MASLD IN CHILDREN

Dr Sara Mona Bitar
PH.D gasrtoenterologist

Introduction

- Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common pediatric liver disease, affecting
- approximately 10% of children. Its prevalence is rising at an alarming rate, with cases increasingly identified even in earlychildhood.
- While MASLD shares key features across the lifespan, its earlier onset reflects developmental
- vulnerabilities and unique mechanistic drivers.

JClin Invest. 2025;135(13):e186422 https://doi.org/10.1172/JCI186422

Epidemiology of pediatric MASLD

Age

Although MASLD is most commonly diagnosed during

the peripubertal period, evidence suggests hepatic steatosis is increasingly prevalent in younger children.

The Viva La Familia study, using elevated ALT as a surrogate marker, identified suspected MASLD in 15% of children aged 4–5 years,

21% in thoseaged 6–11 years,

and 30% in adolescents aged 12–19 years

Notably, children under 6 years of age are

increasingly affected, often presenting with elevated ALT levels and increased adiposity .

JClin Invest. 2025;135(13):e186422 https://doi.org/10.1172/JCI186422

Sex.

Male>Female

In the general pediatric population, approximately 11% of males are affected compared with 7% of females, with this disparity becoming more pronounced during adolescence.

This difference is partly attributed to fat distribution patterns, as males tend to accumulate more visceral fat — a key risk factor for hepatic steatosis — whereas females typically have higher levels of subcutaneous fat, which is less strongly associated with MASLD .

JClin Invest. 2025;135(13):e186422 https://doi.org/10.1172/JCI186422

RACE AND ETHNICITY

Hispanic children and adolescents exhibiting the highest prevalence of hepatic steatosis (11.8%)

Black children the lowest (1.5%).

Asian children demonstrated a prevalence of 10.2%, while White children had a prevalence of 8.6%

Social determinants of health.

Emerging data suggest that food insecurity and other socioeconomic barriers contribute to disparities in MASLD prevalence and severity

J Clin Invest. 2025;135(13):e186422 https://doi.org/10.1172/JCI186422

Obesity and MASLD

Obesity is a major risk factor, yet hepatic steatosis

is not exclusive to children with obesity, nor does obesity alone

explain MASLD susceptibility.

In the United States, 30% of adolescents with elevated alanine aminotransferase (ALT), a surrogate for hepatic steatosis, fall within the healthy weight range,emphasizing that hepatic steatosis can occur independently of obesity .

Conversely, only 1 in 4 children with obesity develop

MASLD, highlighting the role of additional factors in disease

pathophysiology .

The earlier onset of MASLD in children compared with adults suggests distinct drivers and disease

mechanisms, emphasizing the urgent need for pediatric-focused

research to better understand and address this condition.

JClin Invest. 2025;135(13):e186422 https://doi.org/10.1172/JCI186422

Perinatal influences, including maternal obesity, gestational diabetes, and early-life

