

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: A systematic analysis based on the Global Burden of Disease Study 2019
AUTHORS	Wang, Rui; Li, Zhaoqi; Liu, Shaojun; Zhang, Decai

VERSION 1 – REVIEW

REVIEWER	Clough, Jennie Guy's and Saint Thomas' Hospitals NHS Trust
REVIEW RETURNED	06-Jul-2022

GENERAL COMMENTS	<p>This is an important body of data, and the authors attempt to draw out useful trends. However, I found the presentation of the results and the resultant conclusions very difficult to follow and do not think the results would be of benefit to the journal's audience in their current format. The quality of the written English is also inadequate in places, hampering readability. My specific comments are below.</p> <p>Detailed comments:</p> <ol style="list-style-type: none">1. Abstract - SDI is not defined at first use2. Page six - description of SDI - it is not clear from the wording whether the fertility/income/education metrics make up the SDI calculation, or whether these are individual metrics which were assessed by the reviewers.3. I can see from the ghdx.health.data.org/gbd-results-tool that the authors have followed the GBD headings for countries and regions, but find their presentation of them confusing - there is a 'High Income North America', but no low income North America. When the results are presented separately according to SDI, why include an additional income descriptor if the defining features of 'High Income North America' are geographical? Why is there an Oceania region and an Australasia region - is there duplication here in territory covered? (And why is there such discrepancy in the patterns of IBD prevalence in these two overlapping regions?)4. Significant restructuring of the results section would be required to enable readers to draw out useful results - I cannot see the value in discussing all metrics first at a regional and then at a national level. For example, the finding that the lowest age-standardised prevalence rates of IBD were in Solomon Islands, Kiribati and Papua New Guinea is not helpful - I would have thought that rates from these small island nations were likely to be extremely limited by population numbers and limited access to diagnostics. It would be much more helpful to divide the results into subheadings for each metric being analysed i.e. EAPC, age-standardised prevalence, DALYS and death rates5. It is consistently unclear in the text whether the prevalence rates
-------------------------	--

	<p>stated are being reported as absolute numbers or per head of population</p> <p>6. Page 10 Para 3 - the number of deaths is reported as being highest in males aged 80-84 and females aged 85-89 - is this IBD-related deaths? Does this not simply reflect the overall average age of death?</p> <p>7. I am unclear what it means to suggest that the highest number of years of life lost (YLL) was in the 65-69 years group. Is this the generation of IBD patients who have been most affected by IBD morbidity?</p> <p>8. Page 13 Para 2 - the authors suggest that cost is a burden to biologic provision but present no evidence as to the difference in DALYs by countries with different SDIs.</p> <p>9. Figure 2 - it is not very easy to extract useful data from these charts - I would suggest presenting the data by SDI in a different graph within the figure, then ordering the regions in ascending/descending order.</p>
--	---

REVIEWER	Szilagyi, Andrew Jewish General Hospital, medicine , Gastroenterology
REVIEW RETURNED	14-Oct-2022

GENERAL COMMENTS	<p>Re MS ID: bmjopen-2022-065186 `The global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019, based on Global Burden Disease Study 2019` by Wang Riu et al.</p> <p>This study reanalyzes a similar data set from 2017 with some updates in acquired information and represents an outline of the spread and pattern of both forms of IBD. As such it represents a major achievement with multiple assessments of general prevalence, age adjusted prevalence and incidence, death rates and variables related to disabilities. The outcomes show global increased age adjusted prevalence while overall prevalence is diminished. Increasing trends are noted in low SDI and newly developing nations. Western countries have plateaued or are diminishing. Overall death rates and disabilities have decreased since over the span of the study, suggesting improved management and treatments.</p> <p>The article is significant, I have only a few comments. As the authors point out, the study is unable to distinguish rates between ulcerative colitis (UC) and Crohn`s disease (CD). This might be of interest because in the west at least UC was thought to have preceded development of CD and the reason(s) for this is(are) not quite clear. The different pattern distributions in other parts of the globe may shed some hypothetical light on this.</p> <p>Second on pg 10; lines 39-45 I would have thought that ages 80-95 would certainly have the highest rates of death from any cause, therefore it is of interest that IBD would be a cause of high rate of death. Does this suggest good treatment in this age group or that IBD less aggressive in the elderly?</p> <p>Abstract pg 3, line 31; change the word `had ` to `having the highest`</p> <p>Anstratct; Pg 3, results line 45; the contraction SDI should be defined as have other contractions.</p> <p>Page 10, line 21; remove the word ``totally``</p>
-------------------------	---

