UC separately? Why not combine Tables 2 and 3?

- **Thank you for your suggestion. As asked by Reviewer #1, we have now excluded the old Table 2, as Tables 2 and 3 were reporting very similar information and we have split the old Table 3 into more tables (i.e. new Tables 2,3 and 4), since it was deemed too long.**

Discussion.
Page 20: "It was quite surprisingly that the same result", should be surprising.

- **Thank you for your comment. Smoking cigarette have an opposite clinical impact on CD and UC, since smoking increases the risk of CD and worsens its clinical course, but has a protective effect in UC, as stated in our introduction. If the majority of CD patients was aware of detrimental effects of smoking cigarette on their disease, we expected to find only a minority of CD patients restarting smoking after IBD diagnosis, but our data found a high proportion of CD patient restarting smoking after IBD diagnosis. Otherwise, it was not surprising to find a large majority of UC patients restarting smoking after IBD diagnosis. We clarified the sentence as follows (please see page 18): "Among participants declaring to have ever stopped cigarette smoking and restarted, we expected to find a large majority of UC patients restarting smoking after IBD diagnosis. Quite surprisingly, the same result was observed in the CD group of patients while smoking is known to worsen the course of CD."**

"In the Nancy group" This term was not mentioned before, what is it?

- **Thank you for your comment. The study referenced n°27 was a single center study conducted by the IBD team from Nancy, France. This terminology refers to the affiliation of all authors that realized the study. We clarified the sentence as follows (please see page 18): "In a study conducted by the Nancy group…"**

General comments:
1 It should be stated that there is growing evidence that e-cigarettes are detrimental to human health and that their use should be discouraged.

- **Thank you for your comment. As we discussed in our study, the impact of e-cigarettes remains unknown, both in healthy and sick populations. The lack of evidence about safety requires to remain vigilant over potential adverse effects; however, current available research also suggests the potential benefits of e-cigarettes as a harm reduction model for those who use combustible cigarettes, and e-cigarettes may have an important role to play in preventing death and disability from tobacco use. Thus, further research is needed to assess whether e-cigarettes could be an effective smoking cessation tool, and to evaluate both short- and long-term health effects of e-cigarettes. We modified the main text accordingly (please**

see pages 19 and 20) and cited the following references: Fadus et al. Drug Alcohol Depend. 2019; Cooke et al. J Allergy Clin Immunol Pract. 2015.

2 The authors may wish to state that cigarette smoking increases heath care costs in IBD considerably. See for example: Burisch et al. Lancet Gastroenterology & Hepatology. 2020

- **Thank you for your comment. We added a new paragraph in the discussion section referring to the economic impact of smoking in IBD and we cited the recent study by Burisch et al. (please see page 18).**

Reviewer #4:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Catherine Le Berre et al and colleagues assessed differences of smoking perceptions in patients suffering from inflammatory bowel disease (CD vs. UC), with the aim to understand how these different smoker profiles perceived the impact of smoking on their inflammatory bowel disease (IBD). This is a large, European, multicenter survey of over 1000 IBD patients assessing the level of knowledge of patients with IBD regarding the impact of any type of nicotine-containing products. Investigators not surprisingly found significant differences between CD and UC patients in both awareness and perception of the impact of smoking on their disease. Furthermore, despite most CD patients were aware of a detrimental effect of smoking, and a large part of UC patients was aware of possible beneficial impact of smoking in their disease, authors encourage efforts to be done to motivate smoking cessation for all IBD patients because of the well-established beneficial effects of smoking cessation on general health. That said, investigators recommend additional studies are required if not mandatory to explore the safety and impact of the increasing use of alternative nicotine-containing products, like e-cigarettes. There isn't new findings in this reported study but I find it informative with some update educational value. The aims are stated clearly. The title is informative and relevant. The references are relevant and recent. The cited sources are referenced correctly. Appropriate and key studies are included. The introduction reveals what is already known about this topic. The research question and questionnaire items is clearly outlined. The study methods are valid and reliable. There are enough details provided and the data is presented in an appropriate way. Statistics and Tables are relevant and clearly presented. The conclusions answer the aim of the study. The conclusions are supported by references and own results.

- **We thank Reviewer #4 for her/his comment.**

Science Editor:
1 Scientific quality: The manuscript describes an observational Study of the inflammatory bowel disease. The topic is within the scope of the WJG.
(1) Classification: Grade C, Grade C, Grade C, and Grade D;
(2) Summary of the Peer-Review Report: Reviewer# 01587889 thinks it is informative with some update educational value. The aims are stated clearly. The title is informative and relevant. The research question and questionnaire items are clearly outlined. The study methods are valid and reliable. There are enough details provided and the data is presented in an appropriate way. Statistics and Tables are relevant and clearly presented. The conclusions answer the aim of the study. The conclusions are supported by references and own results.

- **We thank Science Editor for her/his comment.**

However, there are some points should to be addressed.
The authors need to clarify how to select the patients, the tables should be shortened to reflect the most important data. The questions raised by the reviewers should be answered;

- **Thank you for your comment.**
- **As said above, we explained the selection of patients in the main text (please see pages 6 and 7), as follows: "National associations were encouraged to promote the survey online by providing their members with an online link on their website. Information on this survey was also displayed in posters and flyers at the clinic of each participating investigator."**
- **Tables were shortened for more clarity.**

(3) Format: There are 3 tables and 1 figure. A total of 36 references are cited, including 7 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A, Grade B, Grade B and Grade B. The authors provided a personal language certificate. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. The Institutional Review Board Approval Form is not applicable. Written informed consent was waived.

- **We thank Science Editor for her/his comment.**

The authors need to fill out the STROBE form with page numbers.

- **Thank you for your comment. This has been done.**

No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by the Philip Morris Products SA. The topic has not previously been published in the WJG. The corresponding author has published 2 articles in the WJG.

- **We thank Science Editor for her/his comment.**

5 Issues raised: (1) I found no "Author contribution" section. Please provide the author contributions;

- **Thank you for your comment. This has been done (please see page 1).**

(2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

- **Thank you for your comment. Please find enclosed a formal email from Linkt Health containing the details regarding the survey sponsored by PMI.**

(3) I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text;

- **Thank you for your comment. This has been done (please see pages 23 and 24).**

(4) Figure 1 was lost.

- **This has been se-submitted as supplemental document as requested by Reviewer #1.**

6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

- **We thank Science Editor for her/his comment.**

Editorial Office Director:
I have checked the comments written by the science editor. The "Abstract" should be rewritten according to the guideline of "Observational Study" manuscript.

- **Thank you for your comment. This has been done.**

Company Editor-in-Chief:
I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

- **We thank Company Editor-in-Chief for her/his comment.**