

# LSG|UK STEATOTIC LIVER GUIDELINE – 2025 version

## **Background:**

Paediatric Metabolic- Dysfunction Associated Steatotic Liver Disease (MASLD) is a condition in children and adolescents characterized by the pathological accumulation of hepatic fat, in association with metabolic dysregulation.

This condition encompasses a spectrum of hepatic steatosis, from simple steatosis (characterized by the presence of excess fat in the liver without significant inflammation) to more advanced forms such as Metabolic-Dysfunction Associated Steatohepatitis (MASH), which is marked by hepatic inflammation and potential progression to fibrosis or cirrhosis.

In association with the rising trend of obesity, MASLD is now the most common chronic hepatopathy in children and adults

Studies have shown that 38-83% of obese children may have a fatty liver (defined as  $\geq 5\%$  of hepatocytes containing macrovesicular fat)

At primary school entry, 1 in 5 children is already overweight or obese and by the end of primary school, this figure increases to 1 in 3. By adolescence, 5% of young people have MASLD.

MASLD may progress to steatofibrosis, steatohepatitis (MASH), cirrhosis, liver failure and hepatocellular carcinoma.

Studies suggest that elevated hepatic transaminases are associated with more severe histological features of MASLD, including steatosis, inflammation, and fibrosis. Liver biopsy is used routinely in the USA for identification of patients with advanced disease.

Currently, the best non-invasive tests for monitoring of MASLD in children are MRI-PDFF, ALT, and GGT. A reduction of 30% in liver fat (on MRI), and  $-20$  IU/L fall in ALT and  $-10$  IU/L fall in GGT is associated with histological improvement. There is no robust data to support specific cut-offs for use of transient elastography (Fibroscan). There is no evidence to support use of Enhanced Liver Fibrosis test in children. Magnetic resonance elastography shows promise but is not yet in routine clinical use. [See Annex 1.]

PNPLA3 p.Ile148Met variant and degree of insulin resistance are the main risk factors for disease progression.

Children and adolescents with MASLD are highly unlikely to decompensate or have liver-related events prior to reaching adulthood. However, MASLD is now amongst the

top three indications for liver transplantation in adults and so it is important to instigate management of this condition when diagnosed.

MASLD may be suspected by either primary or secondary care physicians in children with non-specific symptoms, such as abdominal pain, through the detection of an echo-bright liver and /or elevated transaminases.

This guideline has been designed to aid practitioners in how to proceed when imaging studies identify hepatic steatosis (a bright, hyperechoic liver as compared to the spleen on ultrasound) or raised liver enzymes are detected in an overweight child.

### **The diagnosis of MASLD requires:**

- 1) Confirmation of steatosis – either by imaging or by histology

And at least one of the following cardiometabolic criteria:

1. Overweight, obesity and/or elevated waist circumference (WC)
  - Body mass index (BMI)  $\geq$  85th percentile for age/sex
  - BMI z score  $\geq$  +1
  - OR waist circumference (WC)  $>$ 95th percentile (ethnicity adjusted)
2. Hypertension or treatment for hypertension
  - If age  $<$ 13 years, BP  $\geq$ 95<sup>th</sup> percentile OR  $\geq$  130/80 mmHg (whichever is lower)
  - if age  $\geq$ 13 years,  $\geq$ 130/80 mmHg
  - OR receiving specific antihypertensive treatment
3. Impaired glucose control or diagnosis/treatment for type 2 diabetes mellitus
  - Elevated fasting serum glucose  $\geq$  7mmol/l
  - OR 2h glucose tolerance test glucose  $\geq$  11.1mmol/l
  - OR haemoglobin A1c (HbA1c)  $\geq$  5.7%
  - OR diagnosed/treated type 2 diabetes

4. Hypertriglyceridemia

- If <10 years old  $\geq 2.8$  mmol/L
- If age  $\geq 10$  years,  $\geq 3.8$  mmol/L
- OR lipid lowering treatment

5. Low high density lipoprotein level (or treatment with lipid lowering agents)

- Plasma/serum high-density lipoprotein (HDL)-cholesterol <1 mmol/L
- OR lipid lowering treatment.

