

## 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

<b>TITLE (PROVISIONAL)</b>	Prevalence trends in nonalcoholic fatty liver disease at the global, regional, and national levels, 1990-2017: A population-based observational study
<b>AUTHORS</b>	Ge, Xiaojun; Zheng, Limei; Wang, Mei; Du, Yuxuan; Jiang, Junyao

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Kenichiro Mikami Department of Gastroenterology, Hirosaki University, Japan
<b>REVIEW RETURNED</b>	20-Jan-2020

<b>GENERAL COMMENTS</b>	<p>In this manuscript, Ge et al. reported the increasing global prevalence of NAFLD, and the association between prevalence of NAFLD with human development index (HDI). Now, NAFLD is not only a medical problem but also socioeconomical issue worldwide. Thus, this study is very important, and will be of interest to both specialist and generalist readers. However, I have the following concerns.</p> <p>Major point:</p> <p>1) The authors showed that the global prevalence of NAFLD increased from 8.2% to 10.9% between 1990 and 2017. However, most previous studies and systematic reviews have reported that the prevalence of NAFLD is about 20% to 30%. Although the authors discussed this point as study limitation, but there is a major difference between this study and previous reports. I think that the authors need further discussion in regard to this point.</p> <p>2) HDI is an indicator of socioeconomic development. Although the authors showed the correlation between estimated annual percentage change of NAFLD and HDI, but the discussion is not enough. I think that the authors need to have more discussion about this correlation, for example, from the perspective of life style and health system.</p>
-------------------------	---

<b>REVIEWER</b>	Jorge Simón CIC bioGUNE, Derio, Biscay, Spain
<b>REVIEW RETURNED</b>	27-Jan-2020

<b>GENERAL COMMENTS</b>	I do not find the paper too much relevant regarding the content but, in case of applying major changes, it could be suitable for publication in the journal.
-------------------------	--

	<p>Regarding the major concerns I suggest:</p> <ul style="list-style-type: none"> <li>- Discuss deeper the difference between the prevalence rates mentioned in references widely accepted such as Younossi 2016 or Younossi 2019 (prev. rate around 25%) and the data obtained from the study. This is the main concern and it is not well indicated in the paper why a different rate is indicated.</li> <li>- In Figure 3 the data is represented as number of cases. In general I would quit this figure as it is not too informative, East Asia has one of the biggest density of poblation so it is expected to have more prevalence. Indeed, the criteria for defining regions is not well defined.</li> <li>- Related the increase of the incidence during last years, in the manuscript it is well indicated but, when it is related with other comorbidities or possible causes, none is reported. I miss a graph with some tendencies of increase of such pathologies (diabetes, obesity, CVD...). I suggest to include, at least, in the supplemental part.</li> </ul> <p>Minor concerns:</p> <ul style="list-style-type: none"> <li>- Please check the references. In some points I have missed them, I have another ones without the author and the #11 and #23 are repeated.</li> <li>- The Figure 2 and Figure 5 are missing. In the Figures appear Figure 1, 1, 3, 4 and 1. Please check.</li> <li>- SDI is not well incidated as well as other achronims such as GBD. Please be careful and make it clearer.</li> <li>- A little review of current therapies would be interesting.</li> <li>- In the discussion, when mentioning the causes of the increase, you relate biochemical paremeters with more physiological and behavioral ones. Those two groups of causes are not related so I would separate them. Including the hepatic DNL or adipose IR with the genetic variability seems to be more adequate.</li> <li>- Solutions to avoid the increasing prevalence are really well presented. However, #4 and #2 seem to be almost the same.</li> </ul>
--	---

<b>REVIEWER</b>	Wing-Kin Syn Medical university of South Carolina USA
<b>REVIEW RETURNED</b>	11-Feb-2020

<b>GENERAL COMMENTS</b>	<p>Authors aimed to evaluate the prevalence of nonalcoholic fatty liver disease at the global, regional, and national level, 1990-2017. This is an important addition to the literature and highlights the key public health issues that need to be properly addressed.</p> <p>Prevalence of NAFLD was estimated by a systematic literature review in PubMed; NAFLD was specifically defined by US or other imaging, but not other non-invasive scores (or fatty liver index). The limitations of such an approach is the relative lack of granularity and likely underestimate of disease burden, esp. since this uses a mathematical model</p> <p>Reporting of prevalence alone is insufficient and would need to be reported in association with prevalence of metabolic risk factors. Authors should also adjust prevalence for obesity / risk factors etc.</p> <p>Limitations should be discussed at greater length - including the lack</p>
-------------------------	---

	of fibrosis evaluation (since fibrosis is the key determinant of liver outcomes)
--	--

