Review

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Update in clinical science: MASLD in children and adolescents

Sander Lefere[1,2], Bart G.P. Koot[3], Jake P. Mann[4,5], Philip Bufler[6,7], Ruth De Bruyne[1,8,‡], Christian A. Hudert[6,*,‡]

Summary

Paediatric metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasingly common liver disease, with an estimated global prevalence of up to 7.5% and growing concern regarding hepatic and extrahepatic complications even in early life. In this paper, we review recent advances in epidemiology, genetics, early-life risk factors, natural history and comorbidities, focusing on emerging data published in the last 3 years. We also outline a practical approach to the management of MASLD in children, integrating newly developed non-invasive tests. Lastly, we highlight key research questions to be studied in the coming years.

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Definition of MASLD and challenges in the diagnostic workup

Following an international multi-society Delphi panel consensus process, a terminology change from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) was proposed, with diagnostic criteria consisting of a demonstration of liver steatosis and the concomitant presence of at least one cardiometabolic risk factor (including having overweight/obesity).[1] These criteria have been adopted in paediatrics, with the caveat that the differential diagnostic landscape is different in children, and rigorous testing for other causes of steatosis should be performed when establishing a diagnosis of MASLD, especially in young or lean children. As in adults, the new nomenclature permits the diagnosis of MASLD-overlap in the presence of concomitant liver disease and of metabolic- and alcohol-related liver disease (MetALD) in the setting of alcohol misuse. MetALD, in particular, remains a largely unexplored yet unequivocally important topic in adolescents.

Multiple studies have compared the impact of the novel MASLD diagnostic criteria with those for NAFLD across different paediatric cohorts. The concordance was very high in studies using controlled attenuation parameter (CAP) as an identifier for steatosis (97.2% of children with NAFLD had MASLD using a cut-off of 238 dB/m),[2] while 77.2% of children with elevated alanine aminotransferase (ALT) (defined as ALT >26 U/L in boys and >22 U/L in girls) were deemed to have MASLD and 20.2% had cryptogenic ALT elevation.[3] In this review, we retained the term 'NAFLD' when discussing papers which included patients diagnosed according to the old definition, while using 'MASLD' for newer studies with the updated terminology or when discussing MASLD in general.

While most population-based studies use elevated ALT and ultrasound as proxies for liver steatosis in children, both have only modest diagnostic accuracy. For ALT, different reference populations impact cut-offs,[4] while the low sensitivity of ultrasound for mild steatosis, as well as interobserver variability and misclassification of hyperechogenicity due to competing aetiologies, are known limitations. Among newer diagnostic modalities, CAP on FibroScan© was introduced, yet cross-validated cut-offs in children have not been consistently established. MRI-based hepatic fat quantification, namely MRI-estimated proton density fat fraction (MRI-PDFF), produces the highest diagnostic performance compared to histology,[5] yet its low availability and high cost preclude population-wide use. Therefore, under- or overestimation of liver steatosis is highly likely in children and epidemiological data should be interpreted with these limitations in mind. An overview of epidemiological studies in children is provided in Table S1.

Epidemiology

The prevalence of MASLD in childhood parallels trends in the obesity pandemic and has increased over the past three decades.[6,7] MASLD represents, as in adults, the most common chronic liver disease worldwide. Hartmann *et al.* conducted a systematic review of 19,773 datasets, reporting prevalence data from the Global Burden of Disease study 2019. In adolescents aged 15 to 19 years, the global prevalence of NAFLD in the general population was 4.7%. The highest burden was

* Corresponding author. Address: Department of Pediatric Gastroenterology, Nephrology and Metabolic Diseases, Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany; Tel.: +49 30 450516012, fax +49 30 450516912.
E-mail address: christian.hudert@charite.de (C.A. Hudert).
‡ Shared senior authors
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Keypoints

- 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.
- While, as in adults, the new nomenclature allows for a positive diagnosis of MASLD, the exclusion of alternative or concomitant diagnoses and a rigorous evaluation of red flags for advanced liver disease is essential in paediatrics, particularly in younger children.
- 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.
- Novel non-invasive risk scores reflecting the multisystem nature of paediatric MASLD may assist clinicians in risk stratification, yet further validation in children is warranted.
- 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.
- Multiprofessional lifestyle intervention remains the core of treatment strategies for children and adolescents with MASLD, while paediatric drug trials are urgently needed.

observed in the Arabic-speaking world (ranging from 7.2% in Yemen to 18.4% in Egypt), while the lowest prevalence was found in Europe (4.0%) and Sub-Saharan Africa (4.2%) (Fig. 1)[6]. Regional differences in NAFLD prevalence were positively correlated with high body mass index. Globally, boys (median 5.8%) were significantly more affected than girls (median 3.5%), and this effect was preserved across all regional analyses.[6]

Conversely, a recent meta-analysis estimated that the global prevalence of NAFLD among children aged 2-19 years was 7.6% in the general population,[7] with the same regional trends as well as sex disparities (median 11.5% in boys and