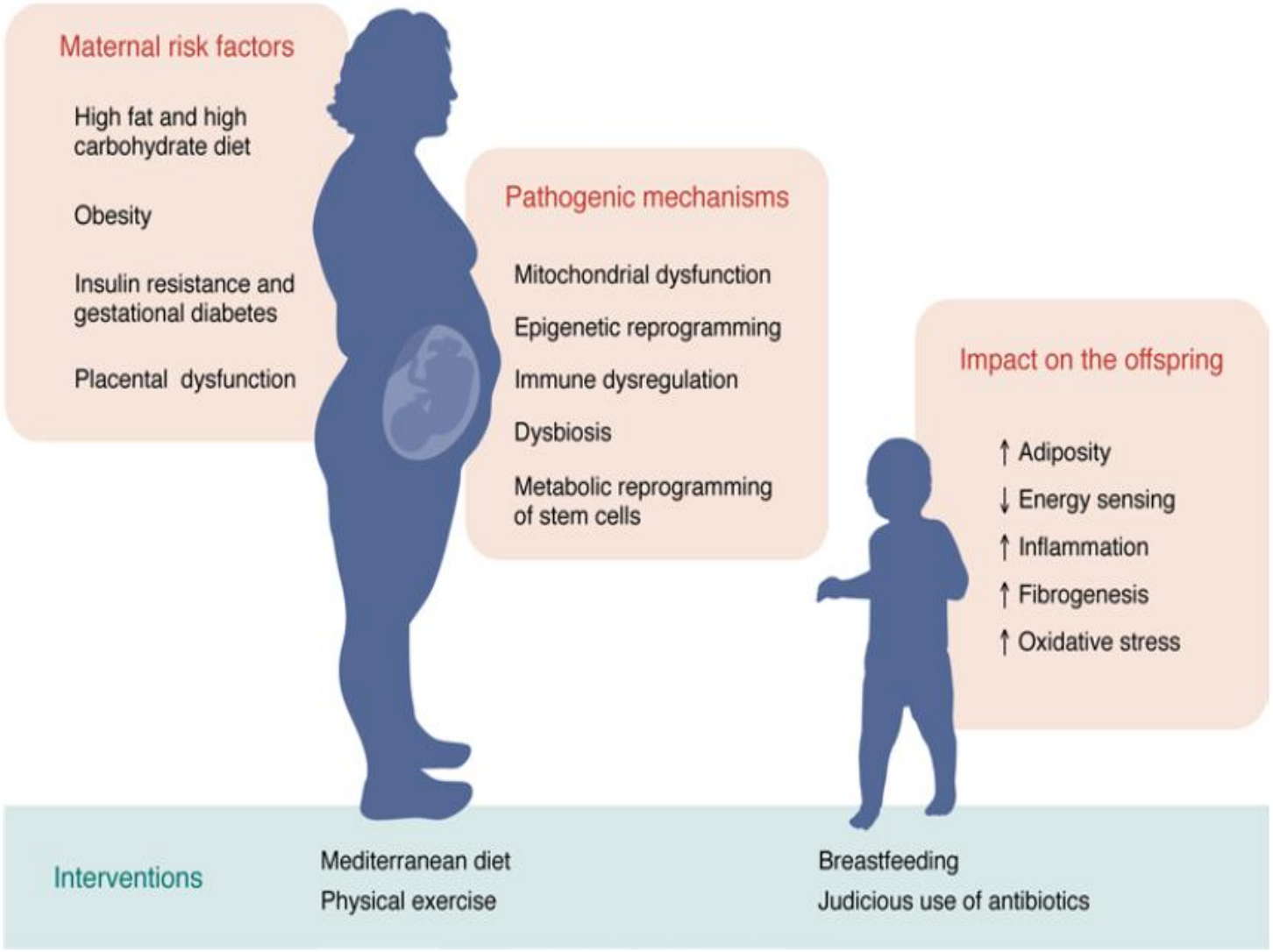
nutritional exposures, play a central role by disrupting metabolic programming, driving mitochondrial dysfunction, and

inducing epigenetic modifications.

