Editorial

# Paediatric non-alcoholic fatty liver disease: a more complex disease than in the adulthood?

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*Comment on:* Trico D, Caprio S, Rosaria Umano G, *et al.* Metabolic Features of Nonalcoholic Fatty Liver (NAFL) in Obese Adolescents: Findings From a Multiethnic Cohort. Hepatology 2018;68:1376-90.

Submitted Dec 19, 2018. Accepted for publication Dec 26, 2018.
doi: 10.21037/hbsn.2018.12.16
**View this article at:** http://dx.doi.org/10.21037/hbsn.2018.12.16

While the association between obesity, type 2 diabetes (T2D) and the presence of steatosis has been established since the beginning of the last century (1), it was not until 1980 that the first references were made about a form of histologic liver lesion designated as non-alcoholic steatohepatitis (NASH). NASH is characterised by the presence of a variable degree of steatosis accompanied by lobular inflammatory infiltrate and hepatocellular damage with or without fibrosis. Subsequently, the broader term of non-alcoholic fatty liver disease (NAFLD) was accepted, which more accurately encompass the entire spectrum of lesions that appear in these patients (2). Ever since then, NAFLD has become progressively the primary cause of chronic liver disease in developed countries (3).

According to the World Health Organization (WHO), by 2014 more than 1,900 million adults were overweight, and more than 600 million were obese (4). The HEPAHEALTH project, hosted by the European Association for the Study of the Liver (EASL) and aimed to define the epidemiology of liver diseases and their risk factors in Europe, has recently published data on trends in obesity and T2D as main risk factors associated to NAFLD. Overall, the prevalence of both conditions has increased in European countries, being the increase in obesity matched by the increase in NAFLD mortality (5). Similarly, Asrani *et al.* have reported comparable data on burden of liver diseases in the world (6). Globally, it has been estimated that the prevalence of obesity has increased 6-fold from 1975 to 2016 (7). Especially disturbing are trends observed in children overweight and obesity in the last four decades. In a global analysis including over 2,400 population-based studies regarding almost 130 million participants aged 5 years and older, the global age-standardized prevalence of obesity has increased in more than 5-fold in girls, and almost 8-fold in boys. This means that, in absolute numbers, in 2016 50 million girls and 74 million boys were obese, and 213 million children were overweight.

The factors driving obesity burden are complex, and may be shaped by geographical and economic elements (8). In western countries, considering a reductionist approach, obesity is generally the result of an imbalance between food intake and calorie consumption. As mechanization, motorization and industrialization since the beginning of the 20th century have led to a lower need of daily energy expenditure, a significant proportion of the worldwide population has embraced a sedentary lifestyle. In fact, a recently published research of pooled data from population-based surveys on physical activity reported that the global prevalence of insufficient daily physical activity was 27.5% (9). This global prevalence strikingly resembles the one of NAFLD (10). But this decrease in physical activity did not immediately reflect an outbreak in obesity in the first half of the 20th century in countries like the US, suggesting that other factors should better explain the obesity epidemic. In this sense, several studies have pointed out the major role of the rise in food energy supply, especially in the late 60s and 70s, as the predominant driver of this epidemic (8). Wide availability of affordable, hypercaloric, ultra-processed food that, in addition, has been highly promoted explains the rise in energy intake, but

probably, it is insufficient to explain the global obesity and obesity-related morbidity epidemic.

Variations in the native gut microbiota and dysbiosis have been linked to childhood development of obesity, with potential modifiers of intestinal microbiome starting as early as prenatally. Maternal factors such as high-fat diet, age, body mass index (BMI), insulin resistance, alcohol or tobacco could affect bacterial colonization of the gut even before birth (11). A wealth of evidence points that maternal diet is a key factor in the development of an adverse intrauterine environment leading to an increased susceptibility to obesity and NAFLD in the offspring as foetus is early exposed to increased glucose, insulin and plasma lipids (12). This adverse environment encompasses a wide spectrum of damage, starting mainly in the placenta. Insulin resistance, hyperlipidaemia or western-style diet may lead to impairment in the placenta functionality, due to oxidative stress, hypoxia and an increased pro-inflammatory cytokine production. This dysfunctional placenta will have a direct effect on the offspring, as it will be exposed to a hypoxemic environment and high levels of oxygen reactive species or pro-inflammatory cytokines (13). In this setting, permanent changes in the foetal liver may take place, including changes in glucose and lipid metabolism, with an increased lipogenesis and lipid accumulation, as well as mitochondrial dysfunction and epigenetic changes in liver macrophage system that may eventually determine a pro-fibrogenic and -inflammatory phenotype and susceptibility to NASH after birth (14).

