

New Haven, October 23 th, 2016

To the Editor of the

**World Journal of Hepatology**

Dear Editor,

We are resubmitting for publication in your Journal the revised manuscript- accordingly to the reviewer's comments - **From the liver to the heart: cardiac dysfunction in obese children with non-alcoholic fatty liver disease** written by Anna Di Sessa, Giuseppina Rosaria Umamo, Emanuele Miraglia del Giudice and Nicola Santoro.

We thank the reviewers for taking the time to review our manuscript and for the insightful suggestions. Below are listed the reviewers' comments and the authors' answers. The changes indicated have been highlighted in the new version of the manuscript.

**Response to the Reviewers' comments**

**Reviewer: 2**

**Comments to the Authors:** I suggest the Author to underline the role of cytokines, in the evolution of low inflammatory status in NAFLD patients, clearly related to heart and vascular diseases (i.e. Abenavoli Rev Recent Clin Trials. 2014)

**Answer:** As required, we explained the role of cytokines in the unfavorable circle of several mediators involved in the progression of NAFLD and linked to cardiac changes. Please see page 5, lines 114 to 132.

**Reviewer: 3**

**Comments to the Authors:** A brief article outlining the risk of cardiovascular disease in obese children with fatty liver. I have a few minor comments: 1. The article has the form of an

editorial more than a review article. As such, I would suggest remove the subtitles, that do not explain what is in the following text.

*Answer:* In the new version of our manuscript we have removed the subtitles, as suggested.

2. The figure is scarcely informative: it does not explain which mediators might be released by the liver to increase the risk of cardiac events.

*Answer:* We have modified the figure accordingly. We report now the role of the major factors (e.g. adipokines, cytokines) involved in the physiopathology of the cardiac damage. Please see new Figure 1.

3. The authors state that changes in cardiac morphology in children with NAFLD do not resemble the changes observed in hypertension. This statement should be explained to be informative to readers.

*Answer:* We discuss now the differences between the cardiac changes observed in hypertension and in NAFLD patients and also highlight the different mechanisms leading to cardiac abnormalities in each disease. Please see page 6, lines 135 through 144.

4. There is a plethora of useless references. I would recommend reduce the number and point recent reviews or editorials (see, Ratziu, J Hepatol 2016).

*Answer:* In the new version of the manuscript we have reduced the references and selected more recent papers.

5. The English language needs some polishing by a native speaker.

*Answer:* The language has been checked and polished when needed.

#### **Reviewer: 4**

**Comments to the Authors:** Dear Editor The article is very good however concise. I suggest in the item discussion subdivided into subtopics following the example atherosclerosis, increased

blood pressure and make a table with the studies and their important data as study design, sample size, age of participants, the population origin and main findings

*Answer:* In the revised version of the manuscript we have subdivided discussion into two subtopics (Atherosclerosis, and Cardiac Abnormalities) and added a table to the text, including the major features and findings of each study (please see table 1).

#### **Reviewer: 5**

**Comments to the Author:** The editorial is well-written and describes how NAFLD leads to cardiac dysfunction in children. However, some topics are missed.

1. NAFLD in children can stem from parental obesity. Hence, the influence of maternal and paternal obesity on offspring's NAFLD should be mentioned. There are evidence from experimental studies (please see: PMID 25880318, PMID 2558208).

*Answer:* We have added the topic regarding the influence of maternal and paternal obesity on offspring's NAFLD in the new version of the manuscript. Please see page 3, lines 55 to 57.

However, the second suggested reference is unrelated to our question and was therefore not included.

2. Also, the effects of insulin resistance on cardiac morphophysiology should be explored

*Answer:* We have discussed the effects of insulin resistance on cardiac morphophysiology in the subtopic of cardiac abnormalities. Please see on page 5 from line 114 to line 121.

There are no prior publication of these data.

This work is not and will not be submitted to any other journal while under consideration by World Journal of Hepatology.

No conflict of interest exists.

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

**Conflicts of Interest:** nothing to declare

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Yours sincerely,

Nicola Santoro

**(Number ID: 02461842)**

Department of Pediatrics

Yale University School of Medicine

330 Cedar Street,

PO Box 208064, New Haven, CT 06520. United States.

Fax: +1-203-7856421

[nicola.santoro@yale.edu](mailto:nicola.santoro@yale.edu)