Editorial Commentary

Shaping the future of pediatric liver health: unraveling the impact of the new metabolic-associated fatty liver disease definition

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Liver steatosis (i.e., excessive triglyceride accumulation within the hepatocyte) is a very common finding in both the adult and pediatric populations. In the latter, epidemiologic data using validated diagnostic techniques (either liver biopsy or ultrasound-based technologies) have shown an alarmingly high prevalence, paralleling the ever-increasing rates of overweight and obesity. In a frequently quoted autopsy study performed in the United States on 742 children aged 2–19 years between 1993 and 2003, the prevalence of liver steatosis was 13%. It increased with age (0.7% for ages 2–4 years up to 17.3% for ages 15–19 years) and was as high as 38% in children with obesity (1). In a more recent study performed on the nationally representative cohort of the 2017–2018 cycle of the National Health and Nutrition Examination Survey (NHANES), we showed that prevalence of liver steatosis in adolescents aged 12–18 years was 24.2% when using a controlled attenuation parameter (CAP) cut-off of 248 dB/m and 11.6% using a higher cut-off of 280 dB/m (2). Importantly, 7.4% of them showed an elevated liver stiffness, indicative of significant liver fibrosis (≥ F2).

Current guidelines describe pediatric nonalcoholic fatty liver disease (NAFLD) as a condition characterized by chronic hepatic steatosis in the absence of other causes of steatosis including genetic and metabolic disorders, infections, alcohol consumption, use of steatogenic medication and malnutrition (3). Recently, the definition of NAFLD, which represents the most common cause of liver steatosis in both the pediatric and adult populations, has been criticized. The main limitations lie in its negative definition (i.e., the diagnosis of NAFLD depends on the exclusion of other forms of liver disease and not on demonstrating its underlying causes), the possible stigma rising from the word "alcoholic" and its inability to reflect the strict relationship with insulin resistance and metabolic dysfunction.

To overcome these drawbacks, a panel of international experts recently proposed a new definition of metabolic (dysfunction)-associated fatty liver disease (MAFLD) for both adult and pediatric patients (4,5). A new set of positive criteria was advanced, in which the presence of liver steatosis has to be accompanied by at least one of the following features: excess adiposity, (pre-) type 2 diabetes (T2D), metabolic dysregulation. In the pediatric population, excess adiposity was defined in accordance to the World Health Organization (WHO) reference body mass index (BMI) for age and sex or in the presence of abdominal obesity (a waist circumference ≥90th percentile), while the same glucose cut-offs used in adults were

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proposed to detect prediabetes and T2D. Finally, metabolic dysregulation was defined using criteria adapted from the IDEFICS (Identification and Prevention of Dietary-Induced and Lifestyle-Induced Health Effects of Children and Infants) study for children younger than 10 years and the International Diabetes Federation criteria for children older than 10 years. Both sets of criteria are based on blood pressure, triglycerides, high-density lipoprotein (HDL) and the triglyceride-to-HDL ratio. Importantly, in the newly proposed classification of pediatric fatty liver disease (PeFLD), MAFLD represents one of three possible subtypes. PeFLD type 1 is related to the presence of an underlying systemic disorder (such as coeliac disease, single gene defects, use of drugs, viral hepatitis, fructose intolerance or Wilson disease); PeFLD type 2 coincides with MAFLD; finally, children with liver steatosis not meeting the definition of the previously mentioned classes are diagnosed as PeFLD type 3 (fatty liver without a clear underlying defect).

A helpful aspect of this proposed definition lies in its positive nature. It is our experience that in every day clinical practice patients and their families are more interested in knowing what a disease is (what causes it and why it affected them in the first place), rather than what it is not. Moreover, at least in children, the need for describing the disease as "non-alcoholic" is in our opinion virtually inexistent before puberty as alcohol is not an issue at this age. On the other hand, it should be carefully evaluated in adolescents, even though prevalence rates of significant and regular alcohol consumption are lower than in the adult population. We also agree that, by removing this aspect from the definition, it avoids the stigma associated with alcohol, without adding a stigma related to obesity, which is not part of the disease name. Furthermore, including metabolic dysfunction in the disease name recognizes the robust body of evidence identifying visceral fat accumulation and insulin resistance as the major pathophysiological determinants of liver fat in most cases. It also paves the way for a multidisciplinary approach to the disease and it stresses the importance of lifestyle changes as the major therapeutic option.

We would also like to underline some controversies and unexplored issues related to the new definition. While the expert consensus panel still recommends evaluation of potential other causes of liver disease (included in the PeFLD type 1 definition), the new positive set of criteria might take the focus off the necessity of excluding coexisting conditions. This may result in children being falsely labelled as MAFLD when, in fact, the underlying reason for the fatty liver is an inherited metabolic disorder (IMD). As pointed out by Hegarty *et al.*, we would like to stress the importance of thinking about IMDs in the differential diagnosis of fatty liver, given the profound therapeutic implications this might have (6). This possibility should be taken into account in particular in younger children (e.g., onset at <5 years), children born from consanguineous parents or with syndromic features and in the absence of excess adiposity or typical MAFLD features. These aspects should be debated among experts from international scientific societies involved in hepatology to provide more detailed recommendations in clinical practice guidelines on what tests should be performed and in which occasions to rule out alternative causes of liver disease. This would make the diagnostic process more reproducible and harmonious.

