

24 February 2022

Dr Jin-Lei Wang

Company Editor-in-Chief, Editorial Office

Baishideng Publishing Group Inc

Dear Dr Wang,

We appreciate the time and effort of the editorial board and reviewers in providing comments to strengthen our work. We have revised our manuscript in response to the comments provided, and hope that it is acceptable for publishing in your journal.

Yours sincerely,

Sabrina Quek

Eunice Tan

Kewin Siah

Comments from Reviewers:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript aims to review the early developmental factors associated with NAFLD. These factors include maternal and paternal factors, intrauterine factors, postnatal factors such as breastfeeding, lifestyle factors in adolescence including sleep, physical activity, nutrition and presently still non-modifiable factors such as genetic polymorphisms. According to the author's results, interventional strategies to ameliorate the developmental programming of NAFLD may thus potentially be more efficacious during the critical windows of developmental plasticity, negating the need for strategies to reverse NAFLD later in life. The topic of the manuscript is very interesting and meaningful, and also conforms to the idea of DOHaD theory. However, there are still several issues to be clarified. The first, NAFLD itself is a characteristic of metabolic syndrome with complex etiology, which is closely related to obesity. The author also repeatedly mentioned obesity in the discussion part, but did not analyze the internal relationship between them. Second, whether there is a definite definition and scope of "developmental plasticity" and "developmental reprogramming", which needs to be clarified. Also, there are many risk factors for NAFLD, and the author focuses on the early stage of life, and you should pay more attention to the key points rather than discussing in general.

Authors' reply: We thank Reviewer #1 the important comments, and we address them in three subsections below:

- a) We have incorporated briefly the internal relationship between obesity and hepatic steatosis in the Discussion section (page 25, lines 5-14): *“Metabolic syndrome and NAFLD is often linked to nutrient excess and obesity, though not all that are obese are metabolically unhealthy and vice versa. The adipose tissue expandability hypothesis by Virtue and Puig suggests that capacity to store lipids by expanding adipose tissue is variable in different individuals. When capacity is reached, adipose tissue then gets*

stored in ectopic tissues like the muscle and liver. Increase in visceral adipose tissue appears to be associated with metabolic disorders¹⁷. This concept suggests that instead of obesity in general, fat distribution, adipose tissue functionality and presence of insulin resistance are the likely key drivers of metabolic syndrome and NAFLD¹⁸, which often exist as a continuum.”

- b) We have included in the Discussion section explanation of the term developmental plasticity (page 25, lines 18-23): *“Developmental plasticity is the ability where a given genotype may produce different phenotypes in response to different environments^{75,76}. An exposure to a suboptimal condition during critical period of developmental programming can result in a diseased state.”*
- c) We have limited the discussion of NAFLD and obesity in general to the second paragraph in the discussion (page 25, lines 3-14). In subsequent sections of the discussion, we discuss the concept of developmental plasticity (page 25, lines 18-23), pathophysiology of maternal obesogenic environment (page 26, lines 4-17) and undernourishment in-utero resulting in offspring NAFLD (page 26, lines 19-23 and page 27, line 1-5), and mechanisms how breastfeeding confers protective effects against NAFLD later in life (page 27, line 7-13). We have excluded more generic associations such as offspring obesity, lifestyle factors such as overnutrition and sedentary lifestyle in the discussion, with only brief mention of this whilst addressing limitations of the study.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: NAFLD is becoming a new global epidemic, which obtains potential risks of cardiovascular diseases and end-stage liver diseases. NAFLD, especially in adolescents, is a serious clinical problem, which will affect the physical and mental health of adolescents. Generally, we believe that unhealthy lifestyles in adolescence, such as high-fructose intake, high calorie diet, sedentary work and lack of sleep, are the main risk factors. This review provides a new understanding on adolescent NAFLD, and points out the effects of

maternal factors, paternal factors, intrauterine factors, especially the maternal metabolic factors are crucial, which provides guidance for the early intervention on these risk factors in adolescent NAFLD patients. Ref 12 suggests the existence of a malnourished NAFLD, which has no significant correlation with the dominating adolescent NAFLD with malnutrition. It is not proper to be included this literature.

Authors' reply: We thank Reviewer #2 the comments. Reference 12 is a study by Zheng et al which describes that undernourishment in-utero is associated with NAFLD in the offspring. This concept that mechanisms that signal early catch up growth in the post-natal period may also modify associations with risks of metabolic disease in adulthood has also been explored previously, such as by Eriksson et al (PMID: 12627317). We have thus elected to keep reference 12, however at the same time added "*While maternal obesity has been widely reported to be associated with NAFLD, poor nutrition in the form of undernourishment in-utero has also been associated with NAFLD in offspring⁶⁶⁻⁶⁹. This hypothesis was explored by Zheng et al¹² as summarized in the Results section earlier.*" in (page 26 lines 19-22) to improve clarity of the discussion.

Comments from editorial office:

1) Science editor:

Authors reviewed early developmental factors in NAFLD. This review could provide a mechanism of NAFLD and be useful for clinicians. This review focus the mechanism of NAFLD during early period of life. Authors should focus and discuss those early developmental mechanism not but general mechanisms as reviewer 1 suggested.

Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade B (Very good)

Authors' reply: We thank the science editor for the comments and have addressed these issue in the first part of the document, in part (c).

(2) *Company editor-in-chief:*

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s)

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Authors' reply: We thank the editor-in-chief for the comments and provided the necessary documents for the manuscript submission.