

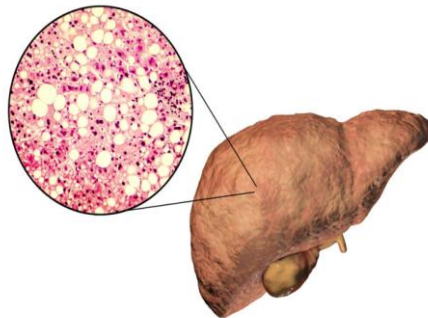


Metabolic dysfunction-associated steatotic liver disease (MASLD), (NAFLD) in Children

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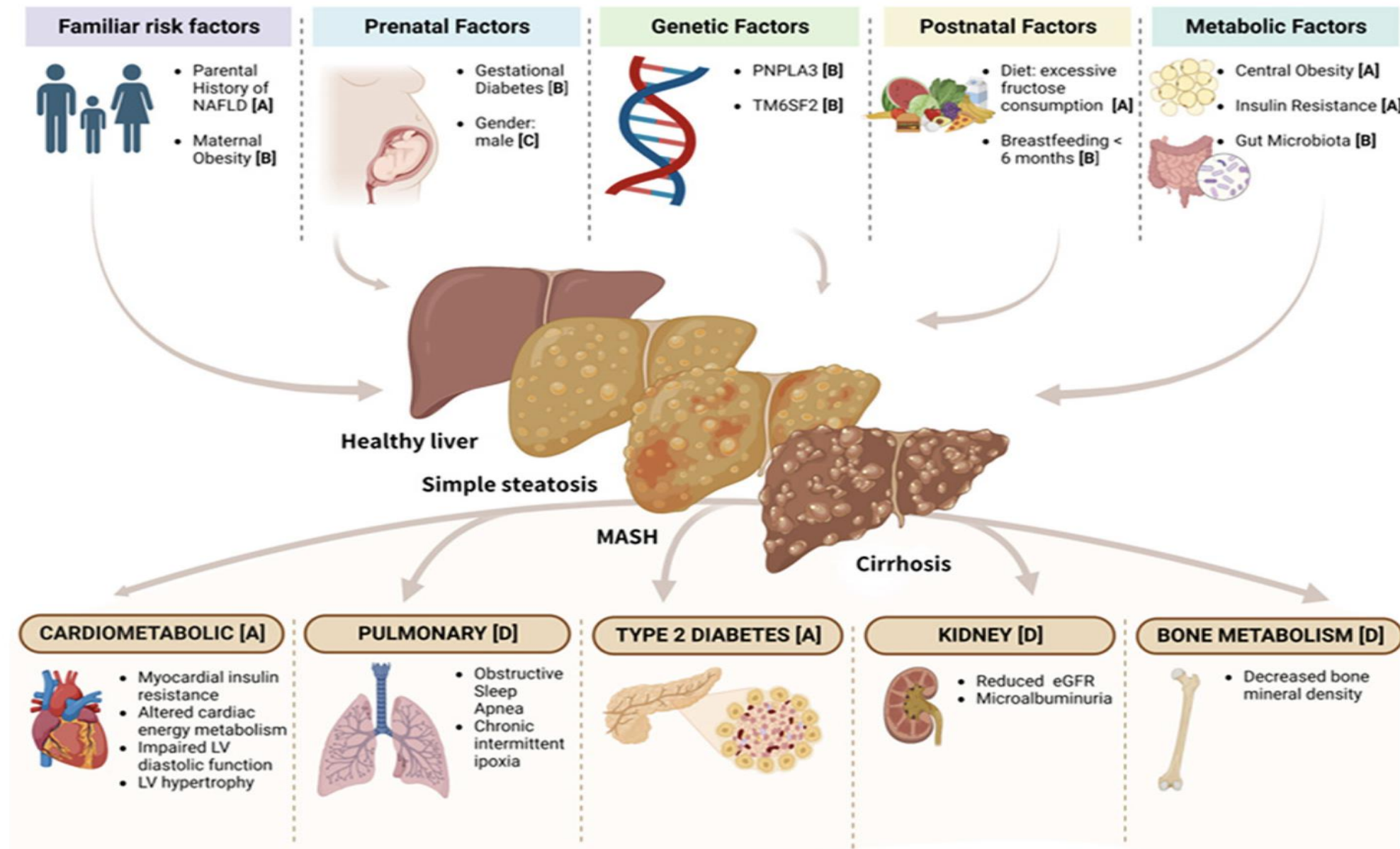
July 2023, nomenclature and diagnostic criteria for steatotic liver disease were revised following an international Delphi consensus process

- **Metabolic dysfunction-associated steatosis liver disease (MASLD)**, formerly known as nonalcoholic fatty liver disease (NAFLD)

is the most common cause of liver disease in children .

