PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is disease activity associated with social support and psychological distress in Crohn's disease patients? Results of a cross-sectional study in a Chinese hospital population
AUTHORS	Huang, mengting; Tu, Lei; Wu, Linxia; Zou, Yan; Li, Xin; Yue, Xiaofei; Huang, Chen; Lei, Ping; Li, Qian; Han, Ping; Yang, Lian; Zhu, Liangru

VERSION 1 – REVIEW

REVIEWER	Sarid, Orly
REVIEW RETURNED	02-Jul-2023

GENERAL COMMENTS	Thank you for letting me review this manuscript. I believe that with incorporating the following remarks it will be suitable for publication in your journal. Due to the relatively low number of participants and non innovative research question I suggest to add an ethno-cultural perspective. Please expand on the Chinese culture and what are the implications for men and women with crohn according to their gender roles in a collectivistic country. Especially expand on the symptoms you have studied. Add many more studies from other countries, western such as Australia, Israel, USA and ct comparing men and women and discuss your findings according to other studies out side of China. This will be an interesting and valuable contribution of your work. Healthcare services for CD are more demanding and costly for patients with symptoms of anxiety and depression- explain and provide references Abstract- correct Setting: A prospective study of adults recruited in China between March 2020 and March 2022. it is not consistent with the paper

REVIEWER	Mulcahy, Hugh E University College Dublin
REVIEW RETURNED	16-Jul-2023

GENERAL COMMENTS	In this cross-sectional study of 162 subjects, the authors found that Crohn's disease activity was independently associated with subjective social support, psychological distress and C-reactive protein. The authors conclude by highlighting the importance of psychological distress and support factors in this disease and suggest further longitudinal and intervention studies.

	The study, though small, appears to have been conducted methodically, the results are appropriately presented and the message is clear. Therefore, there is nothing actually wrong with this paper. The problem is that cross-sectional studies on this subject have been performed and published hundreds of times over the past forty years with the same results. As such the manuscript adds little or nothing to the body of literature on the association of IBD with psychological distress and social support, beyond being in a different population. This, in itself, poses additional problems for a European and North American readership, because the treatment characteristics of the patient population presented, only 15 percent of whom were on biologics, is very different from other populations. As an example, over 50 percent of Crohn's disease patients in our institution commence a biologic within a year of diagnosis, and the low percentage of biologic use in Huang et al's. Population is likely the reason that close to 60 percent of their study subjects had active disease at the time of study. This might imply that, rather than providing psychological and social support, the authors should consider providing contemporary medical therapies to many more of their patients. The authors conclude that "further exploration of these factors in longitudinal and intervention studies may help to develop effective CD management models". This is also problematic. Since these studies have also been performed and effective CD management models are in place in many countries. As an example, large longitudinal studies have assessed the causative relationship between psychological disability and disease activity (e.g. Bitton 2008, Mikocka-Walus 2016, Gracie 2018 among others). Furthermore, Interventional studies, including randomised controlled trials of psychological treatments to combat stress, anxiety and depression have also been performed (e.g. Bennebroek Evertsz 2017, Wynne 2019, (Reviews Knowles 2013, Keefer 2018). Finally, effective management models and society guidelines are established in the United Kingdom, Europe and North America that deal with social and psychological support as well as medical and surgical treatments. Thus, the need for any cross-sectional data on these topics is doubtful. The association between disability and gender is also well known (for review see Fracas 2023). Finally, many of the statements, e.g. "..lower levels of social support result in worsening disease activity" are inappropriate (although true), because they cannot be inferred from the cross-sectional data presented. Overall, this a neat, tidy and well-conducted cross-sectional study of psychosocial disability in a population with a rapidly rising incidence of Crohn's disease. It would likely be of interest to local physicians and researchers, but its content doesn't add anything to current knowledge of the biopsychosocial aspects of Crohn's disease.