Proposed assessment in primary/ secondary care to make a positive diagnosis of MASLD:

**1) Perform anthropometry:**

Plot height, weight, BMI (1), BMI Z score, and waist circumference on a centile chart (6,8-9)

<https://www.rcpch.ac.uk/resources/growth-charts>

[https://www.rcpch.ac.uk/sites/default/files/2018-03/boys\\_and\\_girls\\_bmi\\_chart.pdf](https://www.rcpch.ac.uk/sites/default/files/2018-03/boys_and_girls_bmi_chart.pdf)

**2) History and examination:**

- Elucidate symptoms: malaise, fatigue, abdominal pain
- Drug and alcohol history

<b><i>Hepatotoxic drugs that may cause a fatty liver</i></b>
Nifedipine
Diltiazem
Amiodarone
Corticosteroids
Oestrogens
Methotrexate

Valproate
L-Aspariginase
Certain antipsychotics

- Nutritional history
- Assess for depression, anxiety and psychological stressors
- Family history of:
  - MASLD
  - Type 2 diabetes
  - Cardiovascular disease
  - Dyslipidaemia
  - Metabolic disease
  - Liver disease
- Examination – document presence/ absence of:
  - Organomegaly
  - Peripheral stigmata of chronic liver disease
  - Evidence of insulin resistance (acanthosis nigricans)
- Measure blood pressure and plot on centile chart

[Blood Pressure Levels for Boys and Girls by Age and Height Percentile \(nih.gov\)](#)

### **3) Imaging:**

- Formal abdominal USS

To assess for steatosis, splenomegaly/ evidence of portal hypertension, and evaluation for other liver disease.

The presence of hepatic steatosis may also be confirmed by MRI for liver fat or, controlled attenuation parameter on Fibroscan if available.

### **4) Investigations:**

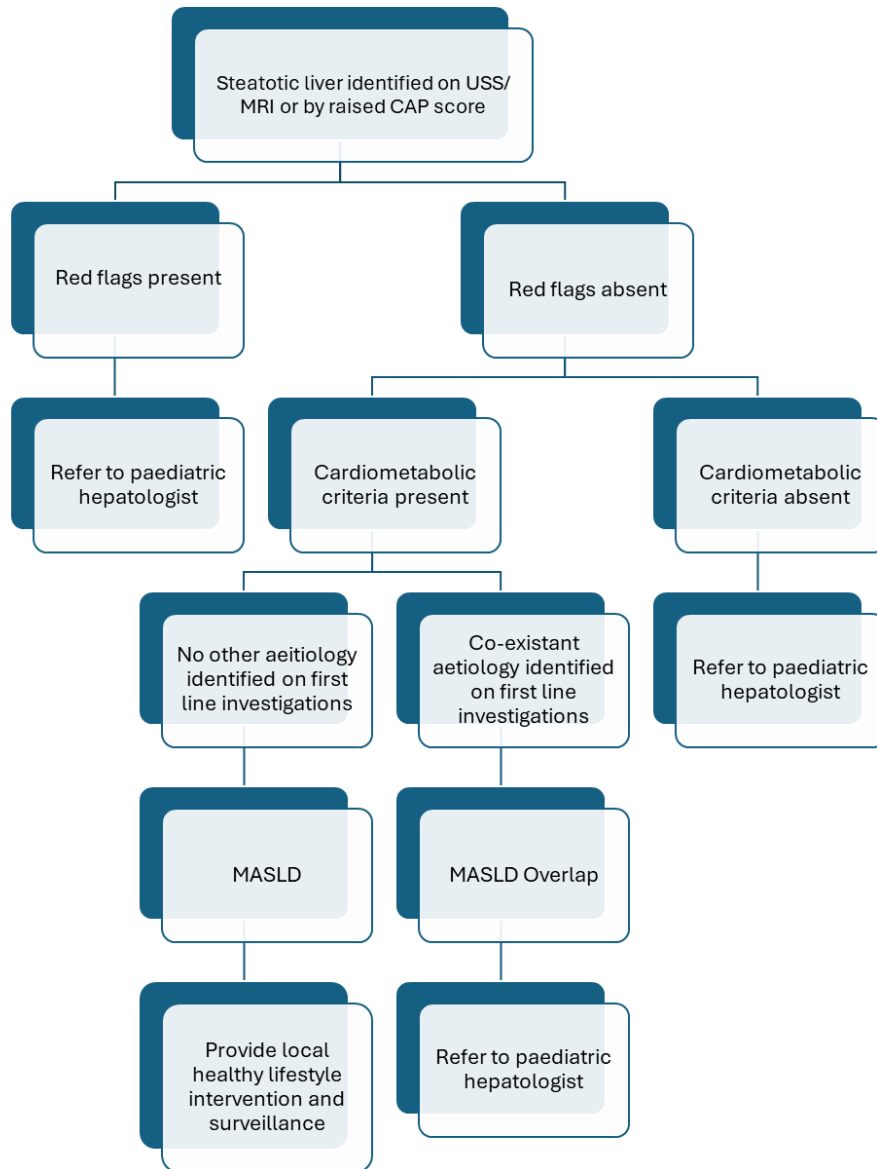
Investigations are performed to evaluate for metabolic dysfunction, severity of liver disease, and to evaluate for other primary liver diseases which may be co-existent or offer an alternative diagnosis to MASLD.