- MASLD is a steatotic liver disease that occurs in the setting of
- visceral adiposity,
- dyslipidemia,
- and/or insulin resistance.

- The prevalence of pediatric NAFLD is higher in certain sub-populations:
 - Overweight/ obese children
 - Males>Females
 - Ethnicity: Hispanics>Asian>Caucasian>Black
 - Pre-diabetes or type 2 diabetes
 - Obstructive sleep apnea (OSA)
 - Hypothalamic dysfunction/ hypopituitarism



- The prevalence of paediatric MASLD is continually rising globally, with the highest rates in the *Middle East and North Africa*.
- Paediatric MASLD increases mortality and the risk of *youth-onset type 2 diabetes* and major adverse liver outcomes in young adulthood.
- Germline variants associated with MASLD severity are broadly similar in children and adults, with *rs738409C>G in PNPLA3* being the strongest risk variant identified.
- A *portal-dominant injury* pattern predominates in pre- and peripubertal children and has been linked to disease progression.
- Nutrition policies aimed at reducing the consumption of *sugar-containing beverages* are highly relevant given the detrimental effects of *fructose* on MASLD and the fact that adolescents are peak consumers.
- *Multi professional lifestyle intervention* remains the core of treatment strategies for children and adolescents with MASLD, while paediatric drug trials are urgently needed.