REVIEWER	Agostini, Alessandro University of Bologna
REVIEW RETURNED	20-Jul-2023

GENERAL COMMENTS	The study by Huang and collaborators addresses a topic that is certainly of great interest. The paper presents some methodological concerns and some general concerns. The literature review presented in the introduction is not particularly up-to-date. The study attempts to establish an association between social support and psychological well-being

	and disease activity. Although the biopsychosocial model is mentioned later in the paper, the introduction and the study hypothesis do not explicitly refer to this model, and more importantly, the bidirectional relationship between illness actvities and psychological problems is not clearly made explicit. The authors state, However, most previous studies have focused on anxiety or depression, rarely focusing on other dimensions. Yet, numerous studies have addressed various psychological dimensions such as quality of life, coping strategies, quality of sexual relationships, etc. In partricular, dimensions such as attachment and mentalizing have recently been evaluated in patients with IBD. These aspects have been neglected by the authors, although their manuscript addresses issues pertaining to the quality of interpersonal relationships and social support. The rationale for some of the inclusion criteria is unclear. The authors write: patients not taking medication for CD. What does this mean? Patients in disease activity inevitably take medication, and even patients in remission usually take maintenance medication. Please explain. The use of the SCL90 questionnaire can be considered questionable for a few reasons. First, it has already been abundantly used in patients with IBD in the past. This makes the results presented in this paper of minor interest. Second, generally this questionnaire is used as an index of global patient distress. Although the questionnaire contains numerous subscales, the scores obtained in the various subscales are not considered particularly reliable as a measure of a given symptom. For example, the depression value of the SCL90R subscale is not considered a truly reliable measure of a patient's depression. In the paper, the authors tend to overestimate the reliability results of the subscales. The discussion suffers from the limitations described above. Once again, the authors write that social support has been little investigated in patients with IBD. Yet much research has focused on this factor. For example: Psychological distress, social support, and disease activity in patients with inflammatory bowel disease. Sewitch MJ, et al. Am J Gastroenterol. 2001. The SCL90R questionnaire was used in this 2001 research as did the authors in their research. Again, more recently: Effect of Social Support on Psychological Distress and Disease Activity in Inflammatory Bowel Disease Patients. Slonim-Nevo V, et al. Inflamm Bowel Dis. 2018 Jun 8;24(7):1389-1400. doi: 10.1093/ibd/izy041. It is not clear in the discussion what significant and new elements the present research adds to current knowledge.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

Orly Sarid:

Comment 1：Due to the relatively low number of participants and non innovative research question I suggest to add an ethno-cultural perspective. Please expand on the Chinese culture and what are the implications for men and women with crohn according to their gender roles in a collectivistic country. Especially expand on the symptoms you have studied.

Add many more studies from other countries, western such as Australia, Israel, USA and ct comparing men and women and discuss your findings according to other studies out side of China. This will be an interesting and valuable contribution of your work.
Response 1: Thank you for your thoughtful comments. I am very grateful for the guidance and positive feedback of the reviewer. We totally agree with the reviewer's opinion. Thus, we have added details description of ethno-cultural perspective, and made the corresponding changes to make it easier for readers to understand in the Introduction (paragraph 1-2) and Discussion (paragraph 8) of our manuscript. At the same time, in order to express accurately the differences between men and women, we have talked the difference analysis between men and women in this study and displayed in Results (Table 3 and Supplementary materials Table 1) and Discussion (paragraph 8). Thank you for your kind suggestions to improve our paper. The revised portions are marked in red font of our manuscript.

Comment 2: Healthcare services for CD are more demanding and costly for patients with symptoms of anxiety and depression- explain and provide references
Response 2: Thank you for your constructive comments. We have added details description of the sentence to make it easier for readers to understand in Introduction (paragraph 3).
The revised sentence as follows:
The uncertainty of treatment results and psychological disorders may lead to disease recurrence, aggravate the course of the disease, and directly lead to the decline of patients' quality of life and the increase of treatment costs [1-2]. Patients with inflammatory bowel disease and anxiety or depression have a higher risk of hospitalization, emergency room visits, readmissions, and use of outpatient services than patients without these symptoms [3]. Thus, healthcare services for CD are more demanding and costly for patients with symptoms of anxiety and depression.

Comment 3: Abstract- correct
Setting: A prospective study of adults recruited in China between March 2020 and March 2022.
it is not consistent with the paper
Response 3: Thank you for your insightful comments. We have corrected this in the manuscript. I am very grateful for the guidance of you.
The revised sentence as follows:
The study was conducted in Wuhan, China between March 2020 and March 2022.