Moreover, there is accumulating data on different factors that can influence the establishment and maturation of the gut microbiome during birth and early after. Thus, the mode of delivery has been shown to have a deep impact on gut microbiota diversity, with a total lower microbial diversity in children delivered by caesarean section (15). Maternal breast milk also modifies and promotes the diversity and development of gut microbiota in the infant (16), and therefore, it has been also intensively analysed its protective role on obesity and overweight in childhood and adolescence (17). Breastfeeding seems to exert a protective role on NAFLD risk in the offspring (18) that interestingly is shared with the mother in terms of NAFLD protection in mid-life (19). Recently, Stark *et al.* have published an interesting work on the role of early prescription of antibiotics and acid-suppression medications on the risk of childhood obesity (20). The authors conducted a cohort study involving more than 333,000 children and analysed the prescription of antibiotics, proton pump inhibitors and histamine-2-receptor antagonist in the first 2 years of life. They observed that these microbiota-altering medications, especially when administered during long periods of time early in childhood, may have a deep impact on weight gain and are associated with an increase in early onset obesity.

As NAFLD burden is progressively increasing globally, affecting one in four adults worldwide (10), there is an ongoing need to better identify patients at risk of disease progression and liver related events. Growing evidence points out to liver fibrosis as the main risk factor not only for liver related events, but also for all-cause mortality and morbidity in adult NAFLD (21). Thus, many efforts are currently focused on the identification and accurate characterization of this high-risk population. Despite liver biopsy remains the gold standard for the histologic characterization (22), it is unacceptable as screening method of high-risk populations. Therefore, different non-invasive methods as clinical prediction rules and blood-based biomarkers have been developed and validated for the porpoise of the correct identification of patients at risk (23). Nevertheless, there is a paucity of data on natural history and non-invasive assessment of NAFLD in infants, and therefore there is a pressing need for a better characterization of patients at risk of disease progression in paediatric NAFLD. Is for this reason that we have read with outstanding interest the recently published research on metabolic features of NAFLD in obese adolescents by Domenico Trico and collaborators (24). The authors performed a prospective study, including more than 500 obese adolescents form the multi-ethnic Yale paediatric obesity cohort. All participants underwent abdominal magnetic resonance imaging in order to identify liver steatosis, as well as glucose oral tolerance tests to determine the presence of insulin resistance. In a subset of 133 patients, the evaluation was repeated after a 2 years follow-up. In our opinion, one of the most valuable contributions of this work is the data on NAFLD epidemiology. There is a paucity of data on paediatric NAFLD incidence. In this paper, risk factors for NAFLD incidence were analysed, identifying that ethnicity, BMI changes and C peptide fasting levels may predict NAFLD onset with an AUR of 0.887, that can rise up to 0.978 when also considering the presence of known genetic risk factors as the presence of the *GCKR* rs1260326 variant. Authors also observed how ethnicity has an important impact not only in NAFLD prevalence, as Hispanics are at the higher risk of NAFLD as previously described (25), but also on the metabolic profile of obese adolescents. Thus, despite black obese

 

adolescents displayed the lowest prevalence of NAFLD, when this condition is present in this population, it has a deleterious impact on the metabolic phenotype, with a higher prevalence of insulin resistance and T2D. Further research is needed to determine the impact of these findings in long-term liver and metabolic outcomes. A limitation of the present study is the limited number of biopsy-proven NAFLD patients and the lack of non-invasive assessment of liver fibrosis, which hampers the evaluation of the impact of different metabolic profiles and ethnicity in the severity of NAFLD and the risk of progression.

Due to the complexity of the underling mechanisms than are driving the obesity and NAFLD epidemics in children and adolescents, we truly believe that more research is needed in order to better identify infant specific risk factors for NAFLD early onset and severity, that might be in part different of those described in adult population. Finally, we consider that further research on clinical prediction rules and blood-based biomarkers tailored to the paediatric population is warranted and it should help the clinician to identify infants at risk of adverse liver related and metabolic outcomes.

## Acknowledgments

*Funding:* The authors report funding support from the Spanish Instituto de Salud Carlos III Grant (FIS - PI18/01304) related to this manuscript.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Arias-Loste MT, Iruzubieta P, Crespo J. Paediatric non-alcoholic fatty liver disease: a more complex disease than in the adulthood? HepatoBiliary Surg Nutr 2019;8(3):270-273. doi: 10.21037/hbsn.2018.12.16

 