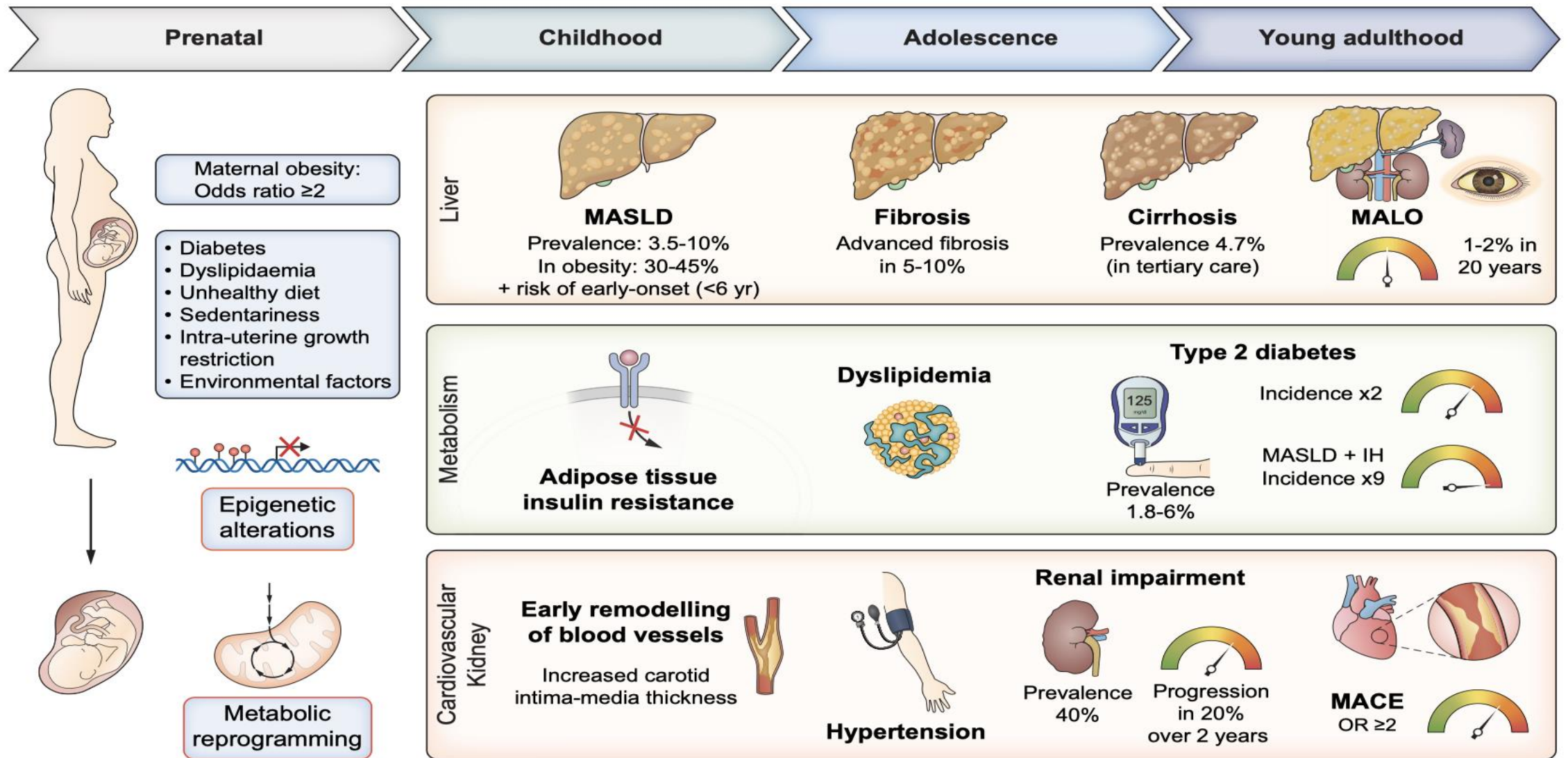


Fig. 2. Potential progression of MASLD and comorbidities over the patients' lifespan. Intrauterine and early life exposures can represent a “first hit” predisposing to MASLD development later in life, mechanistically mediated among others by epigenetic alterations and metabolic reprogramming. Childhood MASLD can progress to cirrhosis and even decompensation in young adulthood, whereas severe MASLD is both a risk factor for and risk indicator of metabolic comorbidities such as type 2 diabetes, renal impairment, hypertension and eventually cardiovascular events. IH, intermediate hyperglycaemia; MACE, major adverse cardiovascular events; MALO, major adverse liver outcomes; MASLD, metabolic dysfunction-associated steatotic liver disease.

Recommendations-Screening

- Screening should be considered between **9 and 11 years** for:
 - Children (BMI $\geq$ 95th percentile)
 - Children (BMI $\geq$ 85th and 94th percentile) with additional risk factors
 - Central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea, or family history of NAFLD/NASH

Screening can be considered at a younger age if there are strong risk factors for MASLD
Other risk factors for NAFLD include maternal obesity during gestation
panhypopituitarism ,
sarcopenia or lower muscle mass [and Hispanic ethnicity (genetic risk factor
(predominantly PNPLA3 variants)

Recommendations-Screening

Continued

- **Best test currently- ALT**
 - Sex-specific **upper limits** of normal in children (**22 U/L for girls and 26 U/L for boys**)
 - Persistently (**>3 months**) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD
 - **ALT of >80 U/L** warrants increased clinical concern and timely evaluation

Next steps – Subsequent steps depend on the degree and duration of ALT elevation:

- For those with normal ALT results, repeat screening in one to three years (or sooner in children with increasing obesity or other risk factors), while providing counseling to promote a healthy body weight.
- moderate ALT elevations (ALT >ULN but <80 units/L), repeat the measurement of serum ALT within a few months. If ALT remains elevated, intensify counseling on diet and exercise to achieve weight loss.
- with ALT that is persistently >2 × ULN (ie, >44 units/L for adolescent girls and 52 units/L for boys) for three or more months, refer to a gastroenterologist for a full evaluation
- Other indications for further evaluation include ALT elevations >80 units/L (on two occasions), signs or symptoms of acute liver disease, or red flags for advanced liver disease.
- Red flags include GI bleeding, jaundice, splenomegaly, firm liver edge, enlarged left lobe, low platelets, low white blood cell count, hypoalbuminemia, elevated direct bilirubin, and abnormal PT or INR

Patients with suspected MASLD typically have no symptoms of liver disease.

