

ROUND 1

Professor Lian-Sheng Ma,

Science Editor, Company Editor-in-Chief, Editorial Office

March 17th, 2021

Subject: Revision Manuscript # 63933 "Association between COVID-19 and Anxiety During Social Isolation".

Dear Professor Lian-Sheng,

On behalf of co-authors, I would like to thank the editorial team and reviewers for their time and consideration in reading our manuscript. The timely and appropriate response from the editorial staff is commendable and we are grateful for the hard work and dedication of the Editor.

In the following pages, we have attempted to respond to the reviewer's comment "point by point" to better clarify the issues raised, as per single annex.

Besides, we have added the text mentioned in the responses, and the references have also been updated.

Be regard,

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REVIEWER'S COMMENT "POINT BY POINT"

#1 Reviewer

1 - The authors performed an accurate meta-analysis of the association between anxiety and social isolation due to pandemic COVID 19. They identify populations and variables at risk for mental health."

Response:

Thank you for the comment, due to the limited context of the pandemic situation it was not possible to apply the meta-analysis. This was a systematic review highlighting the current literature.

The authors designed a systematic review with qualitative assessment according to PRISMA protocol and the Downs & Black checklist, as described in the method. Completed checklist has been uploaded along with comments.

2 - Just a minor review: why is it that in figure 2 Italy is one of the countries from which one of the seven articles selected for the review was derived, but which does not result from the table or the appendix?

Response:

We identified Italy in the first database search. However, when the inclusion and exclusion criteria were applied, the study conducted in Italy was not selected. We felt it was better to suppress figure 2 to avoid confusion for the reader. Thus, the country of origin of the studies was described.

Thanks for the suggestion, changes have already been made in the manuscript.

3 - There is only one spelling error on page 14 for the word "litetature".

Response:

Thanks for the suggestion, changes have already been made to the manuscript.

#2 Reviewer

1.Abstract: 1.1. Quote: "We conclude that there is a strong relationship between social isolation during the COVID-19 pandemic and anxiety symptoms." Please write that this link is potential and possible. There is no definitive and indisputable scientific evidence for this thesis of yours. Please make an adjustment;

Response:

Thanks for the suggestion, changes have already been made to the manuscript.

2 - (2.) Introduction: 2.1. Please write 2-3 sentences on the etiology and origin of the virus (SARS-CoV-2, formerly 2019-nCoV).

Response:

Text has been reworded and inserted in the Introduction of the manuscript: "In December 2019 a group of patients was hospitalized due to viral pneumonia caused by a microbial agent, hitherto unidentified. The patients were epidemiologically linked to the Huanan seafood market in Wuhan, Hubei Province, China. Shortly afterward, a new coronavirus that infects humans, which probably originates from bats, was identified as the etiologic agent that caused the hospitalizations. Until then, among the various types of coronavirus, majority caused only mild clinical symptoms, except for SARS-CoV and MERS-CoV however, the new typing identified in Wuhan also proved to be dangerous."

Thanks for the suggestion, changes have already been made to the manuscript.

2.2 In this regard, I strongly recommend adding the following scientific publications to this section (and to the "References" section):

- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020; 382(8): 727-733. [DOI: 10.1056/NEJMoa2001017] [PMID: 31978945]
- Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implicações para a origem do vírus e ligação dos receptores. *Lanceta.* 2020; 395(10224): 565-574. [DOI: 10.1016/S0140-6736(20)30251-8] [PMID: 32007145]
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. Um surto de pneumonia associado a um novo vírus corona de provável origem de morcego. *Natureza.* 2020; 579(7798): 270-273. [DOI: 10.1038/s41586-020-2012-7] [PMID: 32015507]

Response:

Thanks for the suggestion, changes have already been made to the manuscript.

2.3 Write 2-3 sentences on the clinical features of COVID-19. In this regard, I strongly recommend adding the following scientific publications to this section (and to the "References" section):

- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020; 382(18): 1708-1720. DOI: 10.1056/NEJMoa2002032] [PMID: 32109013]
- Popov GT, Baymakova M, Vaseva V, Kundurzhiev T, Mutafchiyski V. Características clínicas de pacientes hospitalizados com COVID-19 em Sófia, Bulgária. *Vector Borne Zoonotic Dis.* 2020; 20(12): 910-915. [DOI: 10.1089/vbz.2020.2679] [PMID: 33054699]
- Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Características clínicas e epidemiológicas de 1420 doentes europeus com doença do vírus

corona leve a moderada de 2019. J Interno Med. 2020; 288(3): 335-344. [DOI: 10.1111/joim.13089] [PMID: 32352202]