REVIEWER	Hodges, Phoebe Queen Mary University of London, Blizard Institute
REVIEW RETURNED	17-Oct-2022

GENERAL COMMENTS	<p>Major comments: My recommendation is based on the quality of data used in this study. Based on my knowledge of the available literature on IBD in sub-Saharan Africa alone, the data required for the level of extrapolation provided in this study, for example, on estimated annual percentage change, is simply too scarce. GBD 2019 Appendix 1 states that, in this iteration, "hospital discharge data from Botswana" was included in order to make estimates on non-fatal health outcomes of IBD and that "southern sub-Saharan Africa previously did not have data". It seems for this global region alone then, all projections of non-fatal outcomes are made based on hospital discharge data for a single country. Although the authors do state in the discussion "in regions with scarce data...estimates could only rely on predictive covariates or data from a single country...Extra cautions should be made when interpreting data in these areas", greater specificity is required in identifying those regions as the figures convey the impression that quality of data is homogeneous across the globe. Taking the example of Figure 1 which purports to show estimated annual percentage change in the prevalence rate for IBD between 1990 and 2019, if non-fatal outcome data was only available for this region for the first time in 2019 it is difficult to see how extrapolations about EAPC over the past 2 decades have been made as the data does not allow for the level of precision conveyed by the figure. I would suggest either removing all of the results for sub-Saharan Africa based on paucity of data or adding a proviso to the introduction to the effect that scarcity of data from this region renders the value of any extrapolations uncertain (as well as identifying any other regions where extrapolations have been made based on data from a single country).</p> <p>Minor comments: Introduction p5 Line 37" "These significant changes highlights the need..." should read "These significant changes highlight the need" Line 47: suggest remove "most recently" so the sentence reads "The Global Burden of Diseases (GBD) 2019 Study, a systematical worldwide epidemiological study, assessed prevalence, morbidity etc"</p> <p>Results p10 Line 21: remove "totally" from the sentence starting "Overall, the global number of prevalent cases...."</p> <p>Discussion p12 Line 39: should read "previous reports" not "previous report"</p> <p>Conclusions p14 Line 12: sentence should read "However, the trend has shifted substantially since 1990."</p>
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Jennie Clough, Guy's and Saint Thomas' Hospitals NHS Trust

Comments to the Author:

This is an important body of data, and the authors attempt to draw out useful trends. However, I found

the presentation of the results and the resultant conclusions very difficult to follow and do not think the results would be of benefit to the journal's audience in their current format. The quality of the written English is also inadequate in places, hampering readability. My specific comments are below.

Detailed comments:

1. Abstract - SDI is not defined at first use

Response: Thanks for your suggestions. We have defined SDI in the abstract part in the revised manuscript.

2. Page six - description of SDI - it is not clear from the wording whether the fertility/income/education metrics make up the SDI calculation, or whether these are individual metrics which were assessed by the reviewers.

Response: We sincerely apologize for the misunderstanding caused by our poor English description. SDI was constructed based on the geometric mean of three indicators: the total fertility rate, income per capita, and average years of schooling among people aged 15 years or older. We have revised it accordingly.

