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# Fatty liver disease in the pediatric population: history, definitions, and challenges in nomenclature (NAFLD/MAFLD/MASLD)

Raúl Gómez-Mendoza, Fabiola Sánchez-Hernández, Francisco Javier Valentin-Cortez, Norberto Chávez-Tapia

Obesity and Digestive Diseases Unit, Medica Sur, Mexico City 14050, México.

**Correspondence to:** Dr. Norberto Chavez-Tapia, Obesity and Digestive Diseases Unit, Medica Sur, Puente de Piedra 150, Mexico City 14050, México. E-mail: n.chaveztapia@pm.me

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## Abstract

This review focuses on the evolution in the nomenclature of fatty liver disease in the pediatric population, from the initial definition non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD), and more recently to metabolic dysfunction-associated steatotic liver disease (MASLD). These changes in the nomenclature aim to more accurately reflect the relation between the disease and the underlying metabolic alterations, while also seeking to reduce the stigma associated with earlier definitions. Epidemiological data indicate an increase in the global burden of NAFLD in the pediatric population, with a prevalence of 5%-10%, more commonly affecting males. The condition is strongly associated with obesity, type 2 diabetes mellitus (T2DM), and genetic factors, including the PNPLA3 polymorphism. Prevalence rates are significantly higher in Latin America (24%-68%), which is linked to the growing epidemic of metabolic syndrome. In terms of pathophysiology, pediatric NAFLD differs from the adult form in the histological patterns and has a strong link to insulin resistance. Each definition of the disease has pros and cons. NAFLD is a simple definition but exclusionary, while MAFLD incorporates metabolic factors to better characterize the disease. The most recent term, MASLD, aims to reduce the stigma of this disease and emphasize the metabolic factor of this pathology. Various scientific societies consistently recommend lifestyle changes as the first-line treatment, although adherence to this intervention remains a challenge in the pediatric population. In addition, there is a strong consensus on the need for noninvasive tools and longitudinal studies to better understand this disease in children.

**Keywords:** NAFLD, MAFLD, MASLD, pediatric fatty liver disease, epidemiology, metabolism



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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as a growing and leading health problem, not only in adults but increasingly in children. It is defined as the accumulation of fat in the liver without significant alcohol consumption<sup>[1,2]</sup>. NAFLD is characterized by hepatic steatosis, identified through imaging or histology, in the absence of secondary causes of fat accumulation<sup>[3]</sup>. Meanwhile, nomenclature and diagnostic definitions for fatty liver disease have changed markedly, with the initial change from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD), and more recently from MAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD)<sup>[4,5]</sup>. The gradual shifts in this definition demonstrate a growing knowledge of the complex relationship between the disease and metabolic dysfunction, underscoring the need for routine and accurate guidelines for diagnosis.

NAFLD, abbreviated as NAFLD, was initially described as hepatic steatosis occurring in the absence of excessive alcohol consumption<sup>[3]</sup>. This definition, while widely accepted, had drawbacks, not least its exclusionary nature. The term “non-alcoholic” characterizes the disease by what it is not, rather than by its underlying pathophysiology<sup>[4]</sup>. This resulted in the introduction of the term “Metabolic Dysfunction-Associated Fatty Liver Disease”, abbreviated as MAFLD<sup>[6]</sup>, which is a more comprehensive and pathophysiologically relevant terminology. MAFLD is a major conceptual shift from the previous diagnosis; it takes into account fatty liver known to be related to metabolic dysfunctions with obesity, type 2 diabetes, dyslipidemia, and insulin resistance<sup>[6,7]</sup>. MAFLD differed from NAFLD in that the diagnostic criteria for MAFLD absolved liver steatosis from having to occur in the absence of significant alcohol consumption yet required its co-occurrence with at least one of a number of cardiometabolic risk factors<sup>[5]</sup>. It also includes individuals with moderate alcohol consumption who exhibit metabolic risk factors, thereby addressing a clear shortcoming of the original NAFLD definition.