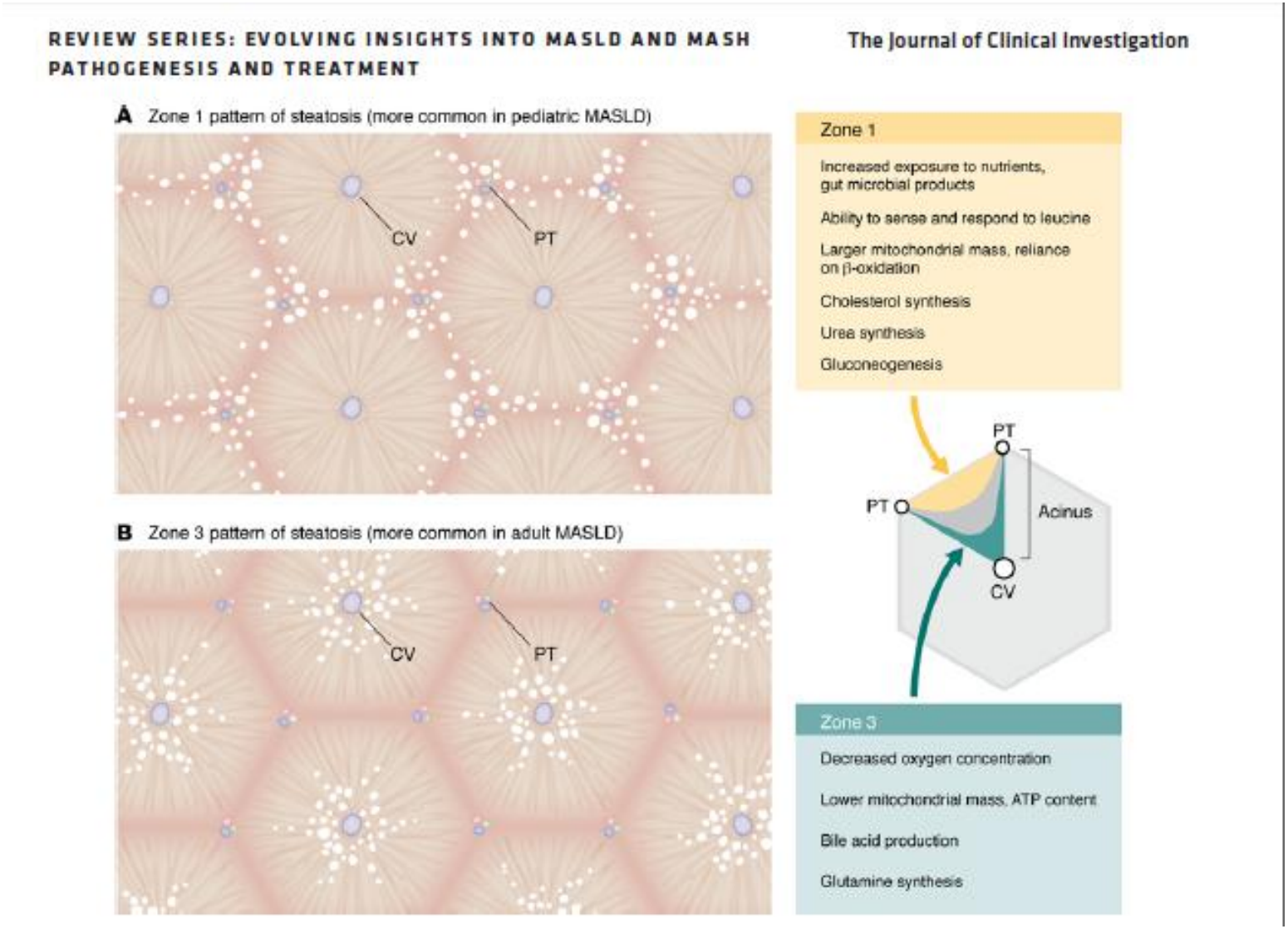
These early stressors interact with genetic predispositions, such as *PNPLA3* and *TM6SF2*

variants, to amplify susceptibility and shape disease severity.

Perinatal influences on pediatric



Pediatric MASLD and zonation



Pediatric MASLD and zonation

children with exclusive periportal (zone 1) versus pericentral (zone 3) steatosis . Their findings revealed that zone1 steatosis was associated with younger age and greater risk of advanced fibrosis, whereas zone 3 steatosis carried a higher likelihood

of steatohepatitis

Data from the CyNCH clinical trial investigating

cysteamine bitartrate delayed release (CBDR) in pediatric NAFLD further demonstrated that children with zone 1–based steatohepatitis responded significantly better to CBDR treatment

than those with zone 3–based steatohepatitis

JClin Invest. 2025;135(13):e186422 https://doi.org/10.1172/JCI186422

Table 1. Important updates and recommendations from the guidelines on the diagnosis and management of pediatric metabolic dysfunction-associated steatotic liver disease published by the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN), 2024