**First line tests:**

- Split bilirubin, ALT, AST, GGT, ALP
- Albumin
- Prothrombin time
- FBC
- Immunoglobulins
- Autoimmune profile to include ANA, AMA, SMA, LKM, ANCA
- Coeliac screen
- A1AT level and phenotype
- Hepatitis B and C screening
- Copper and caeruloplasmin\* testing
- Thyroid function tests
- Creatine kinase
- Fasting lipid profile
- HbA1C
- Fasting glucose

\*If Caeruloplasmin level is  $<2.5$  to complete a 24-hour urinary copper collection

These investigations help differentiate the cause and referral pathway of paediatric steatotic liver disease as outlined below:



### **RED FLAGS:**

Children with the following features should be discussed with a Paediatric Hepatologist for consideration for Hepatology OP assessment as they may be more likely to have an alternate diagnosis or advanced hepatic fibrosis:

- 8 years and under
- Developmental delay
- Neurological signs/ symptoms
- Deteriorating school performance

- BMI z score <1
- Synthetic dysfunction (low albumin/ prolonged PT)
- Splenomegaly
- Thrombocytopenia
- Jaundice
- Sustained rise in ALT/AST  $\geq$  150IU/L
- Panhypopituitarism with ALT/AST  $\geq$  50IU/L
- Co-existent type 2 diabetes mellitus with ALT/AST  $\geq$  50IU/L

## **Management**

There is currently no strong scientific evidence to support the use of any medications to treat paediatric MASLD.

Management involves:

- 1) Education
- 2) Supporting healthy lifestyle change
- 3) Treatment of co-morbidity
- 4) Surveillance

This care is best delivered local to the patient by their named general paediatrician with support provided as required from dietetics +/- a complications of excessive weight service (if BMI  $\geq$ 3.5) +/- paediatric endocrinology (if insulin resistance is present).

### **1. Education:**

Patient information leaflets and guidance for MASLD are available via the Children's Liver Disease Foundation at <https://www.childliverdisease.org> and the British Liver Trust at <https://www.britishlivertrust.org.uk>

Inform families that children with MASLD are at risk of progressive liver disease and liver cancer

Counsel that children with MASLD are also at risk of hypertension, cardiovascular disease, type 2 diabetes and chronic kidney disease

### **2. Lifestyle intervention is the first line of treatment for children with MASLD**

- Lifestyle intervention with diet and increased physical activity induces weight loss and is associated with a significant improvement in both laboratory abnormalities and liver histology
- Weight loss  $\geq 7\%$  improves histological disease activity
- The highest rates of steatosis reduction, NASH resolution, and fibrosis regression occur in patients with weight losses  $\geq 10\%$
- A low-glycaemic load diet and low-fat diet appear equally effective in decreasing hepatic fat content and transaminases.
- Randomised controlled trials shows that reduction in sugar-sweetened drinks improves MASLD in children.
- Both aerobic and resistance exercise training at vigorous and moderate-to-vigorous intensities may reduce hepatic fat content in children and adolescents