The current evolution in terminology resulted in the term “Metabolic Dysfunction-Associated Steatotic Liver Disease”, abbreviated as MASLD<sup>[4,8]</sup>. This change is intended to more accurately reflect the central role of metabolic dysfunction in the disease pathogenesis, while also helping to reduce the stigma associated with earlier terms. MASLD is defined as steatotic liver disease (SLD) in individuals with at least one cardio-metabolic risk factor and without harmful alcohol consumption<sup>[8]</sup>. In addition, a novel category, metabolic dysfunction and alcohol-related liver disease (MetALD), has also been proposed, which is defined as MASLD plus moderate alcohol intake<sup>[4]</sup>.

These conceptual shifts have greatly altered the way we think about fatty liver disease. The transition from NAFLD to MAFLD and, more recently, MASLD has expanded the disease concept and scope, emphasizing the strong association of the disease with metabolic disorders and encompassing metabolic dysfunction as pivotal in its pathogenesis<sup>[9]</sup>. The updated definitions have also helped researchers and practitioners in their efforts to include more diverse patient populations in research, allowing for a better characterization of the disease's epidemiology, natural history, and response to treatment<sup>[5]</sup>.

## EPIDEMIOLOGY

NAFLD has become a global epidemic, with prevalence estimates ranging from 23% to 42% in adults<sup>[10,11]</sup>. The prevalence is also growing in the pediatric population, with a reported prevalence between 5% and 10% in the general pediatric population, with even higher rates observed in obese children<sup>[12]</sup>. In contrast, the global prevalence of NAFLD in adolescents has risen from 3.73% in 1990 to 4.71% in 2019. Notably, this disease exhibits a male predominance in this specific group, with a higher prevalence in males compared to females<sup>[13]</sup>.

NAFLD is a heterogeneous disease with a global distribution that varies significantly due to variations in genetics, lifestyles, and socioeconomic factors<sup>[10,14]</sup>. The highest prevalence rates have been previously reported in the Middle East and South America, while the lowest rates were seen in Africa<sup>[3]</sup>. In Asia, a gradient from higher rates in urban areas to lower prevalence in rural areas is reported<sup>[15]</sup>.

In Latin America, the epidemic of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome has led to a growing burden of NAFLD<sup>[16]</sup>. Reported prevalence rates in these regions range from 24% to 68%, which is likely influenced by a higher prevalence of T2DM, obesity, and genetic predisposition related to the presence of the PNPLA3 polymorphism<sup>[17-19]</sup>.

The prevalence of metabolic syndrome, a key risk factor for the development of NAFLD, has been reported to be among the highest globally, according to a study examining several Latin American countries<sup>[16]</sup>. Moreover, the consumption of highly processed foods, refined sugars, and saturated fatty acids has contributed to the increasing prevalence of NAFLD in this region<sup>[14]</sup>.

This growing epidemic of fatty liver disease continues to worsen and is expected to persist in the coming years, driven by continuing trends in obesity and metabolic risk factors<sup>[16]</sup>. As a result, the increasing prevalence is expected to lead to a higher burden of advanced liver disease, complications, and increased cardiovascular morbidity/mortality<sup>[20]</sup>.