	ISPGHAN guidelines 2024	NASPGHAN guidelines 2017[9]	ESPGHAN position paper 2012[10]
Change in terminology	MASLD	NAFLD	NAFLD
Screening tool	USG and ALT levels	ALT	USG and ALT levels
Population to be screened	Screening for MASLD should be considered in all obese children (BMI >95th percentile) and in all overweight children (BMI ≥85th and <95th) with additional risk factors–prediabetes/diabetes, dyslipidemia, waist circumference greater than 70th percentile, hypertension, positive family history of metabolic syndrome, obstructive sleep apnea, and hypopituitarism Consider screening of siblings of patients with MASLD in the presence of risk factors (overweight/ obesity, prediabetes/diabetes, and/or dyslipidemia)	Screening should be considered beginning between ages 9–11 years for all obese children (BMI ≥95th percentile) and for overweight children (BMI ≥85th and < 94th percentile) with additional risk factors (central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH). Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH or hypopituitarism. Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD (obesity, Hispanic ethnicity, insulin resistance, prediabetes, diabetes, dyslipidemia)	No clear-cut screening recommendations At Risk population defined – obese (>95th percentile) and overweight (sex and age specific BMI >85th percentile), Hispanic origin, children from families with insulin resistance, obesity, type II DM and NAFLD, children with obstructive sleep apnea
Diet	Any hypocaloric diet (low-carbohydrate/low fat/ low sugar) or mediterranean diet	Reduction of sugar-sweetened beverages recommended	No recommendation
Exercise	Exercise (aerobic or resistance or a combination of both) is an effective measure for weight loss and reduction of intrahepatic fat content Moderate-to-high-intensity exercise in 3–5 sessions for a total of 60 min/day is recommended	Moderate-to-high intensity physical activity and limiting screen time activities to < 2 hours per day is recommended for all children including those with NAFLD	No recommendation

	Moderate-to-high-intensity exercise in 3–5 sessions for a total of 60 min/day is recommended for children and adolescents with MASLD	with NAFLD	
Liver biopsy	Liver biopsy in overweight/obese children with suspected MASLD is recommended: In younger children <8 yr, and/ or if there is a high index of suspicion for advanced liver disease, and/or if an alternative diagnosis is considered.	Liver biopsy should be considered for the assessment of NAFLD in children who have increased risk of NASH and/or advanced fibrosis. Potential clinical signs of increased risk of fibrosis in children with NASH may include higher ALT (>80 U/L), splenomegaly, and AST/ALT >1. Known clinical risk factors for NASH and advanced fibrosis include panhypopituitarism and type 2 diabetes	To exclude other treatable disease In cases of clinically suspected advanced liver disease Before pharmacological/surgical treatment
Pharmacological	Pharmacotherapy for weight loss may be considered as an adjunct to lifestyle interventions and started only after a failed trial of life style modifications for 6 months	No medications recommended for NAFLD due to lack of benefit in children	Limited data for pharmacotherapy in children, lifestyle interventions preferred
Bariatric surgery	Children (>12 yr) who had a failure of an appropriate trial of intense lifestyle modifications and pharmacotherapy for at least 6 months and one of the following: class 2 obesity with steatosis/steatohepatitis with significant comorbidities. class 3 obesity with steatosis/steatohepatitis with or without comorbidities	Bariatric surgery is not recommended as a specific therapy for NAFLD. It may be considered for selected adolescents with BMI ≥35 kg/m^2, who have noncirrhotic NAFLD and other serious comorbidities (e.g., T2DM, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with weight loss surgery	No recommendation
Endoscopic intragastric ballon	When bariatric surgery is contraindicated or delayed	No recommendation	No recommendation

ISPGHAN, Indian society of pediatric gastroenterology hepatology and nutrition; NASPGHAN, North American society for pediatric gastroenterology hepatology and nutrition; ESPGHAN, European society of pediatric gastroenterology hepatology and nutrition; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; USG, ultrasonography; ALT, alanine aminotransferase; BMI, body mass index; NASH, nonalcoholic steatohepatitis; AST, aspartate aminotransferase; T2DM, type 2 diabetes mellitus.