Their symptoms, if any, usually are secondary to complications of **obesity** (eg, knee/groin pain due to *slipped capital femoral epiphysis*, *intermittent right upper quadrant abdominal pain* secondary to **gallstones**, **regurgitation due to gastroesophageal reflux disease**, or headaches secondary to **increased intracranial pressure**)

comorbid conditions

- Hypothyroidism –
- Obstructive sleep apnea (OSA) –
- Type 2 diabetes –
- Depression/anxiety –
- Alcohol and drugs –
- Family history –

Evaluate the family history for liver disease (eg, MASLD/NAFLD, autoimmune conditions, Wilson disease, cryptogenic cirrhosis, or liver transplantation) and cardiometabolic disease (type 2 diabetes, heart disease, or stroke).

Physical examination

- Height, weight, and body mass index.
- Risk factors for MASLD (abdominal fat distribution, acanthosis nigricans).
- ☐ • **Signs of comorbid conditions or other causes of hepatic steatosis, including:**
 - Declining height velocity or delayed or accelerated pubertal development – Suggests hypothyroidism or multiple pituitary hormone deficiencies.
 - **Acanthosis nigricans** – Suggests insulin resistance, which may be associated with *diabetes risk* or **polycystic ovary syndrome**. **Hirsutism** is another common feature of polycystic ovary syndrome.
 - **Abnormal fat distribution** – Loss of subcutaneous adipose tissue, sometimes with apparent accumulation of fat in other regions of the body, raises the possibility of a lipodystrophic syndrome.
 - **Hepatomegaly and/or splenomegaly** – Splenomegaly raises the possibility of cirrhosis (with portal hypertension), while hepatosplenomegaly may be secondary to underlying storage disease or lysosomal acid lipase deficiency.
 - **Signs suggesting end-stage liver disease** (eg, jaundice, palmar erythema, edema, spider angiomas, or asterixis). End-stage liver disease has historically been rare in pediatric patients with MASLD.
 - **Elevated systolic and diastolic blood pressure**, measured with an appropriately sized cuff.

Routine laboratory testing

- Complete blood count with differential
- ALT, (AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGTP), total and direct bilirubin, albumin
- Evaluation for cardiometabolic risk factors (included in criteria required for diagnosis of MASLD)
 - Hemoglobin A1c and/or fasting glucose
- Fasting lipid panel (triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein [LDL] cholesterol)

Methods to assess fibrosis severity

- **Vibration-controlled transient elastography** (eg, FibroScan) – This point-of-care ultrasound technique shows some promise in noninvasively assessing the severity of hepatic steatosis and fibrosis .
- **Ultrasound shear wave elastography** – Ultrasound-based (eg, acoustic radiation force impulse) shear wave elastography correlates with significant fibrosis in pediatric patients with NAFLD, but this modality is limited by higher technical failure rates in patients with obesity
- **Magnetic resonance elastography** – *This is a noninvasive approach to evaluate liver stiffness. It can detect advanced fibrosis, with overall accuracy of 89 to 90 percent, negative predictive value of 95 to 96 percent, and positive predictive value of 29 to 30 percent*

These tools may also be useful noninvasive measures to follow disease progression

Paediatric MASLD

Investigate other aetiologies:

- Autoimmune hepatitis
- Wilson's disease
- Celiac disease
- Viral hepatitis
- A1AT deficiency
- Drug-induced liver injury

Assess alcohol intake-
metALD and ALD

Steatosis
+
≥1 cardiometabolic risk factor
(Overweight or obesity, glucose, HDL,
triglycerides, blood pressure)



Risk assessment
for clinically
meaningful disease



Red flags

- <5 years old
- Developmental delay, growth failure or syndromic features
- Synthetic dysfunction
- Splenomegaly
- Absence of overweight or obesity

Low risk

ALT <30 U/L
AND
VCTE ≤6.5 kPa*
pFIB-c <0.15
Fibro-PeN <0.13

Increased risk

ALT 30-79 U/L
OR
VCTE 6.5-8.0 kPa*
pFIB-c 0.15-0.40
Fibro-PeN 0.13-0.44
OR
Prediabetes

