

## Format for ANSWERING REVIEWERS

December 31, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6218-edited.doc).

**Title:** Pediatric fatty liver disease: role of ethnicity and genetics.

**Author:** Pierluigi Marzuillo, Emanuele Miraglia del Giudice, Nicola Santoro.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6218

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

(1) we incorporated in a new paragraph "Prevalence of NAFLD in Asia and Africa" showing the data from emerging economies like China and India.

(2) we discussed the limitations of the review as several of the references are studies conducted in adult populations.

(3) a native English speaker revised the manuscript.

(4) we specified the new limit of 20% to the echographic detection of hepatic steatosis and we cited the new reference.

(5) we deleted the repetitions.

(6) we specified that the diagnostic criteria for the NAFLD are the same in both adults and children.

(7) we added a new column in Table 1 specifying the number of subjects studied in cited papers

(8) we created an additional table (Table 2) summarizing the proposed mechanisms of each gene implicated in NAFLD development.

In the next page there are the detailed answers to reviewers.

We hope that our manuscript will be of interest for the readers of the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in dark ink, appearing to read 'Pierluigi Marzuillo'.

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We thank the reviewers for taking the time to read and comment on our manuscript. All the changes have been highlighted in the text.

Reviewer 02822427

**Comment: Please organize the manuscript with the help of a professional English editorial assistant.**

*Answer: An English native speaker has revised the manuscript.*

**Comment: Please incorporate some data from emerging economies like China and India.**

*Answer: We have incorporated in a new paragraph "Prevalence of NAFLD in Asia and Africa" data from emerging economies like China and India. Please see on page 5 from line 4 to line 18. The new paragraph reads as follows: "Considering the global population in United States, Browning et al. described that the prevalence of NAFLD is the highest in the American Hispanic population (45%) and the lowest among African Americans (24%), with the Caucasians showing an intermediate prevalence (33%)<sup>[17]</sup>. The prevalence of NAFLD in Europe, Australia, and Middle East ranges from 20% to 30%<sup>[18]</sup>. On the basis of studies conducted over the past years the prevalence of NAFLD in Japan and China, such as Latin America, is similar to that in Europe (20-30% in Japan and 15-30% in China, respectively)<sup>[18]</sup>. In the Indian subcontinent, the prevalence of NAFLD in urban populations ranges from 16% to 32%; however in rural India, where most people have traditional diets and lifestyles, the prevalence is lower (about 9%)<sup>[74]</sup>. While some information about the prevalence of NAFLD in Asia is available there is a paucity of data on prevalence of NAFLD in Africa. A Nigerian study estimated the prevalence to be about 9%<sup>[18]</sup>. These data suggest that adoption of a sedentary lifestyle and globalization of Western diet is associated with an increase in the prevalence of NAFLD in developing nations".*

Reviewer 00053950

**Comment: Only in the Introduction and the Risk factors the focus of paper is merely in the pediatric patients.**

*Answer: We have discussed this limitation at the end of the review in the paragraph "future directions" that reads as follows: "a limitation of this review is that several of the quoted studies have been performed in adults, but unfortunately accurate studies in pediatrics are quite limited also because the state of art techniques to assess hepatic fat content (MRI, MRS and liver biopsy) are difficult to perform in the pediatric population and very expensive." Please see on page 12 from line 23 to line 27".*

**Comment: Pag 3. ...can detect the disease when steatosis involves >30%... this finding has been commonly accepted to the clinical practice. However, the equipment has evolved since year 2002, and in fact in the paper of Shannon et al 2011 the detection limit was 20%**

*Answer: We have now specified the new steatosis detection and we cited Shannon et al. See the introduction. Please see the introduction section on line 19 and the new reference 14 (Shannon et al 2011).*

**Comment: Page 4. The fact that NAFLD is more common in male population is mentioned twice.**

*Answer: We cancelled the repetition and mentioned it once.*

**Comment: Pages 4 and 5. The finding that African-Americans have a higher degree of IR is mentioned repetitively. Similarly, lower intraperitoneal fat accumulation in African Americans has also mentioned twice.**

*Answer: We revised these pages according with your suggestions and removed the repetitions.*

Reviewer 00158197

**Comment: Introduction. It is worth mentioning that the criteria for diagnosis of NAFLD in children is the same as of or different from adult.**

*Answer: We have specified that the criteria for diagnosis of NAFLD are the same in the pediatric and adult population. This is now mentioned in the text and reads as follows: "The criteria for the diagnosis of NAFLD are similar in adults and children: hepatic fat infiltration > 5% hepatocytes, as assessed by liver biopsy in patients with no or low daily consumption of alcohol and in absence of either viral, autoimmune or drug-induced liver disease<sup>[3-5]</sup>." Please see page 4*

from line 4 to line 7.

**Comment:** Several of the references were studies conducted in adult population; therefore the author may consider mentioning limitation of the review in regards to this matter, either in the introduction or discussion section.

*Answer:* We have discussed this limitation at the end of the review in the paragraph "future directions" that reads as follows: "a limitation of this review is that several of the quoted studies have been performed in adults, but unfortunately accurate studies in pediatrics are quite limited also because the state of art techniques to assess hepatic fat content (MRI, MRS and liver biopsy) are difficult to perform in the pediatric population and very expensive." Please see page 12 from line 23 to line 27".

**Comment:** Page 11 line 2 "...are need..." should be "...are needed...."

*Answer:* We have corrected the mistake.

**Comment:** Table 1: addition a column of number of subject studied may be helpful. Having an additional Table (Table 2) summarizing proposed mechanism of each genetic variant would be useful to the audiences.

*Answer:* We added a new column in Table 1 indicating the number of subjects studied. According to your suggestion we added an additional Table (Table 2) summarizing the proposed mechanism of each genetic variant.