THE INDIAN SOCIETY OF PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION (ISPGHAN)

Cardiometabolic criteria

(1) BMI ≥85th percentile for age/sex (BMI *z* score ≥+1) or WC >95th percentile (ethnicity-adjusted)

(2) Elevated fasting serum glucose ≥100 mg/dL or 2- hour glucose tolerance test glucose ≥140 mg/dL or hemoglobin A1c (HbA1c) ≥5.7% or diagnosed/treated type 2 diabetes (2-hour glucose tolerance test glucose ≥200 mg/dL or HbA1c ≥6.5

(3) Blood pressure age <13 years, BP ≥95th percentile or ≥ 130/80 mmHg (whichever is lower); age ≥13 years, 130/85 mmHg or specific antihypertensive drug treatment

(4) Plasma/serum triglycerides: if <10-years-old, >100 mg/dl; if >10 years, >150 mg/dL or lipid lowering treatment

(5) Plasma HDL 40 mg/dL or lipid lowering treatment

Diagnostic and screening tools

ISPGHAN guidelines 2024

SCREENING

1. Alanine aminotransferase

Alanine aminotransferase (ALT) has been commonly used for screening but lacks specificity as it may be normal in mild cases. No established Indian cutoff. As per SAFETY study data

the optimal cutoff is 26 IU/L for boys and 22 IU/L for girls (aged 12–18 years). ALT >2 × upper limit of normal is considered significant.

2. Ultrasound

Ultrasound (USG) finding indicating steatosis is a brighter liver as compared to hypoechoic renal parenchyma. It has high sensitivity and specificity if >33% hepatocytes are involved. But low sensitivity when steatosis involve <30% hepatocytes.

Indian guideline recommends using both USG and ALT for screening

ISPGHAN guidelines 2024

3. Role of transient elastography

Transient elastography (TE) (FibroScan) assesses liver stiffness and steatosis with good diagnostic accuracy. Indian guidelines endorse its use for diagnosing and monitoring fibrosis and steatosis.

4. Liver biopsy

Liver biopsy in overweight/obese children with suspected MASLD is recommended: In younger children <8 yr,

and/ or if there is a high index of suspicion for advanced liver disease ALT>80

and/or if an alternative diagnosis is considered.

ISPGHAN guidelines 2024

Medical Therapy

At this time, no licensed or uniformly recommended pharmacological therapies exist

for MASLD .

Among adults with MASH,

weight loss of >5% total body weight can reduce hepatic steatosis,

weight loss of >7% of total body weight can improve MASH, and

weight loss of >10% of total body weight can result in fibrosis regression/stability .

Although improvement in BMI z-score was proportionally associated with resolution of MASH for children failing to respond to standard lifestyle counseling,

. However, at present, There are no FDA-approved pharmacotherapies for pediatric MASLD

Dietary Inflammartory Index (DII)

Apositive score indicates higher inflammatory potential range from –10to +10
Based on the effect of the food parameter on each of six inflammatory biomarkers (IL1B,IL-4,IL-6,IL-10,TNFa and CRP)

Examples of the of food parameters in the DII (source)

Food parameter	Overall inflammatory effect score
Turmeric	-0.785 (ANTI-INFLAMMATORY)
Fibre	-0.663
Isoflavones	-0.593
β-carotene	-0.584
Tea (green/black)	-0.536
Garlic	-0.453
Omega-3 fats	-0.436
Onion	-0.301
Alcohol	-0.278
Omega-6 fats	-0.159
Thyme/oregano	-0.102
Protein	0.021
Iron	0.032
Carbohydrate	0.097
Vitamin B12	0.106
Cholesterol	0.110
Energy (kcal)	0.180
Trans fat	0.229
Total fat	0.298
Saturated fat	0.373 (PRO-INFLAMMATORY)

Metformin

Recent studies have examined the use of metformin in children with MASLD and showed promising results, but they are still controversial .

A systemic review of pediatric MASLD patients treated with metformin demonstrated a decreased steatosis on ultrasound and improved insulin resistance, which may benefit liver histology .

Moreover, a meta-analysis conducted by systematic literature search through major electronic

databases investigated metformin's efficacy and safety in pediatric MASLD patients

until 12 March 2023. Four randomized controlled trials (RCTs) with 309 pediatric patients with MASLD were included in the meta-analysis. In this meta-analysis, metformin failed to improve liver enzymes statistically; however, it may be beneficial in improving lipid parameters and insulin metabolism regulation in pediatric patients with MASLD.