A second aspect that deserves attention is the lack of consensus of what defines "metabolic health" in the pediatric population as well as limited data on the reproducibility of this definition over time. While agreement has been reached on the definition of metabolic syndrome in adults (7), this has been more problematic in children with a multitude of criteria being proposed, leading to significantly different estimates of its prevalence in the same population (8). This is in part due to the difficulty in anchoring the definition to the development of clinical outcomes such as cardiovascular disease, since reaching an adequate number of events would need a large study population and a very long follow-up period. A similar consideration can be made for pre-diabetes. Data on the clinical course of pre-diabetes in children are less robust compared with adults and the pre-diabetic phenotype seems to be somewhat unstable over time. For instance, in a study comprising 79 obese white children and adolescents with impaired glucose tolerance (IGT), at the 12-month follow-up (in the absence of treatment), 66% converted to normal glucose metabolism, 33% remained IGT and one child developed T2D (9). These aspects may reduce the reproducibility of an already dynamic process related to liver fat accumulation and metabolism.

Third, there are several potential utilities of a change in terminology and diagnostic criteria. One is related to the possibility of increasing awareness of the condition among practitioners, leading to earlier diagnoses and better management. While there is initial evidence of such a process in adults (10), data are lacking on this aspect in the pediatric field. Indeed, the debate surrounding the new MAFLD definition seems to have been much more active in the adult field, with multiple studies focusing on the impact

Table 1 Features of published studies evaluating the impact of the recent definition of metabolic (dysfunction)-associated fatty liver disease in the pediatric population

Author, year, (ref.)	Study country; NAFLD diagnosis; study characteristics	Main findings
Ciardullo S, 2022, (12)	1,446 adolescents included in the 2017–2020 cycles of NHANES; CAP and LSM through VTCE; cross-sectional study	Prevalence of steatosis in US adolescents is high (25.9%) MAFLD criteria: ❖ Are met by most US adolescents with elastographic evidence of steatosis (87.7%) ❖ Do not appear to improve detection of subjects with more advanced liver disease in terms of fibrosis
Xing Y, 2023, (13)	Chinese population (CPOOA study, n=1,093) versus US population (2017–2018 cycles of NHANES, n=794); abdominal ultrasonography and VTCE, respectively; cross-sectional study	In the NHANES study, the cases diagnosed by the two methods had a similarity over 75%, while approximately 19% of children with NAFLD could not be categorized as MAFLD The CPOOA study included only overweight/obese children and excluded other causes of liver steatosis patients, resulting in children with NAFLD being identical to children with MAFLD
Lazo-de-la-Vega-Monroy ML, 2023, (14)	223 boys and girls of 6–12 years from Mexico; abdominal ultrasonography; cross-sectional study	Not all individuals diagnosed with NAFLD were classified as MAFLD The sub-group of participants with NAFLD without metabolic dysfunction had milder steatosis MAFLD definition could help identifying more severe steatosis
Di Sessa A, 2021, (15)	954 obese children and adolescents from Italy; abdominal ultrasonography; cross-sectional study	Prevalence of steatosis in the studied population was 85% Children meeting only the overweight/obesity MAFLD criterium had a similar cardiometabolic risk profile compared to overweight/obese children without steatosis

NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; VTCE, vibration controlled transient elastography; MAFLD, metabolic (dysfunction)-associated fatty liver disease; CPOOA, Comprehensive Prevention Project for Overweight and Obese Adolescents.

of diagnostic criteria on the epidemiology of the condition, on the identification of patients with advanced disease and on the risk for cardiovascular and renal outcomes (11). We could retrieve only four studies that applied the new set of criteria in the pediatric field, which are summarized in *Table 1*. In these cross-sectional analyses, 75–85% of children with steatosis met the MAFLD definition. Since it is likely that alternate specific causes, given their low prevalence in general population settings, could not account for the remaining 15–25%, it seems that the new definition misses a significant proportion of children, who could be labeled as PeFLD type 3. Moreover, we did not find any differences in the prevalence of significant liver fibrosis among children with steatosis that met the MAFLD criteria compared to those who did not (12). Finally, the subgroup of patients with MAFLD that only met the excess adiposity criterium does not display worse cardio-metabolic parameters compared with overweight/obese children without steatosis, leaving doubts on whether being overweight itself should be considered a sign of metabolic dysfunction (15).

In conclusion, we believe that a change in terminology was due particularly in the field of pediatrics, where alcohol consumption is rarely an issue and the need to stress the importance of metabolic dysfunction is compelling. In this sense, the new terminology might help underline the importance of lifestyle changes in the management of this condition and facilitate cooperation among hepatologists, endocrinologists, nutritionists and general practitioners. Large, longitudinal cohort studies are needed to provide more definitive evidence on the clinical and epidemiological implications of the new definition in terms of liver disease severity and cardiovascular risk.

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