<b>REVIEWER</b>	HUA WANG Department of Oncology, The First Affiliated Hospital of Anhui Medical University Institute for Liver Disease of Anhui Medical University, Hefei, China, 230032
<b>REVIEW RETURNED</b>	04-Mar-2020

<b>GENERAL COMMENTS</b>	<p>In this study, Ge et al., estimated the current (2017) and the increase (from 1990 to 2017) prevalence of NAFLD at three levels. They found that nearly all countries or territories experienced a significant increase in NAFLD prevalence. The prevalent case number was highest in East Asia, followed by South Asia and North African and Middle East. The highest NAFLD prevalence was observed in North African and Middle East. Whereas the greatest increase was detected in Western Europe, followed by Tropical Latin America and High-income North America. This study provides a comprehensive analysis of the NAFLD prevalence change, with comparisons at different levels.</p> <ul style="list-style-type: none"> <li>- The Discussion section should discuss those key findings: Why the highest prevalence is observed in North African (relatively less developed countries)? Why the greatest increase is found in Western Europe (which maintain highest living standard from 1990 to now)? Is it due to the change of diet habit? Or other perturbing factors?</li> <li>- Table, please use different colors to show different regions. The current table is too long and somehow difficult to follow.</li> <li>- Figure 4, it is suggested to add another panel showing the case number distribution in the world map.</li> <li>- Several minor mistakes (formatting errors and typos) should be corrected.</li> </ul>
-------------------------	---

### VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Kenichiro Mikami

Institution and Country: Department of Gastroenterology, Hirosaki University, Japan

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In this manuscript, Ge et al. reported the increasing global prevalence of NAFLD, and the association between prevalence of NAFLD with human development index (HDI). Now, NAFLD is not only a medical problem but also socioeconomical issue worldwide. Thus, this study is very important, and will be of interest to both specialist and generalist readers. However, I have the following concerns.

Dear Dr. Mikami,

Thanks for your careful review and conducive comments. We have revised our manuscript closely according to your comments. Please see the point-by-point response as follows.

Major point:

1) The authors showed that the global prevalence of NAFLD increased from 8.2% to 10.9% between 1990 and 2017. However, most previous studies and systematic reviews have reported that the prevalence of NAFLD is about 20% to 30%. Although the authors discussed this point as study limitation, but there is a major difference between this study and previous reports. I think that the authors need further discussion in regard to this point.

Response: We appreciate this comment and agree with the reviewer. We acknowledge the difference between results from previous study and our results, and further discuss this point in the revised manuscript. Please see the lines 286-298 in page 10.

2) HDI is an indicator of socioeconomic development. Although the authors showed the correlation between estimated annual percentage change of NAFLD and HDI, but the discussion is not enough. I think that the authors need to have more discussion about this correlation, for example, from the perspective of life style and health system.

Response: We appreciate the reviewer's insightful comments. We have added more discussion about the relationship between HDI and the change of NAFLD. Please see the lines 255-264 in page 9.

Reviewer: 2

Reviewer Name: Jorge Simón

Institution and Country: CIC bioGUNE, Derio, Biscay, Spain

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

I do not find the paper too much relevant regarding the content but, in case of applying major changes, it could be suitable for publication in the journal.

Dear Dr. Simón,

Thanks for your careful review and insightful comments. We have revised our manuscript closely according to your comments. Please see the point-by-point response as follows.

Regarding the major concerns I suggest:

- Discuss deeper the difference between the prevalence rates mentioned in references widely accepted such as Younossi 2016 or Younossi 2019 (prev. rate around 25%) and the data obtained from the study. This is the main concern and it is not well indicated in the paper why a different rate is indicated.

Response: We appreciate the reviewer's insightful comments. We have discussed the potential reasons for the difference between our results and that from previous study. Please see the lines 286-298 in page 10.

- In Figure 3 the data is represented as number of cases. In general I would quit this figure as it is not too informative, East Asia has one of the biggest density of population so it is expected to have more prevalence. Indeed, the criteria for defining regions is not well defined.

Response: We thank this comment. We have removed the Figure 3a. In our study, the regions were defined by geography and have been widely used in previous studies (ref. 1, 2). To be more precise, we have incorporated this point in the revised manuscript. Please see the lines 96-97 in page 4.

Reference:

1, Zhang Y et al. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. *Diabetes Care* 2020 Mar; dc191614.

2. Bcheraoui CE et al. Burden of Disease in Francophone Africa, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet Glob Health*, 8 (3), e341-e351.

- Related the increase of the incidence during last years, in the manuscript it is well indicated but, when it is related with other comorbidities or possible causes, none is reported. I miss a graph with some tendencies of increase of such pathologies (diabetes, obesity, CVD...). I suggest to include, at least, in the supplemental part.