As there were not enough available studies in the literature, the influence of metformin on liver

ultrasonography or histology in pediatric MASLD was not evaluated .

Metabolites **2025**, 15, 287

. GLP-1 Receptor Agonists

The first GLP-1 receptor agonist to be approved for preadolescent and adolescent

populations aged 10 to 17 was liraglutide in 2019 for treating type 2 diabetes. Soon after,semaglutide was also approved for preadolescents and adolescents aged 12 to 17 years of age with obesity

However, there are no randomized control trials of a GLP-1 receptor agonist for the treatment of MASLD in children and adolescents with MASH.

A recent small retrospective case

series by Choi et al., including nine obese children older than 10 with type 2 diabetes or

prediabetes treated with GLP-1 receptor agonists for 12 months, revealed an ALT decrease of an average of 98 points, hemoglobin A1c decrease of an average of 2.2

points, and BMI decrease of an average of 2.4 point

Metabolites **2025**, 15, 287

Resmetirom

Patients with MASH have an impaired function of liver-directed thyroid hormone receptor-ß, resulting in decreased mitochondrial function and ß-oxidation of fatty acids,along with an increase in fibrosi .

Resmetirom is an oral, liver-directed thyroid hormone receptor-ß-selective agonist recently approved for the treatment of MASH in adults with moderate to advanced fibrosis. MASH resolution with no worsening of fibrosis,and an improvement in fibrosis by ≥1 stage with no worsening of the NAFLD activity score,

was achieved in significantly more patients who received resmetirom than in those who received placebo at week 52

Metabolites **2025**, 15, 287

Diarrhea and nausea were the most common adverse

events reported and were generally self-limited. However, the long-term safety of this

medication has not yet been evaluated.

The approval of resmetirom has created new opportunities for MASH drug development

and has offered essential insights into future clinical trial designs and treatment

strategies. This represents a breakthrough for adult patients with MASH, also inspiring

hope for novel therapeutic options in the pediatric population in the future

Antioxidants

Vitamin E is a fat-soluble vitamin and potent antioxidant that effectively neutralizes ROS and nitrogen species and enhances the activity of antioxidative enzymes

The TONIC trial compared the effect of placebo, metformin, and Vitamin E in children diagnosed with histologically confirmed MASLD. The primary outcome measured was a

sustained reduction in ALT levels. The results showed that neither metformin nor Vitamin E significantly improved over placebo regarding the primary outcome.

However, both treatment groups demonstrated evidence of reduced hepatocyte injury on biopsy

Metabolites **2025**, 15, 287

Vitamin D is a fat-soluble steroid vitamin that plays an important role in the function of many organs including the heart and liver.

The results indicated that vitamin D supplementation significantly reduced hepatic steatosis and lobular inflammation, resulting

in improvements in the grades of MASLD in young persons, as confirmed by liver

biopsy.

However, no effects on hepatocyte ballooning or fibrosis were observed. Therefore,adjuvant vitamin D supplementation is recommended in children with MASLD

Metabolites **2025**, 15, 287

Prebiotics and Probiotics

Probiotics positively affect inflammatory liver damage through regulation of c-Jun

N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB), which is associated with regulation of tumor necrosis factor-alpha (TNF-α) and insulin resistance .

Prebiotics can selectively enhance the growth and activity of intestinal microbes

Additionally, oligofructose alters the composition of intestinal microbiota, promoting the growth of Bifidobacterium, which in turn improves mucosal barrier function and lowers endotoxin levels

Metabolites **2025**, 15, 287

Surgical Intervention

Bariatric surgery

Children (>12 yr) who had a failure of an appropriate trial of intense lifestyle modifications and pharmacotherapy for at least 6 months and one of the following: class 2 obesity with steatosis/steatohepatitis with significant comorbidities.