Response to Reviewer 2
Dr. Hugh E Mulcahy, University College Dublin:
Comment 1: In this cross-sectional study of 162 subjects, the authors found that Crohn's disease activity was independently associated with subjective social support, psychological distress and C-reactive protein. The authors conclude by highlighting the importance of psychological distress and support factors in this disease and suggest further longitudinal and intervention studies.
The study, though small, appears to have been conducted methodically, the results are appropriately presented and the message is clear. Therefore, there is nothing actually wrong with this paper.
Response 1: Thank you for your comments. We appreciate your positive comments.

Comment 2: The problem is that cross-sectional studies on this subject have been performed and published hundreds of times over the past forty years with the same results. As such the manuscript adds little or nothing to the body of literature on the association of IBD with psychological distress and social support, beyond being in a different population. This, in itself, poses additional problems for a European and North American readership, because the treatment characteristics of the patient population presented, only 15 percent of whom were on biologics, is very different from other populations. As an example, over 50 percent of Crohn's disease patients in our institution commence a biologic within a year of diagnosis, and the low percentage of biologic use in Huang et al's. Population is likely the reason that close to 60 percent of their study subjects had active disease at

the time of study. This might imply that, rather than providing psychological and social support, the authors should consider providing contemporary medical therapies to many more of their patients.
Response 2: Thank you very much for your suggestion to improve our article. We have carefully read the reviewer's comments and suggestions. In the 20th century, inflammatory bowel disease (IBD) was primarily a disease of westernized countries in North America, Europe, and Oceania. At the turn of the 21st century, IBD has become a global disease with increasing incidence in newly industrialized countries in Asia, South America and Africa. Epidemiological studies have confirmed that there are differences in the incidence of inflammatory bowel disease, and this difference shows significant regional differences. For example, the estimated prevalence of CD ranges from 100 to 200 per 100,000 people in the United States [4], and the annual incidence of CD in Asia is about 0.04-5.00 per 100,000 people [5]. One reason for this discrepancy may therefore have to do with different patient populations. Therefore, we added relevant epidemiological information in the Introduction of the manuscript (paragraph 1).
At present, the treatment of CD mainly includes general treatment, medications therapy. Conventional medications for CD include anti-inflammatory drugs, immunosuppressants and corticosteroids, and surgical treatment, and the biological agents have been widely used in the treatment of CD. If an individual does not respond, or loses response to first-line treatments, then biologic therapies such as tumour necrosis factor-alpha antagonists are considered for treating CD [6]. However, with the increasing number of CD patients exposed to biologics, the long-term safety of has aroused people's concern [7]. Therefore, the choice of treatment for patients with CD is based on a comprehensive assessment of the patient's condition, and it needs to be selected according to the wishes of patients. In future studies, we will further consider the impact of different treatment modalities in patients with CD to improve the reliability of our results. We are very grateful for the guidance of you.

Comment 3: The authors conclude that “further exploration of these factors in longitudinal and intervention studies may help to develop effective CD management models”. This is also problematic. Since these studies have also been performed and effective CD management models are in place in many countries. As an example, large longitudinal studies have assessed the causative relationship between psychological disability and disease activity (e.g. Bitton 2008, Mikocka-Walus 2016, Gracie 2018 among others). Furthermore, Interventional studies, including randomised controlled trials of psychological treatments to combat stress, anxiety and depression have also been performed (e.g. Bennebroek Evertsz 2017, Wynne 2019, (Reviews Knowles 2013, Keefer 2018). Finally, effective management models and society guidelines are established in the United Kingdom, Europe and North America that deal with social and psychological support as well as medical and surgical treatments. Thus, the need for any cross-sectional data on these topics is doubtful. The association between disability and gender is also well known (for review see Fracas 2023).
Response 3: Thank you for your insightful comments. Although there have been many articles on the topic in many countries, there have not been many studies in developing countries such as China. Therefore, we also added " ethno-cultural perspective " to the article, focusing on the relationship between psychological distress and social support in CD patients in developing countries such as China in the Discussion. At the same time, many studies have found that the differences in the psychological performance of IBD patients are related to gender, and females are predictors of IBD combined anxiety and depression [8-9]. However, the study of Nahon et al. pointed out that the incidence of anxiety and depression in female patients with IBD was not significantly increased, and gender was not correlated with the occurrence of anxiety and depression [10]. Thus, one of the strengths of the study was that we found that women with CD tend to report greater depressive symptoms than men in China, and added the details description of the differences between men and women with CD in the results section of the manuscript, and discussed the possible reasons for the gender differences in detail in the discussion section of the manuscript. Therefore, in daily clinical diagnosis and treatment, more attention should be paid to whether women have mental and psychological abnormalities and their severity, and effective psychological support should be provided according to the specific circumstances.

