Point-by-point response to reviewers' comments

We thank the Editor and the Reviewers for their valuable comments.

All the suggested corrections by the Editor and Reviewers have been accepted.

All the actions required for resubmission of the manuscript have been performed and the manuscript has been accordingly modified.

Reviewer 1

Thanks for your favorable comments.

Reviewer 2

1.As for the comment that *primary message needs to be defined more clearly and presented more directly*, we have added in Key Messages, according to reviewer's suggestion, that existing studies are insufficient to determine whether or not pediatric NAFLD patients have an elevated risk of developing detrimental health conditions. As suggested, these statements have been included in the "Key Messages" section and in the text of the revised version of the manuscript. In the Abstract we have added that large-scale longitudinal studies with long-term follow-up of pediatric NAFLD patients are lacking. In "Key Messages", as suggested, we have added that: The available studies are insufficient to determine whether or not children with nonalcoholic fatty liver have an elevated risk of developing detrimental health conditions. Large-scale longitudinal studies with long-term follow-up of children with nonalcoholic fatty liver are desirable. In the paragraph "Risk of progression of pediatric NAFLD toward end-stage liver disease", we have added that "Unfortunately, none of the studies, reported in Table 1, provided long enough follow-up to assess long-term cumulative risk of severe outcomes. In addition, we have clarified, as suggested by reviewer, that almost all the evaluations were assessed in individuals under 20 years of age.

As for the observation "no children with NAFLD required liver transplant in large pediatric series in Europe and USA", appropriate references have been addedin the revised version of the manuscript.

Ref 21. McDiarmid SV, Anand R, Lindblad AS; SPLIT Research Group. Studies of Pediatric Liver Transplantation: 2002 update. An overview of demographics, indications, timing, and immunosuppressive practices in pediatric liver transplantation in the United States and Canada. Pediatr Transplant 2004;8(3):284-94.

Ref. 22. Sze YK, Dhawan A, Taylor RM, et al. Pediatric liver transplantation for metabolic liver disease: experience at King's College Hospital. Transplantation 2009;87:87-93.

Ref. 23. Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatriclivertransplantation. World J Gastroenterol 2009;15(6):648-74.

Ref. 24. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, Mazariegos GV. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology 2014;60(1):362-98. doi: 10.1002/hep.27191.

2.As for the comment "*Negative outcomes for pediatric NAFLD patients – occurrence in childhood versus increased lifetime risk of development",* we first want to thank the reviewer for his comments about the low prevalence of deleterious liver conditions in obese children with NAFLD documented innonlongitudinalstudies, based on single time point evaluations. The reviewer clearly affirms that there is a discrepancy between low prevalence of advanced liver disease in children with NAFLD (supported by evidence) and relative risk of eventual progression over time (currently inknown), on the basis of a hypothesized linear relationship between duration and severity of the disease.
This crucial point has been stressed in the revised version of the manuscript (see above, point 1). As for the limits (stressed by the reviewer) of the longitudinal studies so far available, we have added that "Unfortunately, none of them provided long enough follow-up to assess long-term cumulative risk of severe outcomes".

3.As for the*Tone of manuscript not representative of a review article,*we have accepted the criticism and the statements concerning the relationship between disease mongeringand drug company staff, physicians and consumer groups has been rephrased in the revised version of the manuscript. Each sentence has been supported by appropriate reference. The phenomenon of "disease mongering" has been clarified in the revised version of the manuscript and another reference has been added. Ref 10. Heath I. Combating disease mongering: daunting but nonetheless essential. PLoS Med 2006;3(4):e146.

4.As for ***Lack of support for some claims,***

a. *the claim "there is a widespread tendency to draw alarming scenarios also for childhood NAFLD",* in the revised version, has been supported bythe following references:

Ref. 4. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut 2009; 58:1538-44.:These Authors affirmed, in their conclusions, that "*Children with NAFLD may develop end-stage liver disease with the consequent need for liver transplantation. NAFLD in children seen in a tertiary care center may be associated with a significantly shorter survival as compared to the general population".*Although this concluding statement on the possible unfavorable evolution of NAFLD cannot be rebutted by itself, it seems excessive if we consider that in Feldstein's series there were only two children with cirrhosis and these were the same two who required liver transplantation. Overall, four children were included in the poor prognosis group: the two transplanted and two who died for complications related to bariatric surgery and whose death was not liver related. On the basis of the outcome of these four "atypical" patients with NAFLD, a standardized mortality risk of 13.6 was assigned to the category of children with NAFLD in comparison with general population.In our opinion, there is a **discrepancy between the real number of NAFLD children with a severe prognosis and the title and conclusions of the study.**

Ref. 5. Alkhouri N, Hanouneh IA, Zein NN, et al. Liver transplantation for nonalcoholic steatohepatitis in young patients.TransplInt2016;29:418-424.In this study the Authors affirm that *NASH can progress to end-stage liver disease requiring LT in childhood and early*

adulthood. A significant number of young patients transplanted for NASH cirrhosis required retransplantation. This study is cited to stress the high risk for liver transplantation in obese children (see Nobili's review in Gastroenterology 2016 –Ref. 1 of our manuscript). As discussed in our manuscript, in spite of the alarming tones of Alkhouri'sstudy, the overall frequency of transplantation for NASH and cryptogenic cirrhosis associated with obesity was only 1.67 (330/19904 cases). In addition, among these patients only 4.2% were under 18 years old. Therefore, in our opinion, also in Alkhouri's studythere is a **discrepancy between the real number of NAFLD children with a severe prognosis and the title and conclusions of the study.**