Response:

Text was reworded and inserted in the Introduction of the manuscript: *"In this context, COVID-19 manifests clinically from mild to severe and varies substantially according to the age and sexual characteristics of the patients. One of the most frequent manifestations in mild and moderate cases is predominantly olfactory dysfunction. Severe cases present with a higher risk for older men with comorbid underlying hypertension, cardiovascular, malignant and chronic renal diseases with signs of dyspnoea and nausea."*

Thanks for the suggestion, changes have already been made to the manuscript.

(3.) Materials and Methods:

3.1. "Search method to identify studies": Why didn't you search the database "Scopus" (Elsevier) and "ScienceDirect" (Elsevier)? I want to hear your reasons for this decision. Then, I want you to be able to search and in "Scopus" (Elsevier) and in "ScienceDirect" (Elsevier).

Response:

We understand the importance of the bases suggested. However, the decision made by the authors was to select the databases with the widest content coverage and those most accessed by researchers at the time of the search and in the reference period, such as Pubmed and Medline the *Biblioteca Virtual em Saúde - BVS*, Science.gov, Web of Science and National Library platforms, as explained in the method.

Since the beginning of the pandemic and the current clinical spread, there is a growing number of publications addressing this important issue. We intend to provide an updated review at a later point. We thank you for the suggestion and will carry out the search for a subsequent update of the systematic review.

3.2 "Search method to identify studies": you wrote "... for data extraction was from 1 March to 30 April 2020 ...", I think this is too short a period. I strongly recommend that you search scientific publications in databases for a period from 15 January 2020 to 01 February 2021 (defined period of search for scientific publications: from 15 January 2020 to 01 February 2021). This recommendation is related to the fact that the first scientific publications on COVID-19 (SARS-CoV-2 Infection) were published at the end of January 2020.

Response:

We intend to keep it as a live systematic review. Future iteration will include the updated literature as pointed out in the response above. We thank the reviewer for the suggestion. At the beginning of the pandemic we were very concerned because a large portion of the published articles was about etiology, perspectives of intervention for treatment, it was not known about when there would be a vaccine horizon.

We thank the suggestion, which encourages us to conduct other studies considering a longer reference period. Our study represents the first approach on this important theme, which needs to be revisited from future studies.

3.3 "Data analysis": Please write in 2-3 sentences more information about "meaning condensation matrix".

Response:

The condensation of meanings matrix is part of a set of techniques of communications/content analysis, which enabled the systematization of the items examined after the application of the Downs & Black tool, as to the components of methodological quality assessment.

Thanks for the observation, which we made minor changes in the manuscript leave the matrix or better explained: "[...] which helped in the systematization of the items assessed as to the components of methodological quality [...]"

4. (6.) References: See recommendations for the "Introduction" section.

Response:

Thanks for the suggestion, changes have already been made in the manuscript.

#3 Reviewer

Great review:

1 - The discussion part seems to be descriptive, and it is suggested that: Either explain why there is a correlation (described in the manuscript) between social isolation during pandemic COVID-19 and pathogenesis anxiety symptoms or analyze why there is a correlation of the study variables.

Response:

Thank you for the suggestion, changes have been made to the manuscript.

Minor revision:

2. Given the government's role in strategic mental health measures, it is necessary to focus efforts to plan and implement interventions, which is ambiguous.

A brief description of the interventions to be implemented (such as psychological counseling) is recommended (at least)

Response:

Text was reworded and inserted in the Conclusion of the manuscript: "The psychological routine care services do not absorb the demand generated by a pandemic, requiring an investment by the state, and educational and research institutions, in actions that have the potential to act beneficially on the adverse effects, including late effects, of social isolation in people's lives, such as psychological support that strengthens self-confidence and trust in disease control measures (preventive, therapeutic, educational, and recreational). Besides, promote solidarity and economic support networks, for the less favored social classes, to minimize the effects of the pandemic on the economic health of the population."

Thanks for the suggestion, changes have been made in the manuscript.

And how to implement them (such as using remote psychological counseling systems).

Response:

Text was reworded and inserted in the Discussion of the manuscript: " The role of governments in strategic measures for mental health. From the point of view of public health administrators and policymakers, it is necessary to concentrate efforts to plan and execute interventions on the negative effects of social isolation, particularly anxiety, sadness, loneliness, as well as symptoms of post-traumatic stress, which can effectively meet the needs of individuals ".