This study is a cross-sectional study, which can only objectively reflect the differences in psychological disorders and social support among patients with Crohn's disease at different active periods between March 2020 and March 2022. Therefore, in order to make it easier for readers to understand, we have corrected our expression in the manuscript. And in future studies, we will increase the sample size and conduct longitudinal studies. Thank you again for your comments on our manuscript.

Comment 4: Finally, many of the statements, e.g. “lower levels of social support result in worsening disease activity” are inappropriate (although true), because they cannot be inferred from the cross-sectional data presented.
Response 4: We sincerely appreciate the valuable comments. We agree with the reviewer’s opinion, and we apologize for the ambiguity in the manuscript. This is a cross-sectional study and can only indicate differences in the scale scores of patients with Crohn's disease in active and remission, not a causal relationship between the two. Thus, we have made the corresponding changes in the article. We are very grateful for the guidance of you.

Comment 5: Overall, this a neat, tidy and well-conducted cross-sectional study of psychosocial disability in a population with a rapidly rising incidence of Crohn’s disease. It would likely be of interest to local physicians and researchers, but its content doesn’t add anything to current knowledge of the biopsychosocial aspects of Crohn’s disease.
Response 5: Thank you for your insightful comments. We have studied the comment carefully and have made corrections, which we hope meet with approval. We added an ethno-cultural perspective, focusing on the relationship between psychological distress and social support in CD patients in developing countries such as China in the Discussion, and added the details description of the differences between men and women with CD in the results section of the manuscript, and discussed the possible reasons for the gender differences in detail in the discussion section of the manuscript.

Response to Reviewer 3
Dr. Alessandro Agostini, University of Bologna:
Comment 1：The study by Huang and collaborators addresses a topic that is certainly of great interest. The paper presents some methodological concerns and some general concerns. The literature review presented in the introduction is not particularly up-to-date.
Response 1: Thank you for your comments. We have added some of the recently published literature in the manuscript.

Comment 2：The study attempts to establish an association between social support and psychological well-being and disease activity. Although the biopsychosocial model is mentioned later in the paper, the introduction and the study hypothesis do not explicitly refer to this model, and more importantly, the bidirectional relationship between illness actvities and psychological problems is not clearly made explicit.
Response 2: Thank you for your constructive comments. I am very grateful for the guidance of the editor. This study is a cross-sectional study, which can only objectively reflect the differences in psychological disorders and social support among patients with Crohn's disease at different active periods between March 2020 and March 2022. Although we built the model through logistic regression analysis. In order to make it easier for readers to understand, we have made the corresponding changes in the article in the introduction and the study hypothesis. Thank you for your kind suggestions to improve our paper.

Comment 3：The authors state, However, most previous studies have focused on anxiety or depression, rarely focusing on other dimensions. Yet, numerous studies have addressed various psychological dimensions such as quality of life, coping strategies, quality of sexual relationships, etc. In partricular, dimensions such as attachment and mentalizing have recently been evaluated in

patients with IBD. These aspects have been neglected by the authors, although their manuscript addresses issues pertaining to the quality of interpersonal relationships and social support.
Response 3: Thank you for your thoughtful comments. We agree with the reviewer's opinion, and we are sorry to have overlooked these dimensions. Therefore, we added the relevant discussion on attachment and mentalizing of IBD patients in the discussion part of the manuscript, and added related literature [11-12]. And to increase the research in this direction in the follow-up research. And in the future research, we will increase the research in this dimension. We have made the corresponding changes in the article. Thanks again for your suggestions.