3. I can see from the ghdx.health.data.org/gbd-results-tool that the authors have followed the GBD headings for countries and regions, but find their presentation of them confusing - there is a 'High Income North America', but no low income North America. When the results are presented separately according to SDI, why include an additional income descriptor if the defining features of 'High Income North America' are geographical? Why is there an Oceania region and an Australasia region - is there duplication here in territory covered? (And why is there such discrepancy in the patterns of IBD prevalence in these two overlapping regions?)

Response: Thanks for your professional review work on the article. As described in the manuscript, we closely followed the GBD headings for countries and regions, and the world was classified into 21 regions geographically in the GBD study. Oceania region consists of 18 countries, including American Samoa, Cook Islands, Fiji, Guam, Kiribati, Marshall Islands, Federated States of Micronesia, Nauru, Niue, Northern Mariana Islands, Palau, Papua New Guinea, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, and Vanuatu. While Australasia region consists of Australia and New Zealand. There is no duplicated territory in the region of Oceania and Australasia. So there is no discrepancy in the patterns of IBD prevalence in these two regions.

4. Significant restructuring of the results section would be required to enable readers to draw out useful results - I cannot see the value in discussing all metrics first at a regional and then at a national level. For example, the finding that the lowest age-standardised prevalence rates of IBD were in Solomon Islands, Kiribati and Papua New Guinea is not helpful - I would have thought that rates from these small island nations were likely to be extremely limited by population numbers and limited access to diagnostics. It would be much more helpful to divide the results into subheadings for each metric being analysed i.e. EAPC, age-standardised prevalence, DALYS and death rates

Response: Thank you again for your valuable suggestions to improve the quality of our manuscript. We have restructured the results section in our revised manuscript.

5. It is consistently unclear in the text whether the prevalence rates stated are being reported as absolute numbers or per head of population

Response: We sincerely apologize for the misunderstanding. The prevalence rates in the text were reported as per head of population. We have accurately described prevalence rates in the revised manuscript.

6. Page 10 Para 3 - the number of deaths is reported as being highest in males aged 80-84 and females aged 85-89 - is this IBD-related deaths? Does this not simply reflect the overall average age of death?

Response: Thank you for the question. We think it is most likely IBD-related deaths, since the number of deaths dropped in males older than 85 years and females older than 90 years, which should be bigger theoretically if simply reflecting the overall average age of death.

7. I am unclear what it means to suggest that the highest number of years of life lost (YLL) was in the 65-69 years group. Is this the generation of IBD patients who have been most affected by IBD morbidity?

Response: The highest DALYs number reflects the most affected by IBD morbidity, which was in males aged 50-54 years and females aged 55-59 years.

8. Page 13 Para 2 - the authors suggest that cost is a burden to biologic provision but present no evidence as to the difference in DALYs by countries with different SDIs.

Response: Thank you for the constructive suggestions. We corrected this paragraph in the revised manuscript.

9. Figure 2 - it is not very easy to extract useful data from these charts - I would suggest presenting the data by SDI in a different graph within the figure, then ordering the regions in ascending/descending order.

Response: Thanks for your professional suggestions. We have redrawn Figure 2 in the revised manuscript.

Reviewer: 2

Andrew Szilagyi, Jewish General Hospital

Comments to the Author:

Re MS ID: bmjopen-2022-065186 `The global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019, based on Global Burden Disease Study 2019` by Wang Riu et al.

This study reanalyzes a similar data set from 2017 with some updates in acquired information and represents an outline of the spread and pattern of both forms of IBD. As such it represents a major achievement with multiple assessments of general prevalence, age adjusted prevalence and incidence, death rates and variables related to disabilities. The outcomes show global increased age adjusted prevalence while overall prevalence is diminished. Increasing trends are noted in low SDI and newly developing nations. Western countries have plateaued or are diminishing. Overall death rates and disabilities have decreased since over the span of the study, suggesting improved management and treatments. The article is significant, I have only a few comments.