### **Recommendations:**

- Children and young people should be encouraged to gradually increase the amount of moderate to vigorous- intensity physical activity that they do each day.
- Focus on activities they enjoy, and that can be built into daily life.
- Support children to achieve the nationally advised physical activity target of an average of at least 60 minutes/ day of activity across a week
- Agree dietary changes that are age-appropriate, affordable, culturally sensitive and consistent with healthy eating advice.
- Provide healthy eating advice in accordance with the NHS Eatwell Guide
  - <https://www.nhs.uk/Live-well/eat-well/food-guidelines-and-food-labels/the-eatwell-guide/>
- For overweight/ obese children, total energy intake should be below their energy expenditure
- Support children and their families through local dietetic services as part of a multi-component intervention
- Refer child on to the local complications from excessive weight (CEW) clinic if referral criteria are met

3. Children should be treated/ referred for management of co-morbidities where appropriate, for example:

- Insulin resistance and diabetes
- Obstructive sleep apnoea

- Hypertension
- Dyslipidaemia
- Renal dysfunction
- Depression and anxiety

## **Pharmacotherapy for weight loss**

Metformin:

Metformin is not recommended as a specific treatment for MASLD. However, there is no restriction on using metformin for its approved indications, such as:

- Type 2 diabetes / insulin resistance
- As part of management strategies that may support weight reduction in children and adolescents with metabolic dysfunction.

## **Glucagon-like peptide-1 (GLP-1) agonists**

- Amongst adolescents with obesity, once-weekly treatment with a 2.4-mg dose of semaglutide plus lifestyle intervention results in a greater reduction in BMI than lifestyle intervention alone.
- Semaglutide has a good safety profile and is well tolerated
- Semaglutide has been shown to improve hepatic steatosis, steatohepatitis, and reduce hepatic transaminases but has not been shown to reduce hepatic fibrosis.

There is not enough evidence to recommend GLP-1 agonists as a treatment for MASLD in children, however they are well tolerated and may aid weight loss alongside healthy lifestyle intervention as part of a multidisciplinary supported programme.

## **Weight-loss surgery**

Bariatric or weight loss surgery can lead to clinically meaningful weight loss in severely obese adolescents, with average BMI reductions of approximately 30% at 1 year postoperatively after both roux-en-y gastric bypass and vertical sleeve gastrectomy in a large multicenter adolescent cohort.

The reduction in BMI may improve obesity-related comorbidities including hypertension, dyslipidaemia, obstructive sleep apnoea and insulin resistance and diabetes.

Adolescents undergoing laproscopic sleeve gastrectomy may have improvements in steatosis, steatohepatitis, and a reduction in hepatic fibrosis. Similar benefits have been demonstrated in adults undergoing Roux-en-Y gastric bypass surgery, though data is lacking for children and young people.

### **Recommendation:**

Bariatric surgery may be considered in select adolescents who are morbidly obese and have reached or nearly reached physiological maturity, who have failed to achieve clinically beneficial weight loss with previously organised behavioural / medical treatments

Morbid obesity is defined in National Institute of Clinical Excellence (NICE) clinical guideline 189 as BMI > 40Kg/m<sup>2</sup> or BMI 35-40Kg/m<sup>2</sup> and other significant disease that could be improved with weight loss.

MASLD in the absence of metabolic dysfunction associated steatohepatitis or fibrosis is not an indication for referral.

### **Vaccination**

- Children with MASLD should be vaccinated against hepatitis A and B

### **Follow up**

- Annual follow up for re-assessment of the liver and to screen for co-morbidity development
  - Anthropometrics: height, weight, BMI, waist circumference
  - BP measurement
  - Nutritional assessment and exercise history
  - Drug and alcohol history
  - Blood tests:
    - Bilirubin, ALT, AST, ALP, GGT
    - Urea, creatinine
    - FBC
    - Clotting

- Albumin
- HbA1C
- Fasting glucose
- Fasting lipid profile
- In children and young people with cirrhosis, AFP should be measured
- Urinalysis
- Abdominal ultrasound 2 yearly