Comment 4：The rationale for some of the inclusion criteria is unclear. The authors write: patients not taking medication for CD. What does this mean? Patients in disease activity inevitably take medication, and even patients in remission usually take maintenance medication. Please explain.
Response 4: Thank you for your insightful comments. We are very sorry for the misunderstanding caused by the lack of clarity in our article. The inclusion criteria in the article states that " patients not taking medication for CD " refers to the absence of psychotropic drugs. Thanks to the reviewer's suggestion, we have revised the expression in the manuscript.

Comment 5：The use of the SCL90 questionnaire can be considered questionable for a few reasons. First, it has already been abundantly used in patients with IBD in the past. This makes the results presented in this paper of minor interest. Second, generally this questionnaire is used as an index of global patient distress. This makes the results presented in this paper of minor interest. Second, generally this questionnaire is used as an index of global patient distress. For example, the depression value of the SCL90R subscale is not considered a truly reliable measure of a patient's depression. In the paper, the authors tend to overestimate the reliability results of the subscales.
Response 5: We sincerely appreciate the valuable comments. The Symptom Checklist 90 (SCL-90), originally developed by Derogatis, consists of 90 items that have a broader psychiatric symptomatology component, using 10 factors that reflect each of the 10 aspects of psychological symptoms: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid, psychoticism, and others. Although SCL-90 have been extensively used in IBD patients in the past, fewer studies have combined SCL-90 with Social Support Rating Scale in CD patients. In addition, we also considered the difference of SCL-90 in CD patients of different genders, and found that women showed higher levels of somatization ($P=0.030$) and anxiety ($P=0.050$) than men in China which was shown in Results section of the manuscript, and discussed the possible reasons for the gender differences in detail in the discussion section of the manuscript. Initially, the Hospital Anxiety and Depression Scale (HADS) was also used to investigate the anxiety and depression of CD patients in this study. As you know, the SCL-90 has a total of 90 items with a wide range of psychiatric symptoms. At present, it is widely used in the screening of clinical psychological abnormalities. Although the anxiety and depression value of the SCL90 scale subscale is not considered a truly reliable measure of a patient's depression. We wanted to explore the effects of multiple psychological factors. Secondly, the anxiety and depression indexes in HADS scale were significantly correlated with those in SCL-90 ($r=0.6$, $P<0.001$; $r=0.64$, $P<0.001$, respectively). And the trend of HADS and SCL-90 anxiety and depression were consistent. Therefore, in order to avoid duplication, this study used multiple dimensions of the SCL-90 scale to assess the individual mental health level of CD patients. If the reviewer considers it is necessary to add the content of HADS to the article, we can also modify the article accordingly. In the future study, we will include more CD patients to improve the reliability of our results. Thank you for your suggestions to improve our paper. We have made the corresponding changes in the article.

Comment 6：The discussion suffers from the limitations described above. Once again, the authors write that social support has been little investigated in patients with IBD. Yet much research has focused on this factor. For example: Psychological distress, social support, and disease activity in

patients with inflammatory bowel disease. Sewitch MJ, et al. Am J Gastroenterol. 2001. The SCL90R questionnaire was used in this 2001 research as did the authors in their research.
Again, more recently: Effect of Social Support on Psychological Distress and Disease Activity in Inflammatory Bowel Disease Patients. Slonim-Nevo V, et al. Inflamm Bowel Dis. 2018 Jun 8;24(7):1389-1400. doi: 10.1093/ibd/izy041IF: 4.9 Q2. It is not clear in the discussion what significant and new elements the present research adds to current knowledge.
Response 6: Thank you for your constructive comments. I am very grateful for the guidance of the editor.
Sewitch MJ et al. used the SCL-90 and Social Support Questionaire 6, and Vered Slonim-Nevo et al. used the Multidimensional Scale of Perceived Social Support (MSPSS). The scales used in this study were SCL-90 and Social Support Rating Scale. In contrast to other studies, we studied CD patients in China and expanded the sample size.
In addition, a number of current studies have found that differences in psychosocial performance of IBD patients are related to gender, and female sex is a predictor of comorbid anxiety and depression in IBD [8-9]. However, the study of Nahon et al. pointed out that the incidence of anxiety and depression in female IBD patients was not significantly increased, and there was no correlation between gender and the occurrence of anxiety and depression [10]. Therefore, we have added details description of ethno-cultural perspective, and made the corresponding changes to make it easier for readers to understand in the Introduction of our manuscript. At the same time, in order to express accurately the differences between men and women, we have talked the difference analysis between men and women in this study and displayed in Results (Table 3 and Supplementary materials Table 1) and Discussion (paragraph 8). Thank you for your kind suggestions to improve our paper.