High risk

ALT ≥80 U/L
OR
VCTE >8.0 kPa*
pFIB-c >0.40
Fibro-PeN >0.44
OR
Type 2 diabetes
OR
Signs of aCLD

(Consider) Referral to paediatric MASLD expert
Consider further work-up (e.g. liver biopsy or MRI)
Optimise treatment of comorbidities

Diagnostic tool/ predictor

Evidence level

Comment

ALT

Evidence-based

Widely validated, moderate diagnostic performance for MASH and fibrosis

Prediabetes

Evidence-based

Repeated validation in large cohorts

pFIB-c/
Fibro-PeN

Expert opinion

Emerging evidence from derivation studies. Good diagnostic accuracy for significant fibrosis

VCTE

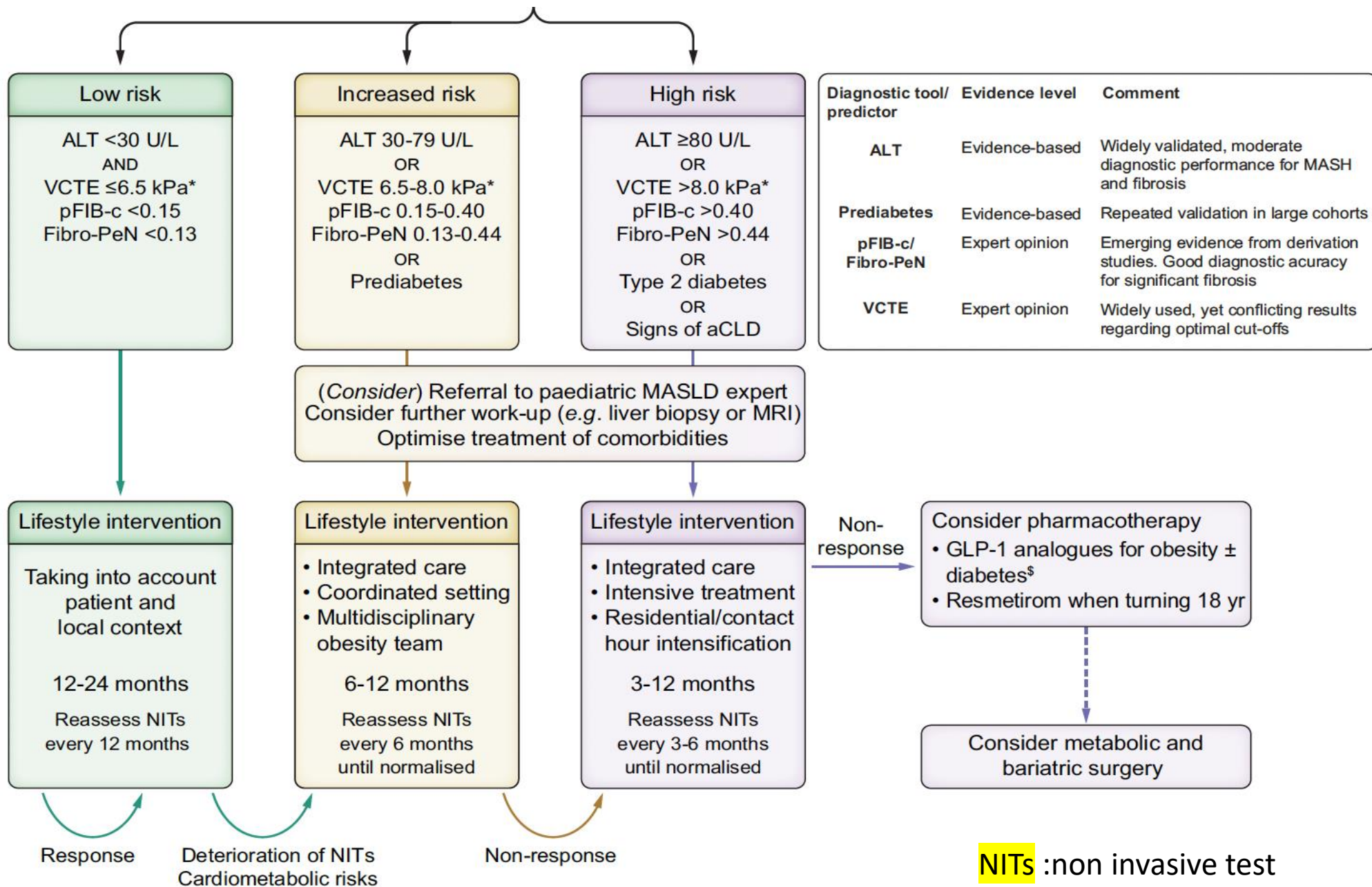
Expert opinion

Widely used, yet conflicting results regarding optimal cut-offs

(vcte)Vibration controlled transient elastography

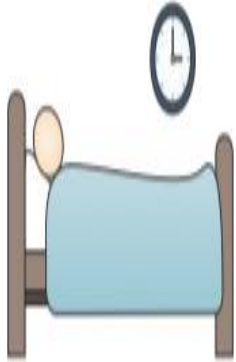
(pFIB-c)Pediatric fibrosis score –continuous

(fibro-pen)Fibrosis in pediatric NAFLD



Key components of lifestyle intervention

Sleep habits



Physical activity
