January 20, 2014

To:

Lian-Sheng Ma, President and Company Editor-in-Chief
BPG CORPORATE HEADQUARTERS
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China

RE:

Manuscript title:

Obesity and Non-Alcoholic Fatty Liver Disease: Disparate Associations Among Asian Populations

Authors:

Robert J. Wong, Aijaz Ahmed

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 6632

Dear Editor,

My co-author and I are grateful of the reviewers' comments and your continued consideration of our manuscript for publication in World Journal of Hepatology. Please find below our point-to-point responses to the reviewers' comments and suggestions.

Reviewer 02541859

Suggestions to change in the manuscript:

1. In Introduction, in 3rd paragraph 4th sentence – relatively instead of relative

2. In the paragraph NAFLD and Liver Transplantation: 12th sentence, change to - as many patients with cryptogenc cirrhosis can in fact be more accurately categorized as NASH.

Response:

The suggested changes have been corrected in the revised manuscript.

Reviewer 01562153

The prevalence of obesity and progression of hepatic damage associated with nonalcoholic steatohepatitis (NASH) exhibits significant ethnic disparities. Asians demonstrate significant prevalences of hypertension, diabetes, metabolic syndrome, and NASH, despite significantly lower body mass index (BMI) and lower rates of obesity. In this manuscript, the authors reviewed and discussed the epidemiology of obesity and NASH, disparate association of non-alcoholic fatty liver disease (NAFLD) and BMI, and natural history of NAFLD in Asians. This is a comprehensive review on the obesity and NAFLD in Asian populations. The manuscript was well prepared. Although the major etiologies of liver diseases in Asia are hepatitis B virus and hepatitis C virus, NAFLD also plays an important role. This review may provide useful information to the clinicians in Asia.

Response:

We thank the reviewer for the helpful comments.

Reviewer 00070635

The review is important and interesting and very well written. I have few minor comments:

1. Page 4, "from 1985 to… (….), all details in parentheses are not needed if it's all described in figure 1.

Response:

We decided to leave the details that are included within the parentheses. This will allow the reader to see the actual numbers without having to look back and forth to Figure 1.

2. End of page 4: was interaction tested between ethnicity and weight gain (with regard to risk of DM)? There seems to be one but is it significant?

Response:

In both of the graphs shown in Figure 2, the odds ratios representing the association between each race/ethnicity group and the odds of hypertension of diabetes was generated with

multivariate logistic regression models that adjusted for potential effect modifiers and confounders. We did not specifically test for an interaction, but the BMI cutoffs indicating odds of diabetes or hypertension were inclusive of BMI in the regression model.

3. Natural history of NAFLD- is NAFLD appearance really more recent in Asian countries or is the possible that the awareness and screening for nafld are more recent?

Response:

We agree with the author that another possibility of the increased prevalence of NAFLD is Asian countries may be the increased awareness and subsequent diagnosis of NAFLD among this cohort. We have added additional comments in the section titled "Natural history of NAFLD" to emphasize this point.

4. How would ethnic disparities in central obesity may alter the natural history of NAFLD? To which direction?

It has been previously reported that ethnic disparities in central obesity results in Asians having more central or visceral deposition of fat compared to blacks of non-Hispanic whites. This more central or visceral deposition of fat can alter the natural history of NAFLD is several ways. First, more central obesity is associated with increased risks of developing co-morbid conditions such as metabolic syndrome, which both directly and indirectly through generation on inflammatory cascades may speed up the progression of NAFLD to NASH. In addition, the increased visceral deposition of fat may lead to more significant development of steatosis among Asians, which may lead to shorted interval from progression of simple steatosis to nonalcoholic steatohepatitis and subsequent fibrosis.

Reviewer 00002726

The article is intended as a review of the differences in NASH in Asians. The topic is of potential interest but much of the article really does not deal with the topic.