Thank you again for your comments on our manuscript. BMJ Open is an influential journal. From all the papers published in your journal, readers have been learning a lot. Hopefully, we could have our article been considered of publication in your journal. Should there been any other corrections we could make, please feel free to contact us.

References：
[1] Kok KB, Byrne P, Ibarra AR, Martin P, and Rampton DS. Understanding and managing psychological disorders in patients with inflammatory bowel disease: a practical guide. Frontline Gastroenterol. 2023;14(1):78-86.
[2] Jordi SBU, Lang BM, Auschra B, von Känel R, Biedermann L, Greuter T, Schreiner P, Rogler G, Krupka N, Sulz MC, Misselwitz B, and Begré S. Depressive Symptoms Predict Clinical Recurrence of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2022;28(4):560-71.
[3] Dubinsky MC, Dotan I, Rubin DT, Bernauer M, Patel D, Cheung R, Modesto I, Latymer M, and Keefer L. Burden of comorbid anxiety and depression in patients with inflammatory bowel disease: a systematic literature review. Expert Rev Gastroenterol Hepatol. 2021;15(9):985-97.
[4] Kappelman, M.D., et al., The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol, 2007. 5(12): p. 1424-9.
[5] Ng S C, Tang W, Ching J Y, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study [J]. Gastroenterology, 2013, 145(1): 158-65.e2
[6] Townsend, C.M., et al., Adalimumab for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev, 2020. 5(5): p. Cd012877.
[7] Pudipeddi, A., et al., Safety of drugs used for the treatment of Crohn's disease. Expert Opin Drug Saf, 2019. 18(5): p. 357-367.

[8] Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT, and Sussman DA. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. Aliment Pharmacol Ther. 2014;39(8):802-10.
[9] Maconi G, Gridavilla D, Viganò C, Sciurti R, Asthana AK, Furfaro F, Re F, Ardizzone S, and Ba G. Perianal disease is associated with psychiatric co-morbidity in Crohn's disease in remission. Int J Colorectal Dis. 2014;29(10):1285-90.
[10] Nahon S, Lahmek P, Durance C, Olympie A, Lesgourgues B, Colombel JF, and Gendre JP. Risk factors of anxiety and depression in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(11):2086-91.

VERSION 2 – REVIEW

REVIEWER	Sarid, Orly
REVIEW RETURNED	25-Aug-2023

GENERAL COMMENTS	Please change CD patients (active) to an active state of disease and inactive state- all through the manuscript The references need to be rechecked and rewritten.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1

Orly Sarid:

Comment 1：Please change CD patients (active) to an active state of disease and inactive state- all through the manuscript

Response 1: I am very grateful for the guidance of you. We have changed regarding "CD patients (active/inactive)" to "active states and inactive states of disease" in the manuscript.

Comment 2: The references need to be rechecked and rewritten.

Response 2: Thank you for your constructive comments and kind suggestions to improve our paper. We have rechecked and updated the references.

Response to Reviewer 3

Dr. Alessandro Agostini, University of Bologna:

Comment 1: The authors have made an effort to improve their paper yet the paper needs some further revisions.

Response 1: Thank you for recognizing our efforts.

Comment 2: In their reply letter they state that they have included two references (11, 12) which do not appear in the reference list of the reply letter. What are they alluding to?

Response 2: Thank you very much for your suggestion to improve our article. First of all, I want to apologize for our mistake. We did leave out the references in the final submitted response letter (11,12) but added them in the final manuscript, which is the reference in the manuscript (29,30). I apologize for our mistake.

Comment 3: Consistently, the authors have inserted a paragraph that mentions studies on attachment and mentalization (a paper is cited in the bibliography, reference 30) yet the paragraph is unrelated, disconnected from the rest of the text.

Why are insecure attachment styles and low mentality important for the social support of patients with IBD? Authors must specify these logical steps otherwise the discussion appears fragmental.

