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17 Sep 2013

Dear Editor,

re: Revision: invited review manuscript 4708

Please find enclosed the edited manuscript in Word format (file name = IBD Risk Factors Review WJG 13.2.doc).

Title: Epidemiological Studies of Migration and Environmental Risk Factors in the Inflammatory Bowel Diseases. (Running title: IBD Migration Studies)

Authors: Ms Yanna Ko

Associate Professor Rupert W Leong, MBBS, MD, FRACP, AGAF

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 4708

Reviewer 00503437.

“The paper could be improved by providing a table of the essential and new findings presented therein.”

This has been incorporated as a “highlights summary”. All changes have been highlighted.

Thank you for your suggestion.

“What exactly have you learned about IBD epidemiology that will help you in Australia, and other workers around the globe, in understanding changing rates of incidence and risk factors?” – thank you. We have clarified this further by extrapolating migration studies to immigration patterns pertaining to Australia supported by the census data of 2006. This review has allowed us to focus on possible research opportunity to study epidemiology of IBD. In particular, it gives us the possibility of identifying environmental risk factors that may induce or prevent the onset of IBD by studying a genetically homogenous population in their traditional homeland in the Middle East versus their new homeland in Australia.

Any difference in the incidence of IBD is likely to be triggered by environmental issues. This needs to be prospectively explored.

“The impact of migrant studies is not clearly emphasized. Are there changing rates of incidence when population migrate?” “Are there mitigating risk factors in the new environment?”

Thank you. We have strengthened these points within the whole review stressing the importance of migrant studies and their advantages, and providing evidence for the findings in the existing migrant studies regarding incidence rate changes in migrants populations.

“Technical points: This reviewer had trouble understanding Figure 2 - what do the arrows mean?”

We agree that Figure 2 adds little value and as such it has been deleted.

“On page 26, Krawiec without the 2nd a. On page 27, Abdul-Baki is the only HMO based study quoted. This is good and is the modern approach to epidemiological work, but the article should be checked for methods of verification of the diagnosis and this should be given in the text.

Thank you for your suggestion and we have to our best confirmed these but note that studies do not always provide complete verification especially when it comes to diseases that do not have simple diagnoses.

“Tables: the size of the populations studied should be given.” Total population size was not released in the majority (20 out of 30) studies reported and only a minority would have the necessary data to include in an otherwise-busy table. For simplicity this was deemed to overcomplicate the table that was designed to provide an overview of general data. For complete detail readers should refer to the full published articles.

Reviewer 00503513.

No comments released.

Dear Editors,

Thank you for the reviewers' responses and I take each in turn.

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02456810 comment:

This study focuses on an interesting epidemiological model of migrants as a study case for IBD epidemiology and ethiology. However, the aims of the project and the data presentation are extremely confusing.

> The study is a review of migratory populations and IBD. For IBD epidemiologists this is an invaluable opportunity to study the interactions between genetics and the environment. As stated in the text "Groups migrating from areas of low IBD incidence to areas of high IBD incidence will provide insight into the effects of environmental triggers on disease development better than populations without such a transition in environment due to the shortened interval between risk factor exposure and IBD onset. Furthermore, studying the offspring of migrants will provide new cohort data on generational changes and their relationship with IBD development and highlight the contribution of these environmental factors at different ages." We hope this clarifies your confusion.

1.The study aim is not well defined. It is not clear what variables were addressed in the literature review.

> This has been clarified and expanded in the Methods section.

2.It is unclear why the study population are migrants to Australia and not any other westernized society. If that indeed is the case I would expect addressing studies describing the characteristics of IBD patients in Australia and a comparison with the original country data

> One of the conclusions of the study was that we have identified a research opportunity to study a very large group of population migrating to a Westernized country over a very short time period with sufficient first- and second- generation migrants to focus further on disease presentation. The review itself looked at data obtained from other Westernized societies including UK and Sweden on migratory populations on IBD.

3. The process of the literature review is poorly defined. Exclusion and inclusion criteria should be clearly defined, with a clear literature review chart. Specific research questions should be defined

> This has been revised with inclusion and exclusion criteria. Figure 1 discloses a flow diagram of the various articles.

A comprehensive search on the Ovid MEDLINE database (1946 to present) was performed using the following keywords: "inflammatory bowel disease", "Crohn's disease",

“ulcerative colitis”, “epidemiology”, “incidence”, “prevalence”, “clinical characteristics”, “extraintestinal manifestations”, and “risk factors” The search was limited to the English language. A manual search of reference lists of all original articles retrieved was also conducted. For migrant studies, we included the keyword “migrant” to the above. We excluded those studies which did not include at least two generations of migrant groups being studied for IBD characteristics including incidence and prevalence. Three were finally selected. To study potential new migration groups that might provide new IBD research opportunities, we chose to focus on the epidemiology of IBD in the Middle East and Australia. The search terms “Middle East”, “Arabic”, “Australia” and “risk factors” were added to the above keywords. We excluded those studies that did not report original data such as review articles, did not contain original data from the regions of Middle East and Australia, and those that were not observational studies. Studies were independently included if they reported incidence and/or prevalence rates for CD and/or UC. A total of 23 IBD epidemiological articles pertaining to the Middle East and 2 pertaining to Australia were finally included.

We clarified the hypothesis and raised the question of whether the Middle Eastern migration would result in higher IBD incidence in this population. Other migrant groups from similar research opportunities have resulted in higher incidences and support the importance of the environment in developing IBD phenotypes.

4. The conclusions are unclear- it is indeed true that migrants from the Middle East to Australia could be an interesting study population but this conclusion seems also to be the baseline assumption and it is not clear how the literature review process is supporting this conclusion

> Conclusion is that that a prospective collection of data would further clarify the interactions between genes and the environment. The concept is exploratory and raises hypotheses. This review compares the invaluable research opportunity that can be only conducted in a few places / time periods in the world. As such there have been very few previous publications on these research opportunities to date.

02520738 comment:

We have read through the manuscript and we think that it is a well-written manuscript. Nevertheless, minor changes should be performed:

> We thank you for your review.

- The authors should better outlined the total number of studies considered, the total studies excluded and the final number of studies considered, because such information is not clear.

- The authors should express inclusion and exclusion criteria that they adopted for their analysis.

> We have included the flow diagram including the included and excluded articles and the numbers as well as clarifying the numbers of articles as suggested. Thank you for the suggestion.

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- It would be better if the authors provide a figure gathering the design of these review, i.e. the study firstly included, the ones excluded, etc in order to make the design of the research more clear.

> We have included as Figure 1 the flow diagram of the included and excluded articles. Thank you for this suggestion.

With kind regards,
Yours sincerely,
Associate Professor Rupert Leong