Response: We appreciate the reviewer's insightful comments. We analyzed the obesity and type II diabetes prevalence at the global and regional level. And we analyzed the correlation of prevalence of obesity and diabetes with NAFLD prevalence. We also discussed this point in the manuscript. Please see the lines 173-180 in page 6, lines 250-252 in page 9, Figures 5 B & C, and Figure S1.

Minor concerns:

- Please check the references. In some points I have missed them, I have another ones without the author and the #11 and #23 are repeated.

Response: We thank the reviewer's careful review. We have checked the references throughout the manuscript. The repeated reference has been removed.

- The Figure 2 and Figure 5 are missing. In the Figures appear Figure 1, 1, 3, 4 and 1. Please check.

Response: Thanks. We have uploaded all five figures and mentioned them in the manuscript.

- SDI is not well indicated as well as other achronims such as GBD. Please be careful and make it clearer.

Response: Thanks. We detailed the SDI and GBD in the revised manuscript. Please see lines 84-87 in page 3 and lines 98-100 in page 4.

- A little review of current therapies would be interesting.

Response: Thanks. Per the reviewer's request, we added a little review of current therapies in the discussion. Please see lines 225-234 in page 8.

- In the discussion, when mentioning the causes of the increase, you relate biochemical parameters with more physiological and behavioral ones. Those two groups of causes are not related so I would separate them. Including the hepatic DNL or adipose IR with the genetic variability seems to be more adequate.

Response: We appreciate the comments. Per the reviewer's request, we have separated the two group of causes and further discussed the contribution of DNL and IR to the development of NAFLD/NASH. Please see lines 217-225 in page 8.

- Solutions to avoid the increasing prevalence are really well presented. However, #4 and #2 seem to be almost the same.

Response: We appreciate the comments. We rephrased these statements in the manuscript. Please see the lines 271-280 in page 10.

Reviewer: 3

Reviewer Name: Wing-Kin Syn

Institution and Country: Medical university of South Carolina USA

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Authors aimed to evaluate the prevalence of nonalcoholic fatty liver disease at the global, regional, and national level, 1990-2017. This is an important addition to the literature and highlights the key public health issues that need to be properly addressed.

Dear Dr. Syn,

We appreciate your careful review and insightful comments to our study. We have addressed all concerns in the revised manuscript. Please see the point-by-point response as follows.

Prevalence of NAFLD was estimated by a systematic literature review in PubMed; NAFLD was specifically defined by US or other imaging, but not other non-invasive scores (or fatty liver index). The limitations of such an approach is the relative lack of granularity and likely underestimate of disease burden, esp. since this uses a mathematical model

Response: Thanks. We agree with the reviewer. We have acknowledged this point as a limitation in the revised manuscript. Please see lines 304-308 in page 11.

Reporting of prevalence alone is insufficient and would need to be reported in association with prevalence of metabolic risk factors. Authors should also adjust prevalence for obesity / risk factors etc.

Response: We appreciate the reviewer's professional comments. In the revised manuscript, we assessed the correlation between NAFLD prevalence and prevalence of overweight and diabetes. We also assessed the correlation between temporal trends of NAFLD and that of overweight and diabetes at the national level. Please see the lines 173-180 in page 6, lines 250-252 in page 9, Figures 5 B & C, and Figure S1.

Limitations should be discussed at greater length - including the lack of fibrosis evaluation (since fibrosis is the key determinant of liver outcomes)

Response: We thank this comment. Per the reviewer's request, we have extended the discussion on limitation. Please see the lines 282-308 in pages 10 and 11. We also discussed the lack of fibrosis evaluation. Please see lines 301-304 in page 11.

Reviewer: 4

Reviewer Name: HUA WANG

Institution and Country:

Department of Oncology, The First Affiliated Hospital of Anhui Medical University

Institute for Liver Disease of Anhui Medical University, Hefei, China, 230032

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

In this study, Ge et al., estimated the current (2017) and the increase (from 1990 to 2017) prevalence of NAFLD at three levels. They found that nearly all countries or territories experienced a significant increase in NAFLD prevalence. The prevalent case number was highest in East Asia, followed by South Asia and North African and Middle East. The highest NAFLD prevalence was observed in North African and Middle East. Whereas the greatest increase was detected in Western Europe, followed by

Tropical Latin America and High-income North America. This study provides a comprehensive analysis of the NAFLD prevalence change, with comparisons at different levels.

Dear Dr. Wang,

Thanks for your careful review and instructive comments. We have fully addressed all your concerns in the revised manuscript. Please see the point-by-point response as follows.