Thanks for the suggestion, changes have been made to the manuscript.

3. There are a small number of spelling errors in the manuscript, such as missing spaces before the full stop at the end of the sentence and the first capital letter of the next sentence.

Response:

Thanks for the suggestion, changes have been made to the manuscript.

#4 Reviewer

I think the conclusion needs to be more specific, not clearly show the results.

Response:

Thanks for the suggestion, changes have already been made to the manuscript.

#5 Reviewer

The writing is good. the suggestion that the author should add references within a week the conclusions obtained are even better.

Response:

Thanks for the suggestion, changes have already been made to the manuscript.

ROUND 2

Dear Editor-in-Chief and Dr Wu Yun-Xiaojian,

On behalf of all the co-authors, I would like to thank the editorial office and the peer-reviewers for the time and consideration given to our manuscript. We appreciate all the constructive feedback that has significantly improved the quality of our manuscript for the edification of the readers.

In the following pages we have tried to address the comments from the peer-reviewers in a point-by-point pattern.

We look forward for a quick and positive response from the editorial office due to the time sensitive nature of this manuscript for its timely publication.

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Response to the reviewers:

Reviewer #2

Comment: *the authors have corrected point by point all requests.*

Response: We thank the reviewer for the encouragement and appreciation for our work. We are hopeful that this manuscript will be of significant clinical use to the readers of this prominent journal.

Reviewer #1

Comment: *After reading Reviewer 1's feedback, we went back to the manuscript and reviewed all the work done in the first round of reviewers' suggestions, in which we found that we answered the questions point by point and adjusted the items that were recommended by all reviewers.*

Response:

It is important to highlight that the biggest changes in the above mentioned content by the reviewer were only carried out in what was requested and pertinent in the 1st review, respecting the rules of the journal, which deals the quantity of words.

Comment: *There is no discussion about "why there is a correlation (described in the manuscript) between social isolation during the COVID-19 pandemic and symptoms of anxiety", which happens to be important for this article.*

This narrative review provides an insight on the risk factors for anxiety associated with the current pandemic. The reviewer has made a very astute observation about the causality of the anxiety component. This is beyond the scope of the manuscript, review article and would need original (observational studies) to establish and explore the causal factors.

Despite that, in the discussion item, we have already started the paragraph stating that the selected studies presented the evidence, as shown in the following fragment:

This systematic review identified from the studies selected in the sample the presence of a significant correlation between COVID-19 and anxiety in the period of social isolation. The most significant findings confirmed: the predominancy of anxiety generated during the period of social isolation in the younger age group (20-40 years), the important role of the internet in the pandemic, and government action on strategic measures for mental health was insufficiente (1st paragraph of the Discussion).

In addition, even within the Discussion, there is another sub-item called "The anxiety genetated during the period of social isolation", in which we discuss, based on the literature, specifically the correlation between social isolation and anxiety. Thus, we understand that we respond to the reviewer's questioning, including demonstrating various social and emotional aspects as potential associated risk factors, bringing the interactivities with age, gender, place of residence, among others, as per the fragment below:

"The prevalence of mental disorders during periods of the epidemic, especially anxiety, reduces individuals' resilience against virus infection and can cause irreparable economic, social, cultural, and psychological problems for people in the future (immune system under shock)[22]. The COVID-19 pandemic has a significant influence on mental health. In this perspective, close monitoring of the vulnerable group and early recognition and treatment is a priority according to a study that analyzed psychological health during this global pandemic crisis[25-27]. Another study supports the findings of our review, we show that female gender, higher education, and younger age are associated with a higher risk of experiencing anxiety ($P < 0.05$). Women, young people, with low physical activity, and singles were associated with higher depression levels ($P < 0.05$)[24]" (3rd paragraph of the subitem The anxiety genetated during the period of social isolation in the Discussion).

Still following the comments of Reviewer 1, who says: "The changes made in other aspects are also very small", we think, as mentioned above, that all the changes that were requested and were pertinent to the discussion in the 1st review were appropriately made, respecting the rules of the journal.

We believe that all the points questioned were answered, confirming the findings of the comments made by Reviewers 1. Due to the still evolving nature of the pandemic this is an active issue and we are hopeful to provide updated information in the subequent manuscripts.