Exercise



Limit intake of fructose
and ultra-processed foods



Socioeconomic counseling
Participation, family support



Media habits
Screen time



Mediterranean
diet

Psychological assessment
Anxiety, depression, bullying

Liver biopsy

we generally suggest a liver biopsy for patients with the following features:

1-Clinical features that are associated with more severe or progressive liver disease, such as ALT persistently >80 units/L or splenomegaly, thrombocytopenia, or increased liver stiffness by elastography, particularly in patients with prediabetes or diabetes or significant dyslipidemia.

2-Patients with severe obesity who are candidates for *weight loss surgery* but are undecided about whether to proceed.

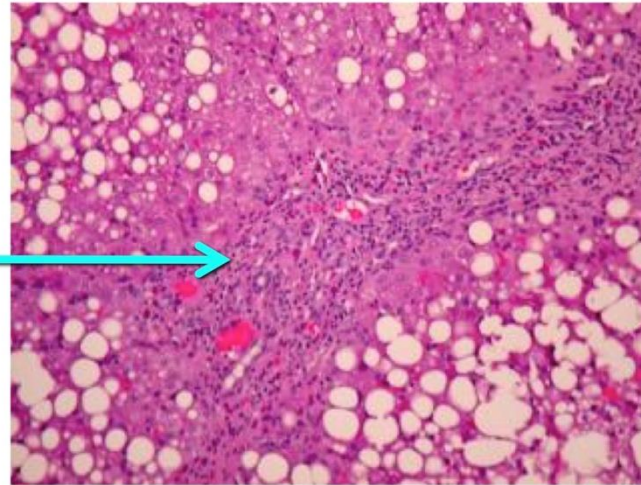
3-Patients with features that suggest an alternate or additional cause of the liver disease for which liver biopsy would be useful or essential to confirm the diagnosis (such as *autoimmune hepatitis*).