Response 2: We have carefully read the reviewer's insightful comments and suggestions. Crohn's disease is chronic, nonspecific intestinal inflammatory disease, which is associated with stress, social interactions and attachment insecurity [1]. Chronic diseases are thought to affect a patient's mental capacity and determine the patient's transition to attachment insecurity. Recently, several studies have begun investigating attachment dimensionality in people with inflammatory bowel disease. According to attachment theory and research and social interaction are regulated by individual's attachment system, which begins to develop in infancy. Individuals with secure attachment styles may form positive relationships, experience a sense of self-confidence and have realistic perceptions of others. Conversely, people with anxious attachment types may have a sense of insecurity in relationships. Social support is known to be a positive health resource that contributes to the well-being of people with chronic diseases. Sound social support may provide individuals with positive emotional experiences and secure attachment styles [2-3]. Social support for family members and friends includes the ability to communicate stress problems, discuss fears and worries, make decisions together, plan social activities together, and get along together in difficult situations. This positive support helps individuals overcome difficulties and challenges in life, especially the stress associated with coping with chronic diseases. On the contrary, patients with insecure attachment may be less able to form positive relationships with doctors and less able to receive help and support from close people, which can lead to worsening disease management.

I am very grateful for the guidance of the reviewer. In order to make it easier for readers to understand, we have made the corresponding changes in the article in the discussion. However, if the reviewer feels unnecessary, we can also delete this paragraph.

Thank you for your kind suggestions to improve our paper.

The revised paragraph as follows:

IBD is considered a bio-psychosocial disease characterized by psychological distress and psychological or psychiatric disorders, which is associated with stress, social interactions and attachment insecurity29,30. Chronic diseases are thought to affect a patient's mental capacity and determine the patient's transition to attachment insecurity. Recently, several studies have begun investigating attachment dimensionality in people with IBD. According to attachment theory and research and social interaction are regulated by individual's attachment system, which begins to develop in infancy. Individuals with secure attachment styles may form positive relationships, experience a sense of self-confidence and have realistic perceptions of others. Conversely, people with anxious attachment types may have a sense of insecurity in relationships. Sound social support

may provide individuals with positive emotional experiences and secure attachment styles31,32. Social support for family members and friends includes the ability to communicate stress problems, discuss fears and worries, make decisions together, plan social activities together, and get along together in difficult situations. This positive support helps individuals overcome difficulties and challenges in life, especially the stress associated with coping with chronic diseases. On the contrary, patients with insecure attachment may be less able to form positive relationships with doctors and less able to receive help and support from close people, which can lead to worsening disease management.

Thank you again for your comments on our manuscript. BMJ Open is an influential journal. From all the papers published in your journal, readers have been learning a lot. Hopefully, we could have our article been considered of publication in your journal. Should there been any other corrections we could make, please feel free to contact us.

Reference (Main Document):

[29] Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. Gastroenterology. 2013;144(1):36-49.

[30] Agostini A, Scaioli E, Belluzzi A, Campieri M. Attachment and Mentalizing Abilities in Patients with Inflammatory Bowel Disease. Gastroenterol Res Pract. 2019;2019:7847123.

[31] Nolte T, Guiney J, Fonagy P, Mayes LC, Luyten P. Interpersonal stress regulation and the development of anxiety disorders: an attachment-based developmental framework. Front Behav Neurosci. 2011;5:55.

[32] Colonnello V, Agostini A. Disease course, stress, attachment, and mentalization in patients with inflammatory bowel disease. Med Hypotheses. 2020;140:109665.

Reference (Response letter):

[1] Agostini, A., et al., Attachment and Mentalizing Abilities in Patients with Inflammatory Bowel Disease. Gastroenterol Res Pract, 2019. 2019: p. 7847123.

[2] Nolte, T., et al., Interpersonal stress regulation and the development of anxiety disorders: an attachment-based developmental framework. Front Behav Neurosci, 2011. 5: p. 55.

[3] Colonnello, V. and A. Agostini, Disease course, stress, attachment, and mentalization in patients with inflammatory bowel disease. Med Hypotheses, 2020. 140: p. 109665.

VERSION 3 – REVIEW

REVIEWER	Agostini, Alessandro University of Bologna
REVIEW RETURNED	15-Sep-2023

GENERAL COMMENTS	no other comments

VERSION 3 – AUTHOR RESPONSE