Response:

We thank the review for this comment. However, the purpose of the current review article is not intended as a review of the differences in NASH in Asians as suggested by the reviewer. In fact, the objective of the manuscript is to provide a review of the NAFLD among Asians to highlight the important disease burden in this population. Through this review, we highlight the important epidemiology and outcomes associated with NAFLD in Asians, including the disparity in the

relationship between BMI on the development of diabetes and hypertension and try to link this with the development of NAFLD in this cohort.

1. The opening pages are very repetitive as for example the points that there is an obesity epidemic and Asians have a high prevalence of NASH despite a lower rate of obesity are made several times.

Response:

We have reviewed the manuscript and have made several revisions to limit the repetition referred to by the reviewer.

2. The authors state that a disparity in insulin levels has been noted in Asians but then only figures on prevalence of the metabolic syndrome are provided. Have insulin levels by BMI been documented to be different in Asians? This should be clarified in the review.

Response:

In paragraph 3 of the section titled "Obesity Disparities", we state

"For example, using data from NHANES, Palaniappan et al demonstrated that fasting insulin levels, a marker of insulin sensitivity and risk of diabetes, was 19-26% higher in blacks and 17-22% higher in Hispanics when compared to non-Hispanic whites with similar BMI [30]. "

" . . . This disparity was also noted among Asians, with one study demonstrating significantly higher rates of metabolic syndrome in Asians compared to other ethnic groups with similar BMI. For example, Palaniappan et al demonstrated that the predicted prevalence of metabolic syndrome in non-Hispanic white women aged 55 years with BMI 25 kg/m2 was 12% compared to 30% in Asians with similar demographics and BMI. Furthermore, compared to white men with BMI 25 kg/m2, comparable prevalence of metabolic syndrome was seen in Asian men with BMI 19.9 kg/m2 [20]."

Disparities in insulin levels have only been reported in Hispanics and blacks by the Palaniappan study referred to above. A subsequent study by the same author did demonstrate ethnic disparities in metabolic syndrome and BMI, which specifically included Asians as described above.

3. It is not clear what data Fig. 1 is based on.

Response:

Figure 1 is based on data from the California Department of Public Health and the U.S. Centers for Disease Control and Prevention. This has been stated in the first sentence of paragraph 4 of the section titled "Obesity Disparities"

4. The Wong study cited on progression of simple steatosis to NASH had a very high rate of progression that is not consistent with other studies. The extensive discussion on progression is on NASH in general and not related to differences in Asians.

Response:

We thank the reviewer for this comment. The main objective of this manuscript was to review the natural history of NAFLD among Asians and not necessarily to compare the differences in epidemiology in Asians compared to non-Asians. As such, the Wong study aforementioned is especially important in highlighting the natural history of progression of simple steatosis to NASH in a predominantly Asian cohort. This data from this study are important to help our understanding of the natural history of NAFLD among the Asian populations.

5. The HCC section is also not really focused on differences between Asian and non-Asian populations. Same for transplantation section.

Response:

We would again like to state that our objective was not to highlight differences in the natural history of Asians vs. non-Asians with NAFLD. Rather, we sought to emphasize the natural history of NAFLD among the Asian populations. In both the HCC and liver transplantation section, we attempted to utilize data from both the Asian-Pacific regions as well as other world regions to help support a better understanding in the natural history of NAFLD progression to HCC as well as the liver transplantation outcomes associated with NAFLD and NASH.

6. Pages are not numbered so it is difficult to cite all of the examples, but there are a number of typographical/grammatical errors.

Page 2, line 7 should be "exhibit" not exhibits.

Page 2, line 9 "prevalences" is not a word, it should be singular, and the sentence should be reworded, "…continue to have an increased prevalence of..."

Wordage and style is very repetitive and should be improved upon. One sentence has "in addition" and "additionally" twice.

The statement that differences in Asians may be due to their fat distribution is repeated multiple times. Too much actual numerical data is cited from the papers when more summary and interpretation is needed.