Portal Predominant NASH in Many Pediatric Patients, Rarely in Adults

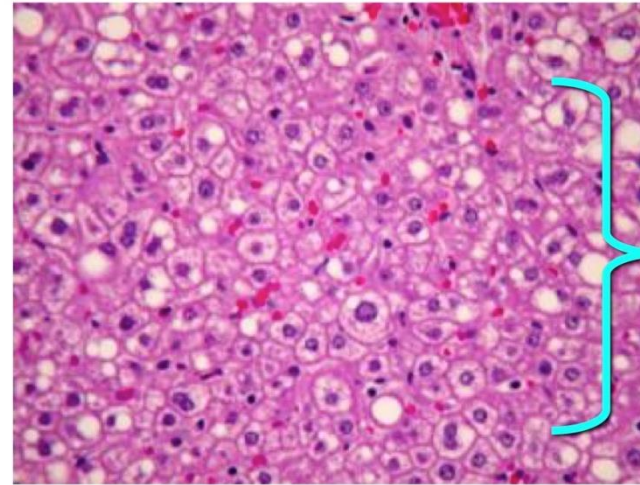
“Pediatric” pattern

Typical adult pattern

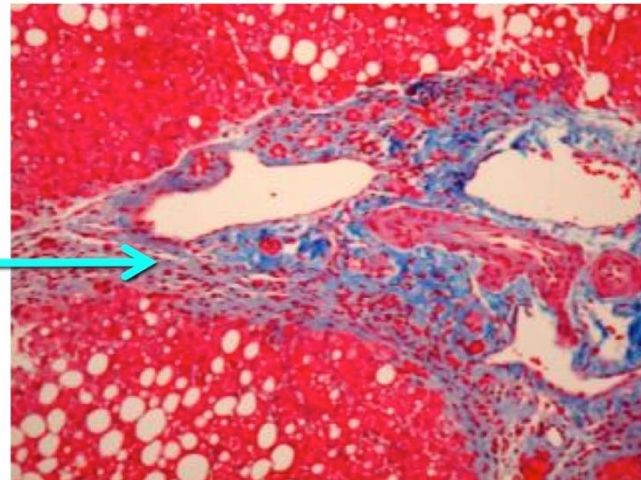
**Zone 1 - portal
inflammation
(often no
ballooning)**



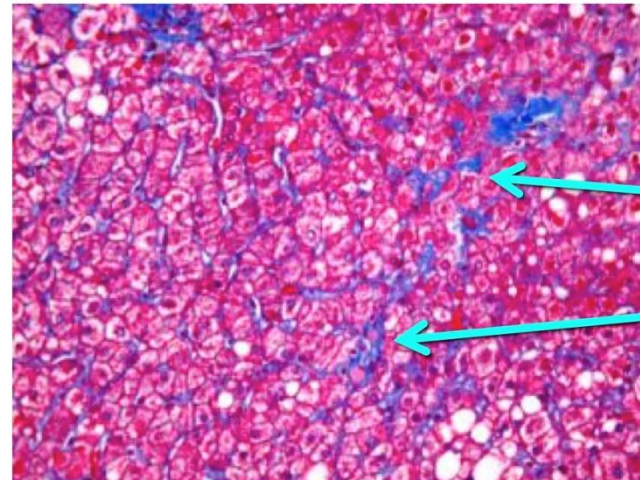
**Zone 3 centered
injury, more
ballooning**



**Portal and
periportal
fibrosis**



**Sinusoidal
Fibrosis**



Tests to exclude other liver diseases

- including
- celiac disease, autoimmune hepatitis, hemochromatosis, viral hepatitis, and Wilson disease.
- Particularly in younger children (<5 years of age) or in those without overweight or obesity, there should be increased suspicion for causes other than MASLD, such as inborn errors of metabolism.

Diagnosis of Exclusion

Other causes of hepatic steatosis need to be excluded

Genetic/Metabolic disorders	Medications	Dietary causes	Infections
LAL-D	Corticosteroids	Alcohol	Hepatitis C (genotype 3)
FACD, citrin deficiency	Amiodarone	Rapid weight loss e.g., surgical	
Wilson's disease	Methotrexate	Parenteral nutrition	
Lipodystrophies	Antipsychotics	Protein-energy malnutrition	
Abeta-/hypobeta-lipoproteinemia	Antidepressants		
Uncontrolled diabetes	HAART		

Lifestyle Targets

- **Avoid sugar-sweetened beverages**
- **Healthy, well-balanced diet**
- **Moderate to vigorous exercise**
- **Limit screen time to < 2 hours per day**

Weight loss surgery or obesity-directed pharmacotherapy (eg, a glucagon-like peptide 1 [GLP-1] receptor agonist) may be appropriate for selected adolescents with moderate or severe obesity, especially if liver biopsy shows evidence of advanced MASLD.

Bariatric surgery may be considered for selected adolescents with:
BMI > 35 Kg/m². who have :
Non-cirrhotic MASLD
Absence of other serious comorbidities