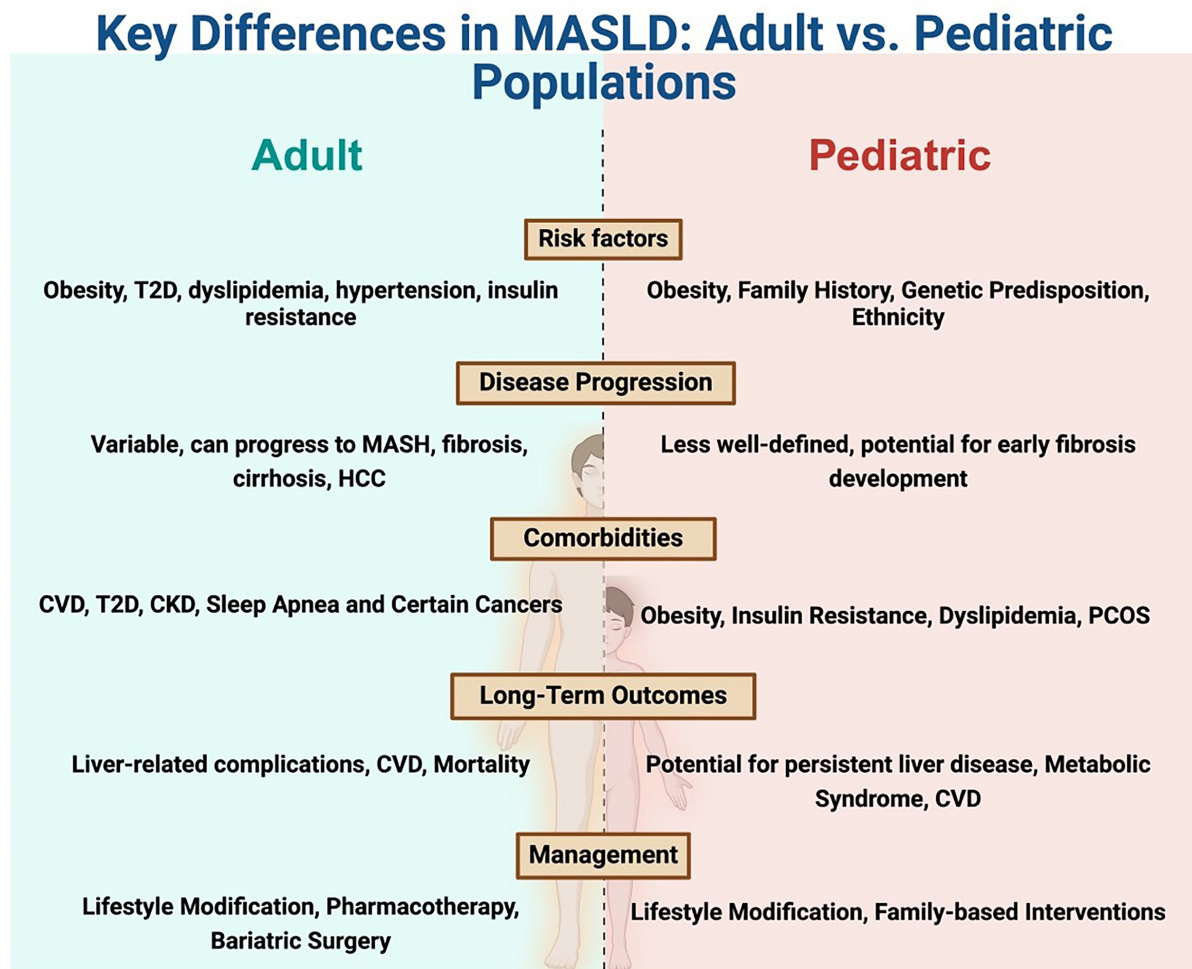
The epidemiology of NAFLD also diverges between adult and pediatric populations. The prevalence of NAFLD rises with age in adults and reaches its highest level in middle age<sup>[3]</sup>. Similarly, in children, NAFLD prevalence increases with age, peaking at 15 years<sup>[12]</sup>. There are also significant sex and ethnic variations in the prevalence of NAFLD. Boys, in general, have higher rates of NAFLD than girls, and Hispanic and Asian children have higher rates than White and African American children<sup>[12]</sup>.

Sex-related differences are observed in both adult and pediatric NAFLD. Among adults, men are more frequently and severely affected by NAFLD during reproductive age, whereas women start to develop an increased risk post-menopause, indicating a protective role of estrogen<sup>[21]</sup>. In children, boys have higher rates of NAFLD compared to girls<sup>[12]</sup>. These sex differences might be associated with differences in body composition, as well as etiological factors such as hormonal and genetic factors<sup>[22]</sup>. Computer modeling has further predicted that male and female livers are metabolically distinct, with different regulatory mechanisms contributing to sex-specific metabolic outcomes<sup>[21]</sup>.

The responses to NAFLD treatments may also vary between adults and children. Lifestyle changes, such as diet and exercise, remain the foundation of treatment for both groups<sup>[3,23]</sup>. Nonetheless, adherence to these lifestyle changes can be difficult, especially in adolescents<sup>[24]</sup>. Although many pharmacological agents have shown promise in improving adult NAFLD, their safety and effectiveness in children remain unproven<sup>[3,23]</sup> [Figure 1].