Response: Thank you so much for your valuable opinion. We really appreciate it.

As the authors point out, the study is unable to distinguish rates between ulcerative colitis (UC) and Crohn's disease (CD). This might be of interest because in the west at least UC was thought to have preceded development of CD and the reason(s) for this is(are) not quite clear. The different pattern distributions in other parts of the globe may shed some hypothetical light on this.

Response: Thanks for your professional review work on the article. We agree that to understand the distinct disease pattern of UC and CD is critical. However, GBD database doesn't distinguish the pattern distributions. Therefore, our study is unable to analyse UC and CD separately.

Second on pg 10; lines 39-45 I would have thought that ages 80-95 would certainly have the highest rates of death from any cause, therefore it is of interest that IBD would be a cause of high rate of death. Does this suggest good treatment in this age group or that IBD less aggressive in the elderly?

Response: Figure 5 suggests that the number of deaths was highest in males aged 80-84 years and females aged 85-89 years, however, the death rate increased with aging. However, from the present numbers, we cannot conclude better treatment in which age group. The highest number of DALYs was in males aged 50-54 years and females aged 55-59 years, suggesting affected most by IBD morbidity.

Abstract pg 3, line 31; change the word `had` to `having the highest`

Response: We are very sorry for our careless mistake. We have corrected it in our revised manuscript.

Abstract; Pg 3, results line 45; the contraction SDI should be defined as have other contractions.

Response: Thanks for your suggestions. We have defined SDI in the abstract part in the revised manuscript.

Page 10, line 21; remove the word ``totally``

Response: Thank you for your constructive suggestions. We have revised the manuscript according to your suggestion.

Reviewer: 3

Dr. Phoebe Hodges, Queen Mary University of London

Comments to the Author:

Major comments: My recommendation is based on the quality of data used in this study. Based on my knowledge of the available literature on IBD in sub-Saharan Africa alone, the data required for the level of extrapolation provided in this study, for example, on estimated annual percentage change, is simply too scarce. GBD 2019 Appendix 1 states that, in this iteration, "hospital discharge data from Botswana" was included in order to make estimates on non-fatal health outcomes of IBD and that "southern sub-Saharan Africa previously did not have data". It seems for this global region alone then, all projections of non-fatal outcomes are made based on hospital discharge data for a single country. Although the authors do state in the discussion "in regions with scarce data...estimates could only rely on predictive covariates or data from a single country...Extra cautions should be made when interpreting data in these areas", greater specificity is required in identifying those regions as the figures convey the impression that quality of data is homogeneous across the globe. Taking the example of Figure 1 which purports to show estimated annual percentage change in the prevalence rate for IBD between 1990 and 2019, if non-fatal outcome data was only available for this region for the first time in 2019 it is difficult to see how extrapolations about EAPC over the past 2 decades have been made as the data does not allow for the level of precision conveyed by the figure. I would suggest either removing all of the results for sub-Saharan Africa based on paucity of data or adding a proviso to the introduction to the effect that scarcity of data from this region renders the value of any extrapolations uncertain (as well as identifying any other regions where extrapolations have been made based on data from a single country).

Response: We sincerely thank the reviewer for the constructive criticisms and insightful suggestions. We have revised the introduction part according to your suggestions by adding statement that "in the data-scarce locations, estimates mainly rely on predictive covariates or global trends with consideration of SDI level and data from a single country".

Minor comments: Introduction p5 Line 37" "These significant changes highlights the need..." should read "These significant changes highlight the need"

Response: We are very sorry for our careless mistake. We have corrected it.

Line 47: suggest remove "most recently" so the sentence reads "The Global Burden of Diseases (GBD) 2019 Study, a systematical worldwide epidemiological study, assessed prevalence, morbidity etc"

Response: Thank you for your constructive suggestions. We have revised the manuscript according to your suggestion.

Results p10 Line 21: remove "totally" from the sentence starting "Overall, the global number of prevalent cases...."