- The Discussion section should discuss those key findings: Why the highest prevalence is observed in North African (relatively less developed countries)? Why the greatest increase is found in Western Europe (which maintain highest living standard from 1990 to now)? Is it due to the change of diet habit? Or other perturbing factors?

Response: We appreciate these professional comments and interesting questions. Why the highest prevalence was observed in North Africa and Middle East? This is a very intriguing question. Per the reviewer's kind suggestions, we have reviewed the related literatures and further discussed the main findings in the revised manuscript. Please see the lines 196-201 in page 7 and lines 250-264 in page 9.

- Table, please use different colors to show different regions. The current table is too long and somehow difficult to follow.

Response: Thanks. Per the reviewer's suggestion, we have used different color to show different regions. Please see the revised Table.

- Figure 4, it is suggested to add another panel showing the case number distribution in the world map.

Response: We thank the reviewer's suggestion. We have updated the Figure 4 and added the case number distribution. Please see Figure 4B and line 164 in page 6.

- Several minor mistakes (formatting errors and typos) should be corrected.

Response: We thank the reviewer's careful review. We have asked a favor from a native speaker to polish the writing. All language mistakes were corrected.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Kenichiro Mikami Hirosaki University Graduate School of Medicine, Japan
<b>REVIEW RETURNED</b>	25-Mar-2020

<b>GENERAL COMMENTS</b>	Author well wrote the revised manuscript.
-------------------------	---

<b>REVIEWER</b>	Jorge Simón Liver Disease Lab, CIC bioGUNE, Spain
<b>REVIEW RETURNED</b>	03-Apr-2020

<b>GENERAL COMMENTS</b>	From my point of view I find this manuscript suitable for publication. I appreciate the effort performed by the authors regarding the first
-------------------------	---

	<p>revision and, therefore, I have found this new version much easier to read.</p> <p>I would like to suggest some minor changes that I think they could give the manuscript a slight added value:</p> <ul style="list-style-type: none"> <li>- The main one is that, when you mention the limitations of the study, you focus on the cohort of patients from Younossi and the GBD. You should also pay attention, and at least make a mention, about the lack of effective diagnosis methods for daily use during clinical practice. One of the main reasons of the difference between diagnosed and estimated patients is that, during routine tests to diagnose NAFLD, there is a low-sensibility problem.</li> <li>- I think that the paragraph to the molecular mechanisms underlying NAFLD should be excluded. Your study is mainly an epidemiological one and this part seems to have no relationship with the study nor the introduction.</li> </ul>
--	--

<b>REVIEWER</b>	Wing-Kin Syn MUSC, Charleston South Carolina USA
<b>REVIEW RETURNED</b>	30-Mar-2020

<b>GENERAL COMMENTS</b>	<p>Thank you for revising the manuscript</p> <p>Authors need to clarify what they actually mean by prevalence, prevalence case number, prevalence rate?</p> <p>Please have the manuscript re-read / corrected by native English speaker</p>
-------------------------	---

### VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name: Wing-Kin Syn

Institution and Country: MUSC, Charleston South Carolina

USA

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Thank you for revising the manuscript

Authors need to clarify what they actually mean by prevalence, prevalence case number, prevalence rate?

Please have the manuscript re-read / corrected by native English speaker

Response: We thank the reviewer's careful review and helpful comments.

We have added the statements regarding prevalence, prevalence case number, and prevalence rate.

Please see the main text page 5 lines 123-127.

In addition, this manuscript has been revised by a native English speaker.



Reviewer: 2

Reviewer Name: Jorge Simón

Institution and Country: Liver Disease Lab, CIC bioGUNE, Spain

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

From my point of view I find this manuscript suitable for publication.

I appreciate the effort performed by the authors regarding the first revision and, therefore, I have found this new version much easier to read.

I would like to suggest some minor changes that I think they could give the manuscript a slight added value:

- The main one is that, when you mention the limitations of the study, you focus on the cohort of patients from Younossi and the GBD. You should also pay attention, and at least make a mention, about the lack of effective diagnosis methods for daily use during clinical practice. One of the main reasons of the difference between diagnosed and estimated patients is that, during routine tests to diagnose NAFLD, there is a low-sensibility problem.

Response: we appreciate the reviewer's insightful comments. We have mentioned the lack of effective diagnosis methods of NAFLD for daily use during clinical practice. Please see main text page 11 line 320.

- I think that the paragraph to the molecular mechanisms underlying NAFLD should be excluded. Your study is mainly an epidemiological one and this part seems to have no relationship with the study nor the introduction.

Response: We thank this comment. Per the reviewer's kind suggestion, we have removed the related contents in the revised manuscript.