**Achieving lifestyle change and weight loss is paramount to managing MA SLD.**

**Studies have demonstrated that intensive, multi-disciplinary programmes, involving dietetic teams are more effective, and so frequency of follow-up for obesity may need to be higher to optimise outcomes.**

- **If ALT is persistently  $\geq 80$  IU/L on repeated surveillance bloods, following supported weight loss, for discussion with paediatric hepatology.**

In children with metabolic dysfunction associated steatohepatitis (MASH) or hepatic fibrosis care will be shared with a paediatric hepatologist. Frequency of review to be determined by severity of disease.

Transition Pathway:

Refer to adult hepatology if:

- $\geq 16$  years old with an ALT  $\geq 150$  IU/L
- $\geq 16$  years old with Fibroscan score of  $\geq 8$  kPa

Refer to an adult investigatory hub for repeat blood investigations and fibroscan in 2 years if:

- $\geq 16$  years of age with an ALT  $>80$  IU/L  $< 150$  IU/L
- $\geq 16$  years of age with a fibroscan reading of 5-8 kPa

**Role of the National Paediatric Liver Units:**

1. Exclude alternative diagnoses and identify co-existent liver conditions (MASLD overlap)
  - *This is the main indication for liver biopsy in children and young people with MASLD, outside of clinical trials*
2. Monitor for disease progression and development of fibrosis using non-invasive tests: ALT, GGT, MRI-PDFF (or controlled attenuation parameter, where MRI not available).
3. Risk stratify children for follow-up under adult hepatology services
  - Recruitment of children to trials in MASLD
  - Resmetiron is an oral, liver directed, thyroid hormone receptor beta-selective agonist, with FDA approval, for the treatment of MASH with liver fibrosis in adults. Paediatric trials are anticipated within coming years.
4. Contribute to Paediatric MASLD registries to improve understanding of the natural history of MASLD
  - EU-P-MASLD registry is currently in development
5. Monitor children on a variceal banding programme if evidence of portal hypertension
6. Monitor children with cirrhosis for timing for liver transplantation

## **Annex 1.**

### **Non-invasive tests and risk stratification in children with MASLD**

#### **Biomarkers**

#### **Summary**

The two principal aims of non-invasive tests (NITs) in paediatric MASLD are staging and monitoring of progression. NITs should demonstrate consistent replication in at least two independent cohorts of substantial size before being used in clinical practice. Whilst biopsy may be affected by sampling variability, it can diagnose fibrosis stage and steatohepatitis. Histological fibrosis stage (and to a lesser extent, steatohepatitis) has a strong, reproducible causal relationship between liver-related mortality in MASLD.

In preparation of this updated guidance, we have performed a systematic review of non-invasive tests in paediatric MASLD and reviewed the evidence with a panel of international experts (Jeffrey Schwimmer, Stavra Xanthakos, Miriam Vos, & Bart Koot at The Liver Forum, AASLD 2024).

## Summary of key points:

- Liver biopsy is the only method to assess fibrosis stage.
- Liver fat can be accurately measured using MRI proton density fat fraction (MRI-PDFF).
- Inflammatory activity correlates with elevation of ALT and GGT, but exact cut-offs are unclear.
- There is no evidence to support the routine use of Fibroscan, ELF, shearwave elastography, or magnetic resonance elastography in routine practice.
- PNPLA3 p.Ile148Met genotype has strong predictive value.
- Markers of improvement in disease are:
  - Reduction in MRI liver fat by 30%
  - Reduction in ALT by more than 20 IU/L
  - Reduction in GGT by more than 10 IU/L

## MRI measurement of liver fat

>5% liver fat on MRI is diagnostic of hepatic steatosis, though most children included in clinical studies have >20% liver fat. Amount of liver fat correlates with fibrosis stage and all-cause mortality in adults. There is compelling evidence from multiple, independent liver biopsy studies that MRI liver fat correlates with histological steatosis (n>300)<sup>1-4</sup>. There is almost complete correlation between MRI-PDFF and magnetic resonance spectroscopy (MRS) modalities<sup>5</sup>. MRI-PDFF also shows reproducible dynamic change with histological disease improvement, where a 30% fall (i.e. 15% liver fat to 10% liver fat) is associated with falls in ALT<sup>6</sup>.