Response: Thank you for your kind suggestions. We have revised the manuscript accordingly.

Discussion p12 Line 39: should read "previous reports" not "previous report"

Response: Thanks for your kind suggestions. We have revised the manuscript accordingly.

Conclusions p14 Line 12: sentence should read "However, the trend has shifted substantially since 1990."

Response: Thanks for your suggestions. We have corrected in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Szilagyi, Andrew Jewish General Hospital, medicine , Gastroenterology
REVIEW RETURNED	07-Dec-2022
GENERAL COMMENTS	The revision of MS: ID bmopen-2022-065186.R1j .The global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019, based on Global Burden Disease Study 2019 by Wang Rui et al is better.

	<p>There are a few minor corrections to be made.</p> <p>In the Methods section line 29 `the 25th and 975th`` Should be probably 25th and 75th</p> <p>In the results line 58 the title `Death of IBD` should be `Death related to`` or `from IBD``</p> <p>In the results pg 79/90 line 19 “ From 1990 to 2019 most of GBD “ remove’ of ‘</p> <p>Same pg line 56 “ 1990 and 2019, the deaths of IBD... “ Should read “1990 and 2019, deaths related to IBD” or “deaths from IBD”</p>
--	--

REVIEWER	Hodges, Phoebe Queen Mary University of London, Blizard Institute
REVIEW RETURNED	17-Dec-2022

GENERAL COMMENTS	<p>1. Abstract - I would suggest adding a sentence to the 'Strengths and limitations of this study' section of the abstract to the effect that results for some geographical regions will be severely limited by the paucity of data (not just variability in study design - lack of studies!) and should be treated with caution.</p> <p>2. Results - please add a proviso to the first paragraph (line 8) stating that although graphical representation suggests homogeneity of data quality across the globe, this is not the case and in some regions estimates are based on extremely limited data and again should be treated with caution.</p>
-------------------------	--

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Andrew Szilagyi, Jewish General Hospital

Comments to the Author:

The revision of MS: ID bmopen-2022-065186.R1j .The global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019, based on Global Burden Disease Study 2019 by Wang Rui et al is better.

Response: Thank you so much for your valuable opinion. We really appreciate it.

There are a few minor corrections to be made.

In the Methods section line 29 `the 25th and 975th`` Should be probably 25th and 75th

Response: Thank you for your constructive suggestions. We have revised the manuscript according to your suggestion.

In the results line 58 the title `Death of IBD` should be `Death related to`` or `from IBD``

Response: Thanks for your suggestions. We have revised the manuscript accordingly.

In the results pg 79/90 line 19 “ From 1990 to 2019 most of GBD “ remove’ of ‘

Response: Thank you for your kind suggestions. We have revised the manuscript accordingly.

Same pg line 56 “ 1990 and 2019, the deaths of IBD... “ Should read “1990 and 2019, deaths related to IBD” or “deaths from IBD”

Response: Thanks for your suggestions. We have corrected it in the revised manuscript.

Reviewer: 3

Dr. Phoebe Hodges, Queen Mary University of London

Comments to the Author:

1. Abstract - I would suggest adding a sentence to the 'Strengths and limitations of this study' section of the abstract to the effect that results for some geographical regions will be severely limited by the paucity of data (not just variability in study design - lack of studies!) and should be treated with caution.

Response: We sincerely thank the reviewer for the insightful suggestions. We have revised the abstract part according to your suggestions by adding statement that "The third limitation is that the results for some geographical regions were severely limited by the paucity of data (not just variability in study design but lack of studies) and should be treated with caution".

2. Results - please add a proviso to the first paragraph (line 8) stating that although graphical representation suggests homogeneity of data quality across the globe, this is not the case and in some regions estimates are based on extremely limited data and again should be treated with caution.

Response: We sincerely thank the reviewer for the thoughtful review. We have re-written this part accordingly and marked it in red.