Fig. 2, lower panel title "Diabetes" is misspelled. Manuscript title should really read between Asian and non-Asians not among Asians which means among various types of Asians.

Response:

We have made the suggested corrections as noted by the reviewer above.

Reviewer 02861131

GENERAL COMMENTS

(1) The importance of the research and the significance of the research contents;

Against a background of increasing rates of obesity worldwide, Non-Alcoholic Fatty Liver Disease (NAFLD) has become the commonest cause of liver disease in many developed countries, affecting up to a third of the population[1]. Increased waist circumference is probably the best single clinical predictor of underlying insulin resistance and the presence of NAFLD[2].

Asians as a group generally have lower BMI and lower prevalence of obesity compared to other ethnic groups. Despite lower obesity prevalence, higher rates of metabolic syndrome have been reported in Asians compared to other ethnic groups at similar BMI levels. These findings demonstrate that BMI thresholds for defining overweight and obesity should not be applied uniformly to all ethnic cohorts[3].

(2) The novelty and innovation of the research;

This study has reported on ethnic disparities in the prevalence of obesity as well as the impact of weight gain on overall risk of obesity-related diseases. Despite lower obesity prevalence, higher rates of metabolic syndrome have been reported in Asians compared to other ethnic groups at similar BMI levels.

The *Wong* group has performed an in-depth analysis of ethnic disparities in obesity and obesity-related diseases with a focus on Asian populations (using data from the California Department of Public Health and the U.S. Centers for Disease Control and Prevention). They created a multivariate logistic regression model to assess the effect of each one unit increase in BMI on the

risk of hypertension or diabetes mellitus. This date suggest that despite having lower BMI, weight gain as measured by BMI disproportionately affects Asians to a greater degree.

(3) Presentation and readability of the manuscript; and

Review is well organized, and systematic theoretical analyses and valuable conclusions are provided. This review is a classically presented scientific article.

(4) Ethics of the research.

Not relevant for this article (authors used official data from the California Department of Public Health and the U.S. Centers for Disease Control and Prevention)

SPECIFIC COMMENTS

Title: accurately reflects the major topic and contents of the study.

Abstract: it gives a clear delineation of the research background, objectives and main point presented in this review. Significant ethnic disparities in central adiposity and visceral fat distribution have been hypothesized to contribute to the prevalence of obesity and the progression of hepatic histologic damage associated with NASH.

Review is well organized, and systematic theoretical analyses and valuable conclusions are provided.

Introduction: present relevant information about significant difference in epidemiology of obesity and NAFLD, dependent of ethnic group.

Obesity Disparities: present original analysis of ethnic disparities in obesity and obesity-related diseases with a focus on Asian populations, performed using data from the California Department of Public Health and the U.S. Centers for Disease Control and Prevention in period 1985 to 2011. These data suggest that despite having lower BMI, weight gain as measured by BMI disproportionately affects Asians to a greater degree.

Disparate Association of NAFLD and BMI: present that phenomenon of "metabolically obese", namely the increased risk of insulin resistance, metabolic syndrome, and NAFLD despite normal or lean BMI has been more commonly seen in Asian populations

Natural History of NAFLD in Asians: present how ethnic disparities in central obesity and visceral fat distribution influence disparate association between BMI am metabolic syndrome and alter the natural history of NAFLD among this population

NAFLD and HCC: authors show importance of new studies to better understand the risk factors associated with HCC development among NASH patients with and without cirrhosis.

NAFLD and Liver Transplantation

This study demonstrated a significant increase in the proportion of patients undergoing liver transplantation for NASH, making NASH the third leading indication for liver transplantation.

Conclusions

Wong demonstrate that the phenomenon of global obesity epidemic contribute to an increasingly number of patients that will develop NASH-related cirrhosis, decompensated liver disease, and HCC.

The main point of this study is presence in Asian population the significant risk of metabolic syndrome and NAFLD despite having lower BMI. Interest in the role of genetic factors has increased following the identification of this significant ethnic disparity.

