

Editorial Office

*World Journal of Gastroenterology*

February 21, 2019

**Dear Editor,**

**Re:** Revision of Manuscript (ID: No. 45937)

Please find attached a revised version of our manuscript "**The growing burden of alcoholic liver disease in China: a review**" (Manuscript NO: 45937), which we would like to resubmit for publication as a review in *World Journal of Gastroenterology*.

Your comments and those of the reviewers are highly insightful and have enabled us to greatly improve our manuscript. We have studied the comments carefully and have made corrections, which we hope will be met with approval. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using **yellow highlighting** for additions and strikethrough font *[example]* for deletions. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *World Journal of Gastroenterology*. We shall look forward to hearing from you at your earliest convenience.

We appreciate Editors/Reviewers' hard work earnestly and hope that the corrections will be met with approval. I am Yanhang Gao. Correspondence and phone calls about the paper should be directed to me at the following address, phone and fax number, and e-mail address:

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Thanks very much for your attention to our paper.

Sincerely yours,

Yanhang Gao

**The manuscript has been improved according to the suggestions of the editor and reviewers:**

## Responses to the comments of Reviewer #1

Thank you for your critical comments. We are in agreement with your suggestions, which have been of great help for improving our manuscript.

### **1. Epidemiology of ALD in China (pages 6-7): If available, please provide mortality data from chronic liver diseases (and alcohol-related liver diseases) registered in China**

**Response:** We have added this information in the section Epidemiology of ALD in China, with the addition of the following paragraph (Page 7, Line 6):

*In addition, the number of deaths caused by cirrhosis due to alcohol use among all ages and the age-standardized death rate per 100000 people in China were 41792 (95% UI36399–46769) and 5.23 (95% UI4.59–5.82) in 1990, compared with 41163 (95% UI34830–46935) and 2.89 (95% UI2.47–3.27) in 2013, respectively [14]. Moreover, the number of deaths caused by alcohol use disorders among all ages and the age-standardized death rate per 100000 people in China were 16488 (95% UI 12374–27257) and 1.69 (95% UI 1.28–2.77) in 1990, compared with 15459 (95% UI 10132–22104) and 0.97 (95% UI 0.64–1.39) in 2013, respectively [14].*

### **2. ALD and pathogenesis in the Chinese population (pages 7-8): it's a general section on the pathogenesis of ALD, nothing specific for the Chinese population. I suggest to summarize it and to move at the beginning of the paragraph "Genetics"**

**Response:** We have summarized the pathogenesis of ALD and moved this text to the beginning of the paragraph "Genetics". The revised text is as follows (Pages 10-12):

*Although the pathogenesis of ALD is complex and remains unclear, the oxidative metabolites of alcohol, including acetaldehyde and ROS, are the main culprits for ALD. Acetaldehyde is reactive with DNA and proteins and may form adducts, which act as neoantigens that elicit an immune response and contribute to liver injury. Acetaldehyde also interferes with DNA synthesis, methylation and repair, facilitating HCC susceptibility.*

*There are two major enzyme systems that metabolize EtOH into acetaldehyde (AA) via oxidative degradation.*

*On the other hand, chronic alcohol consumption up-regulates cytochrome P450 2E1 (CYP2E1) gene expression in response to the need to convert alcohol to acetaldehyde. This CYP2E1-dependent Microsomal Ethanol Oxidizing System (MEOS) generates more ROS [48]. Hepatocytes injured after alcohol intake release endogenous DAMPs. DAMPs can activate Toll-like receptor 4 (TLR4) on Kupffer cells to promote the secretion of proinflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$*

(TNF- $\alpha$ ) and to activate the inflammasome [49]. The activated Kupffer cells also secrete CXC chemokines to attract infiltrating neutrophils and other mononuclear cells, which may aggravate hepatic necroinflammation [50].

**3. Gender (page 10): is an increase of ALD expected also among females in the future? According to data provided in the previous section, among high school students the prevalence of alcohol consumers among females is lower than in males but not negligible**

**Response:** We are very grateful to the reviewer for raising this important question regarding the increase in ALD among females. This information has been further clarified in the revised version of the manuscript with the addition of the following text (Page 9, Line 9):

*According to the Global status report on alcohol and health 2018, in absolute numbers there were about 91000 more women who drank alcohol in 2016 than in 2000 despite a 5% decrease in the current worldwide drinking prevalence from 37.3% to 32.3% [7]. The prevalence rates of current drinking among women in the WHO Western Pacific Region were 39.3%, 36.4%, 42.0%, and 40.7% in 2000, 2005, 2010, and 2016, respectively. In China specifically, the total, including recorded and unrecorded, alcohol per capita consumption for women were 2.2 (95% CI 1.9–2.5) and 2.5 (95% CI 2.4–2.6) in 2014 and 2018, respectively [7, 33]. However, the age-standardized death rates for liver cirrhosis in females were 5.8 and 8.3 per 100000 population (15+) in 2012 and 2016, while the alcohol-attributable fractions were 59.8% and 41.6% in 2012 and 2016, respectively [7, 33].*

**4. BMI and obesity (pages 13-14): please provide data on time trends in the prevalence of these risk factors in the Chinese population**

**Response:** We are very grateful to the reviewer for raising this important issues upon question regarding BMI and obesity. This information has been further clarified in the revised version of the manuscript with the addition of the following text (Page 13, Line 1):

*Data from the China Health and Nutrition Survey collected in 1997, 2000, 2004, 2006, 2009 and 2011 showed an increasing trend in the BMI of Chinese adults, with that of males increasing by 0.21 kg/m<sup>2</sup> per year and that of women increasing by 0.16 kg/m<sup>2</sup> per year [62].*

**5. Public health policy: I think it's the wrong place for this section; I suggest to move these important part to the Discussion section (regulation of alcohol consumption....)**

***Response:** According to the reviewer's suggestions, we moved this section to the Discussion section and changed the subtitle to "Regulation of alcohol consumption".*

**6. Hepatocellular carcinoma: please summarize and move data of hepatocellular carcinoma to the Introduction**

***Response:** We appreciate the reviewer's valuable suggestion and have made the recommended changes. We have summarized and moved the data for hepatocellular carcinoma to the Introduction.*

**Responses to the comments of Reviewer #2**

**It is a well-made and presented manuscript. Congratulations**

***Response:** Special thanks to you for your review and encouraging comments.*