## Liver enzymes

Across multiple cohorts, higher ALT, AST, and GGT are associated with more advanced steatohepatitis and fibrosis stages in children<sup>7-9</sup>. This is in contrast to adults, where there is limited relationship between liver enzymes and histology stage<sup>10</sup>. However, there is insufficient evidence to recommend a specific cut-off to accurately identify patients with more advanced disease in children.

Robust paired biopsy studies show that reductions in ALT (or AST) and GGT are associated with histological improvement<sup>11</sup>. A fall in at least 20 IU/L in ALT and 10 IU/L in GGT is correlated with disease regression. Reductions in liver enzymes are also strongly correlated with improvement in insulin resistance.

## **PNPLA3 p.Ile148Met**

This common variant in PNPLA3 is the strongest genetic influence on liver-related outcomes, which has been extensively replicated with histology in children<sup>12</sup>. This variant confers a hazard ratio of 2.9 for liver-related mortality<sup>13</sup>.

## **Transient elastography (TE) and controlled attenuation parameter (CAP)**

There have only been two studies to demonstrate correlation between fibrosis stage and transient elastography readings<sup>14</sup>. (There was a second publication using the same patients<sup>15</sup>.) In a separate cohort of 33 patients there was some correlation between fibrosis stage and TE, though the cut-offs were considerably lower than Nobili *et al.*<sup>16</sup>. There was no correlation between fibrosis and TE in a third independent cohort<sup>17</sup>. It is also the opinion of the panel that the values reported in Nobili *et al.* 2008 are not consistent with their clinical experience. It is well recognised that TE varies substantially by disease aetiology (e.g. PSC versus Fontan-associated liver disease)<sup>18-20</sup>. It is likely that TE of 5 kPa or less is reassuring and that TE of >10 kPa is abnormal, but there is insufficient evidence to support these cut-offs in paediatric MASLD.

There is some data to suggest that TE is lower in patients who have substantial weight loss, but it is unclear how this correlates to liver inflammation or fibrosis<sup>21,22</sup>.

There are several other studies that have compared controlled attenuation parameter to MRI-derived liver fat. There is some correlation but only a single study demonstrating association between histological steatosis and CAP in 23 patients<sup>23</sup>.

## **Enhanced liver fibrosis test**

There is only a single study that has demonstrated association between ELF and histology in paediatric MASLD<sup>24</sup>. These findings could not be replicated using samples from the same cohort (J Mann, Unpublished data). ELF is composed of hyaluronic acid, TIMP-1, and PIIINP. Associations between histology and hyaluronic acid have also only been demonstrated in the Rome cohort<sup>25</sup> and could not be replicated by two independent studies<sup>26,27</sup>.

## **Shearwave elastography (SWE)**

Three cohorts have described the association between SWE and liver histology<sup>28-32</sup>. However, these all use different modalities and therefore different cut-offs.

## MR elastography (MRE)

Two independent cohorts have demonstrated weak associations between MRE and fibrosis stage<sup>1,33</sup>. However they had few patients with advanced fibrosis and it is not possible to define cut-offs from this data.

## Composite scores

pFIB is a promising tool for risk stratification in patients with obesity to determine whether they should be assessed by a hepatologist, but needs replication in Hispanic cohorts<sup>9</sup>. Fibro-PeN (<https://fibro-pen.shinyapps.io/Fibro-PeN/>) is a promising risk-stratification score to be used when patients have been seen in specialist paediatric gastro-hepatology clinics, but needs replication in caucasian cohorts<sup>7</sup>. All other previously reported scores do not out-perform ALT >50 IU/L<sup>8</sup>.

## Additional references:

MRI studies<sup>1-6,28,33-39</sup>

Systematic reviews<sup>40</sup>

Ultrasound / shear-wave<sup>28-32,41</sup>

Transient elastography / CAP<sup>14,15,17,21-23,30,42</sup>

CT<sup>43</sup>

US or CAP to MRI comparisons<sup>44-56</sup>

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