References: references are appropriate, relevant, and updated.

Tables and figures: reflect the major findings of the study, and they are appropriately presented.

Response:

We thank the reviewer for the thorough and detailed review and comments regarding out manuscript.

Reviewer 00006071

The review by Wong and Ahmed addresses the issue of ethnic influence among Asian populations on the association of obesity and NAFLD. The subject is clearly of interest, and the review is well written and documented. After carefully reading the manuscript, some questions arise:

Major questions: Ethnicity is clearly a factor related to differences in the association of obesity and NAFLD between Asians and other human populations, but other factors are surely playing a role. By tradition and culture, Asians consume higher amounts of carbohydrates than other human population in their daily diet. Carbohydrates are highly lipogenic through the activation of the transcription factor ChREBP, favoring, when consumed in excess, the development of fatty liver. As in other parts of the word, Asian countries have improved the access to food of their populations over the years, thus favoring the intake of hypercaloric diets enriched in carbohydrates in wide segments of their inhabitants. Clearly, this issue should be properly addressed in the present revision.

Response:

Thank you for this interesting suggestion. We have added additional comments on page 10 of the manuscript to highlight the potential contributing role that a high carbohydrate diet may have in the prevalence of NAFLD. We have also made reference to additional papers that explore the role of ChREBP as suggested by the reviewer.

Reviewer:

The two last paragraphs of the review "NAFLD and HCC", and "NAFLD and liver transplantation", should specifically include and comment data on these issues obtained from Asian populations.

Response:

Thank you for this suggestion. In the NAFLD and HCC section, our current manuscript already makes references to several studies from the Asia-Pacific regions including Japan and Korea. We have added additional references in the NAFLD and liver transplantation section to include studies from the Asia-Pacific regions.

Reviewer:

Minor questions: Please correct: Abstract: “Asians continue to demonstrate significant prevalences of hypertension”, prevalence . Introduction: “Non-alcoholic fatty liver disease (NAFLD) spans a spectrum of liver disease that ranges”, diseases.

Response:

These areas have been corrected as suggested.

Reviewer:

Please, every time a reference is cited, such as “western countries.[6-12]”, move the point mark to the end “western countries[6-12].”

Response:

This has been corrected.

Reviewer:

Obesity disparities, page 7: “Cognizant of these disparities” for “Acknowledging these disparities” .

Response:

This has been revised as suggested.

Reviewer:

The sentence “Shao et al demonstrated that a waist-hip ratio of 0.50 achieved an area under the receiver operating curve of 0.794 for men and 0.901 for women, both significantly better at predicting risk of metabolic syndrome than BMI or waist circumference alone” is difficult to understand, please rewrite.

Response:

The sentences has been revised as: “Using a cross sectional population-based survey study of 2,947 patients in China, Shao et al demonstrated that waist-height ratio was significantly better at predicting risk of metabolic syndrome than BMI or waist circumference alone.”

Reviewer:

Natural History of NAFLD in Asians, page 10, substitute “However, simple steatosis is not always benign, and progression of disease, while slow can occur.” For “However, simple steatosis is not always benign, and progression of disease, while slow, can occur. “

Response:

This has been revised as suggested.

Reviewer:

NAFLD and HCC, page 12, substitute “the risk of HCC among patients with NASH are less well known” for “the risk of HCC among patients with NASH is less well known”

Response:

This has been corrected

Reviewer:

References: Please correct references 26, 46, 77, 78, 80, 83, 85, 86, 88, and 94.

Figure 2: Please, change “Diabtese” for “diabetes”.

Response:

This has been corrected.

Thank you again for the opportunity to revise our manuscript for your continued consideration.

Sincerely,

Aijaz Ahmed, M.D.
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Stanford University School of Medicine
750 Welch Road, Suite #210

Palo Alto, CA 94304
Phone: 650-498-6091
Fax: 650-498-5692
Email: aijazahmed@stanford.edu