Ref. 6. Betancourt-Garcia MM, Arguelles A, Montes J, Hernandez A, Singh M, Forse RA. Pediatric Nonalcoholic Fatty Liver Disease: the Rise of a **Lethal Disease**AmongMexican American Hispanic Children. Obes Surg. 2017;27(1):236-244. doi: 10.1007/s11695-016-2440-5.

b.the claim *"the majority of obese children are not adherent to lifestyle modifications and hypocaloric diets"*is supported by the following reference:

Ref.27. Kovacs E, Siani A, Konstabel K, Hadjigeorgiou C, de Bourdeaudhuij I, Eiben G, Lissner L, Gwozdz W, Reisch L, Pala V, Moreno LA, Pigeot I, Pohlabeln H, Ahrens W, Moln ár D; IDEFICS consortium. Adherence to the obesity-related lifestyle intervention targets in the IDEFICS study. Int J Obes (Lond). 2014 Sep;38Suppl 2:S144-51. doi: 10.1038/ijo.2014.145.

c. the statement *"To reinforce the concept that fatty liver due to obesity is rarely leading to liver transplantation is the observation that no children with NAFLD required liver transplant in large pediatric series in Europe and USA*" is supported by the following references:

Ref 21. McDiarmid SV, Anand R, Lindblad AS; SPLIT Research Group. Studies of Pediatric Liver Transplantation: 2002 update. An overview of demographics, indications, timing, and immunosuppressive practices in pediatric liver transplantation in the United States and Canada. Pediatr Transplant 2004;8(3):284-94.

Ref. 22. Sze YK, Dhawan A, Taylor RM, et al. Pediatric liver transplantation for metabolic liver disease: experience at King's College Hospital. Transplantation 2009;87:87-93.

Ref. 23. Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. World J Gastroenterol 2009;15(6):648-74.

Ref. 24. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, Mazariegos GV. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology 2014;60(1):362-98. doi: 10.1002/hep.27191.

d.The statement *"However, what is proved by the evidence is that childhood obesity by itself increases the risk of liver cancer in adulthood, as well as other carcinomas"* is supported by the thefollowing reference:

Ref. 26. Berentzen TL, Gamborg M, Holst C, et al. Body mass index in childhood and adult risk of primary liver cancer. J Hepatol 2014;60:325-330.

5. As for*Unjustified criticismofprior study*:*The authors criticize the Feldstein study (Reference 9 of the original version of the manuscript, Reference 4 of the revised version) for referring to "well-documented cases of cirrhotic stage disease", apparently arguing against the use of the term "well-documented" based on the small number of cases. Clearly the cases are well-documented, as the authors go on to discuss each of them in some detail. The term was used to describe the individual cases, not the concept of cirrhosis in pediatric NAFLD itself.* We accept the criticism of the reviewer because, in spite of the small number of patients (only 4 patients), cases of cirrhosis were actually well-documented. Accordingly, we have modified the text of the revised version of our manuscript.

6. As for the role of probiotics in children with NAFLD, we accept reviewer's suggestion to provide*more introduction of the topic, along with an appropriate background reference on the functional role of gut microbes in NAFLD*. Accordingly, the revised version of the manuscript has been modified and references added.

Since many studies in humans have shown a relationship between gut bacterial overgrowth, enhanced gut permeability, increased paracellular leakage of gut luminal antigens and liver disease progression through an increased exposure of the liver to gut-derived bacterial products (30, 31), modulating gut microbiota with probiotics, prebiotics, and synbiotics has become an attractive, safe and well tolerated treatment strategy of obesity and NAFLD.Nevetheless, also in adults, their therapeutic use is not supported by high-quality clinical studies (31,32). Unfortunately, the only two pediatric RCTs, evaluating the influence of either single strain (Lactobacillus rhamnosus strain GG) (33) or multistrain VSL#3 (34) probiotic supplementation on hepatic biomarkers in small groups of patients (20 and 40, respectively), gave different results. Vajro et al (33) reported no effect of L rhamnosus strain GG on liver echogenicity, but a decrease in serum alanine aminotransferase levels in children treated with L rhamnosus strain GG as compared to placebo. Conversely, Alisi et al (34) found that VSL#3 supplementation reduced the severity of steatosis as assessed by US. These findings were observed in short periods (2 and 4 months, respectively) and with a single evaluation at the end of the study.

Reviewer 3

We thank the reviewer for his positive comments.

As suggested, in the revised version of the abstract we have clarified the specific goal of the review and major conclusions made. In particular, we have clarified that "Here, we propose a critical appraisal of the best available evidence about long-term course of pediatric NAFLD and efficacy of treatments other than hypochaloric diet and physical exercise. As a result, the number of NAFLD children with a poor outcome is small in spite of the alarming tones used in some papers; large-scale longitudinal studies with long-term follow-up of pediatric NAFLD patients are lacking; the studies on ancillary pharmacological interventions have been performed in few patients with inconclusive and conflicting results".

As for "Feldstein's series", we have modified the text and corrected the references regarding Feldstein. We confirm that the coauthor of the reference no. 12 (Adams LA, Feldstein A, Lindor KD … Hepatology 2004; 39:909-914 is Feldstein A and not Feldstein AE (see PubMed).