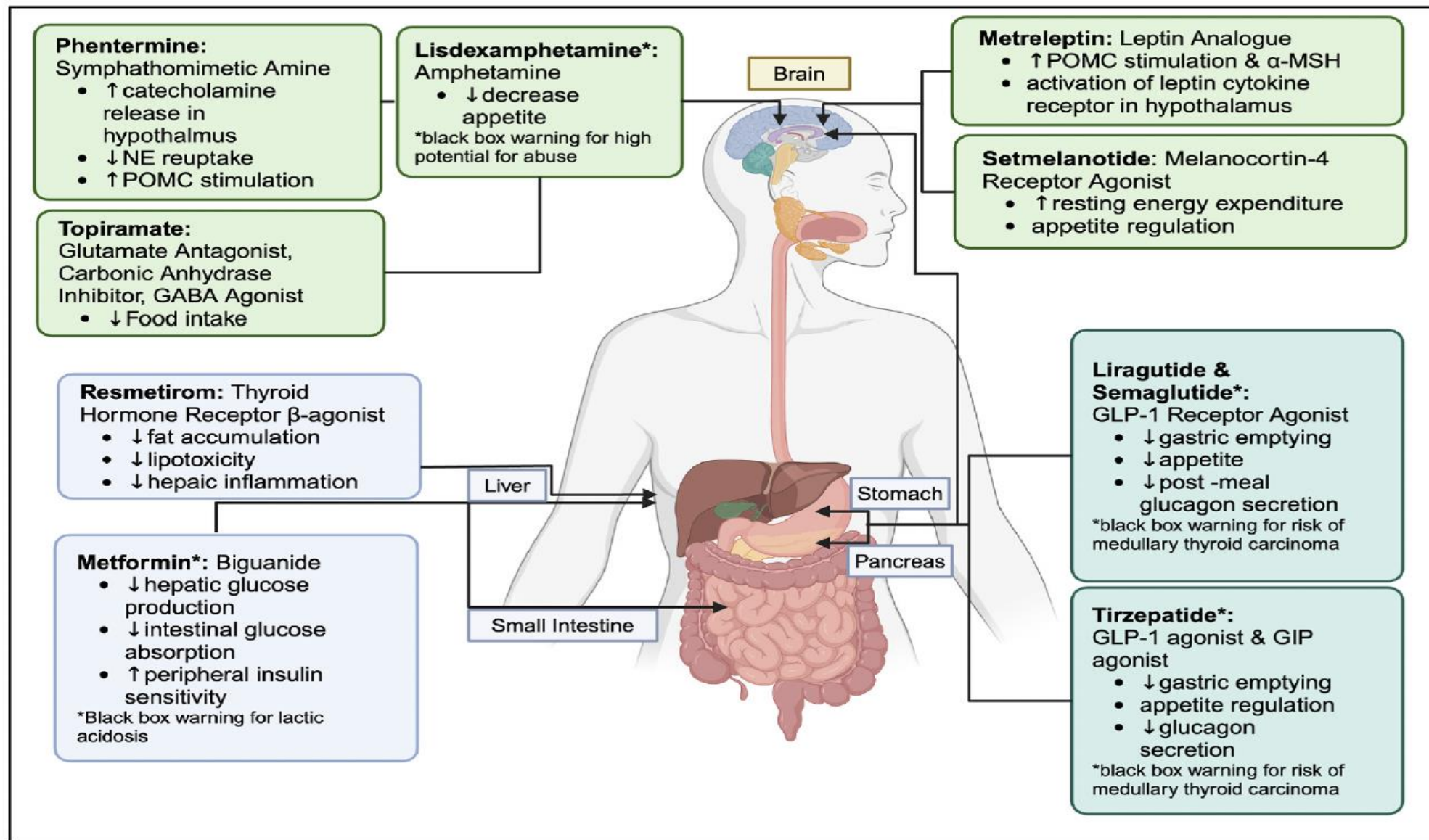


Fig. 3. Mechanisms of action for key pharmacological agents in the management of obesity and metabolic dysfunction. Created in BioRender. Ramirez, c. (2025) <https://BioRender.com/b07w012>.

Noninvasive Stratification Tools

- Fibrosis stage as predictor of all-cause, CV, and renal mortality
- Should focus less on steatosis, more on fibrosis
- Fib-4, NFS, FFAST score
- Fibroscan
- MR-Elastography
- Biomarkers - **PRO-C3**
- AI-based prediction

The Multidisciplinary Future

MASLD is no longer a hepatology-only issue.

- Cardiologist
- Nephrologist
- Endocrinologist
- Mental Health Specialist
- Dietitian
- Sports Specialist
- Bariatric Surgeon
- GI / Hepatologist
- Primary Care Practitioner

Thanks for
your attention