class 3 obesity with steatosis/ steatohepatitis with or without comorbidities

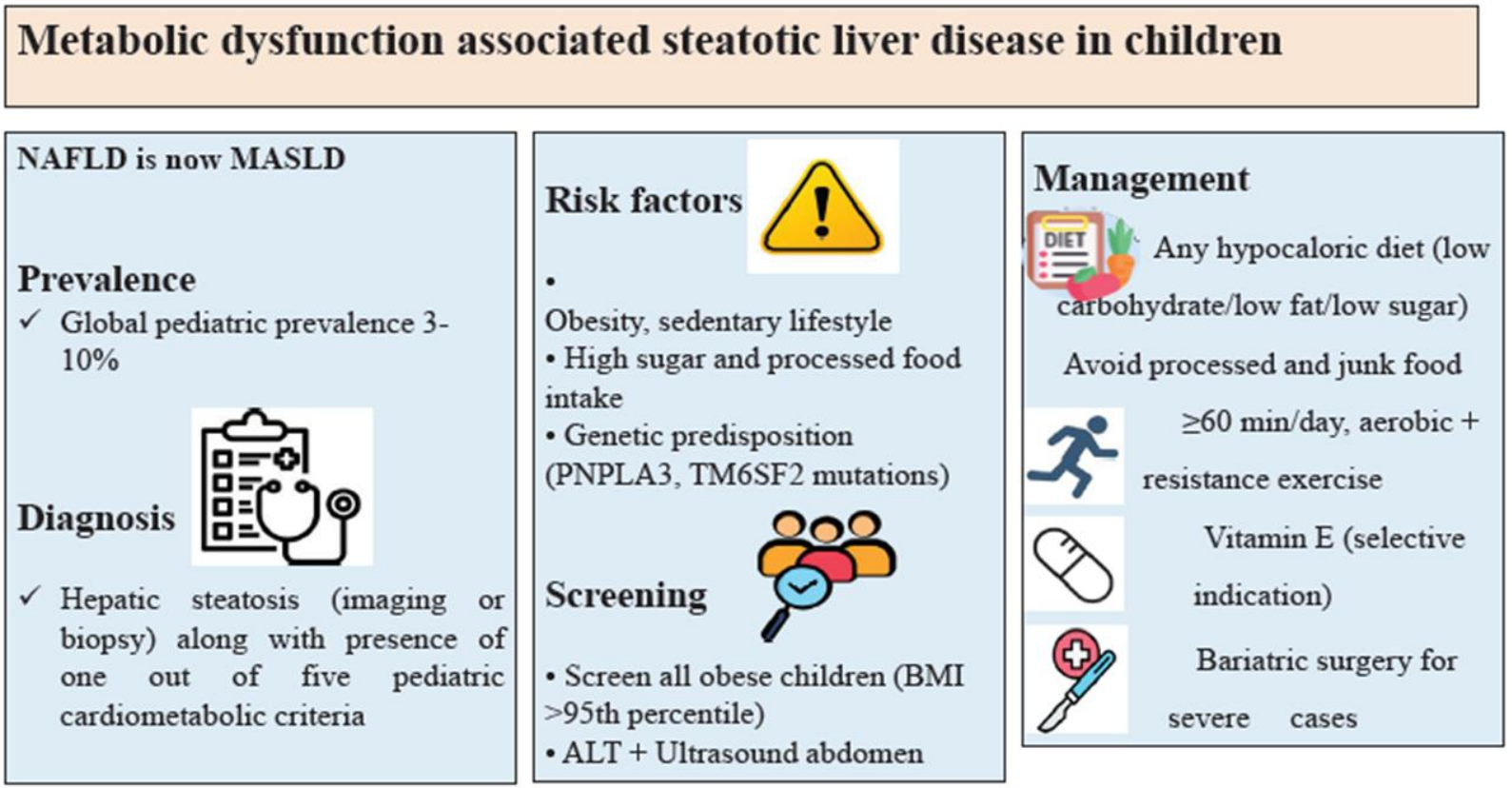
Endoscopic intragastric ballon

When bariatric surgery is contraindicated or delayed

Arghya Samanta iD https://orcid.org/0000-0002-1768-0263

Conclusions

- MASLD is a growing silent pandemic. Increasing awareness is important for early detection, management, and prevention.



Graphical abstract. NAFLD, nonalcoholic fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; ALT, alanine aminotransferase

شكراً لإصغائكم