## **PATHOPHYSIOLOGY**

Although the underlying pathophysiology of fatty liver disease is similar between the child and adult populations, there are significant differences in clinical presentation and disease progression<sup>[25]</sup>. In pediatric cases, the presentation of NAFLD is more prominent during the peripubertal phase, with the mean age of diagnosis around 12-13 years<sup>[12]</sup>. Pediatric NAFLD is closely linked to obesity and associated insulin resistance, although it has also been reported in non-obese children<sup>[26]</sup>.



**Figure 1.** Key differences in MASLD between adults and children. T2D: Type 2 diabetes; MASH: metabolic dysfunction-associated steatohepatitis; CVD: cardiovascular disease; CKD: chronic kidney disease; PCOS: polycystic ovary syndrome; MASLD: metabolic dysfunction-associated steatotic liver disease; HCC: hepatocellular carcinoma.

Aside from the speculations regarding histological differences between zone 3 and zone 1 NASH, there may also be histological variants specific to the pediatric population<sup>[12]</sup>. Zone 3 NASH with pericentral lobular inflammation and ballooned hepatocytes is similar to adult NASH, while zone 1 NASH is defined by periportal inflammation<sup>[12]</sup>. These differences could be useful in predicting disease progression patterns and prognosis in children.

### THE PROS AND CONS OF THE DIFFERENT DEFINITIONS OF NAFLD/MAFLD/MASLD

While historically informative, the NAFLD definition has limitations in pediatric practice and research. One of the key strengths of the NAFLD definition is its simplicity and broad recognition<sup>[3]</sup>. However, its exclusive definition of the disease by the absence of significant alcohol consumption does not account for the underlying metabolic dysfunction driving the disease<sup>[4]</sup>.

The MAFLD definition helps bypass some of the obstacles to NAFLD by focusing on the composition of body fat and its relationship to other metabolic risk factors<sup>[6]</sup>. This broader definition allows for the inclusion of individuals with moderate alcohol consumption who also have metabolic risk factors<sup>[5]</sup>.

However, the MAFLD definition may exclude children with fatty liver disease who do not meet the criteria for metabolic dysfunction, potentially overlooking a subgroup of patients with distinct pathophysiological traits.

The MASLD definition is the latest effort by its proponents to refine nomenclature and diagnostic criteria for fatty liver disease<sup>[4]</sup>. By focusing on metabolic dysfunction and introducing “steatotic liver disease” as an umbrella term, MASLD should minimize stigma and increase familiarity with the disease<sup>[5]</sup>. Whether the MASLD definition will be ultimately accepted, and its long-term consequences on clinical practice and research, are still uncertain.

Depending on the chosen definition, the consequences of the diagnosis, treatment, and follow-up of pediatric patients with fatty liver disease can vary substantially. The NAFLD definition may lead to underdiagnoses in children who do not meet the classic profile of obesity and metabolic syndrome<sup>[3]</sup>. In contrast, the MAFLD and MASLD definitions share a stronger focus on metabolic dysfunction, which could help identify at-risk children and allow for earlier intervention<sup>[4,6]</sup>. However, such definitions may also result in overdiagnosis in some cases, especially in children with only mild steatosis and one or two metabolic risk factors.

## STATEMENTS FROM SCIENTIFIC SOCIETIES

The American Association for the Study of Liver Diseases (AASLD) has published practice guidance on the clinical assessment and management of NAFLD<sup>[27]</sup>. This guidance offers actionable recommendations based on the best available evidence to inform clinical practice<sup>[27]</sup>. The AASLD recommendations give significant importance to noninvasive risk stratification and the use of biomarkers to exclude advanced disease or detect a very high probability of cirrhosis<sup>[27]</sup>.

Regarding the new definition, the AASLD agrees that MASLD better reflects metabolic physiopathology and emphasizes its relevance in the existing guidelines, noting that the overlap in diagnosis between NAFLD and MASLD is > 99%. They assert that this new definition avoids stigmatization, highlights metabolic dysfunction as the root cause, and allows inclusivity with other liver diseases<sup>[28]</sup>.

Clinical practice guidelines on the diagnosis and treatment of NAFLD in children were recently published by the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)<sup>[1]</sup>. Rinaldi and Stine first describe these guidelines as they relate to screening, diagnosis, and management of NAFLD in the pediatric population<sup>[1]</sup>. Diet and exercise are established as first-line therapies for pediatric NAFLD based on the current NASPGHAN guidelines<sup>[1]</sup>.

Guidelines for the evaluation and management of NAFLD have also been published by the Asia-Pacific Working Party on NAFLD. These guidelines address different aspects of NAFLD, including its definition, risk factors, assessment, and treatment, with a special emphasis on the unique features of NAFLD in the Asia-Pacific region<sup>[29]</sup>. Furthermore, the guidelines recognize that NAFLD requires attention in both children and adolescents, as well as in patients with chronic viral hepatitis<sup>[29]</sup>.

Clinical practice guidelines for the management of MASLD have been simultaneously released by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO)<sup>[8]</sup>. These guidelines include updates on the definition, prevention, screening, diagnosis, and treatment regarding MASLD<sup>[8]</sup>. Lifestyle modifications and optimal management of comorbidities are important aspects of the guidelines, as is the

potential role of pharmacological agents in adults with MASH with advanced liver fibrosis<sup>[8]</sup>.

The Latin American Association for the Study of the Liver (ALEH) has also endorsed the shift of the NAFLD definition to the “metabolic-associated fatty liver disease” as the official term for this pathology. This change is particularly significant as this new definition improves the understanding and awareness of the condition within the Latino-American population<sup>[30]</sup>.

## IMPACT OF MULTIPLE DEFINITIONS IN PEDIATRIC POPULATIONS

Previous studies have compared MAFLD and NAFLD definitions in the pediatric population. Xing *et al.*, in a cross-sectional observational study involving populations from China and the U.S., reported that more than 75% of the patients with NAFLD met the criteria for MAFLD, while 19% of children with NAFLD did not fulfill the MAFLD criteria, most of whom were of normal weight and without metabolic alterations<sup>[31]</sup>. Di Sessa *et al.*, in a transversal study of 396 patients, found a prevalence of 39.6% for MASLD and 60.4% for NAFLD, suggesting that MASLD identifies better than NAFLD children with obesity<sup>[32]</sup>.

Another study involving a U.S. population reported that 99% of patients with NAFLD also fulfill the criteria for MASLD, with Kappa = 0.90, indicating a strong agreement between the two definitions<sup>[33]</sup>.

## CONCLUSION

The former nomenclatures NAFLD, MAFLD, and recently MASLD represent an evolution in the understanding of fatty liver disease as a complex metabolic syndrome, moving away from the exclusionary and stigmatizing past definitions of fatty liver disease. This change in the nomenclature offers a more accurate approach based on underlying metabolic pathophysiology. In the pediatric population, these new definitions are particularly important, as the physiopathology in this group is more related to metabolic causes like obesity and metabolic risk factors, which are increasing in children and adolescents. Although this new nomenclature has improved diagnostic precision, challenges remain in terms of diagnosis, management, and long-term outcomes for the pediatric population.

We recommend that the future research agenda should be focused on conducting longitudinal studies to better understand the natural history of pediatric fatty liver disease, evaluate the safety and efficacy of various therapeutic interventions for pediatrics, and develop and implement effective prevention strategies to reduce the burden of this pathology. In addition, it is important to assess the impact of the MASLD definition on the diagnosis, treatment, and follow-up of pediatric patients with fatty liver disease, comparing its performance with earlier definitions.

## DECLARATIONS

### Authors' contributions

Performed data acquisition, as well as providing administrative, technical, and material support: Gómez-Mendoza R, Sánchez-Hernández F, Valentin-Cortez F, Chavez-Tapia N

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.



## Conflicts of interest

All authors declared that there are no conflicts of interest.

## Ethical approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

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