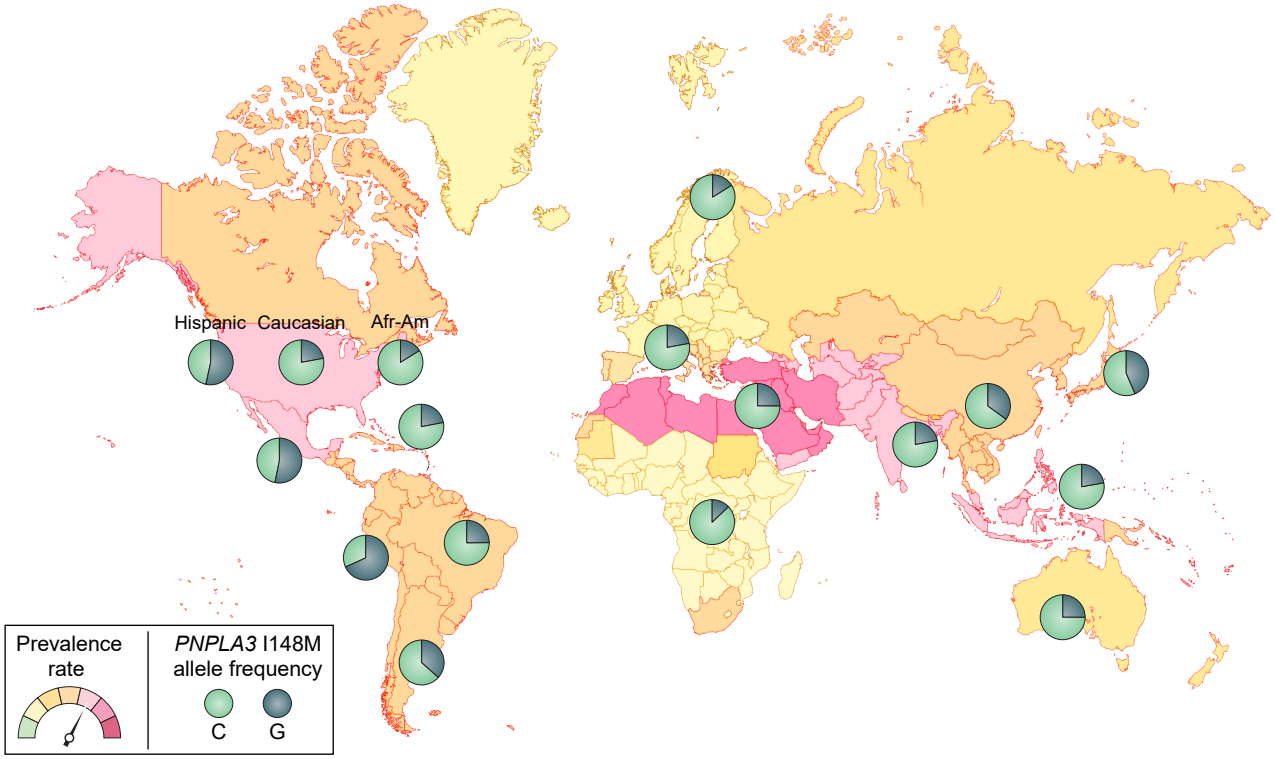

Fig. 1. Global prevalence of paediatric MASLD and minor allele frequency of *PNPLA3*. Given the limitations in determining the exact prevalence of paediatric MASLD in specific countries, a five-point grade scale was applied, with darker shades of orange and red indicating higher prevalence. *PNPLA3* is presented as minor allele frequency (dark blue section of the pie chart). MASLD, metabolic dysfunction-associated steatotic liver disease.

6.0% in girls). Among children with overweight and obesity, the pooled prevalence of NAFLD was 39.2%, while among those with obesity it was 52.5%,[7] and boys with obesity were found to be more frequently affected than girls with obesity (58.4% *vs*. 44.3%). The authors projected that the prevalence of childhood NAFLD will increase to 30.7% by 2040.

In a landmark autopsy study of 742 US children, the prevalence of NAFLD was relatively low up to age 4 (0.7%), but increased markedly from early childhood (5-9 years: 3.3%) to early adolescence (10-14 years: 11.3%).[8] In the NHANES (National Health and Nutrition Examination Survey), prevalence rates further increase from early adolescence to young adulthood.[9] Most worryingly, more recent studies indicate that rates for suspected NAFLD, as detected by elevated ALT, have increased significantly in young children under 6 years of age.[10]

Regional divergences in MASLD prevalence are attributable to both environmental and genetic factors (Fig. 1). For instance, in a comprehensive study employing the alternative healthy eating index, the lowest food quality scores were reported for children living in Latin America/Caribbean and the Middle East/North Africa.[11] Indeed, the rapid globalisation of the food supply chain has facilitated distribution and reduced the cost of ultra-processed, high-sugar, energy-dense food and beverages worldwide, the consumption of which has increasingly been linked to poorer cardiometabolic health.[12] There is compelling evidence that excessive fructose intake contributes to MASLD pathogenesis in susceptible children and adolescents.[13] Sugar-containing beverages (SSB) are the main source of added sugar and fructose intake both in children and adults, with adolescents being the peak consumers of SSB. In a population-based prospective cohort study of 1,940 infants, infants who consumed more than two SSB servings per day had the highest odds of liver steatosis on MRI-PDFF at 10 years of age.[14] Thus, the intake of free sugars, fructose in particular, should be discouraged in children with MASLD. At the societal level, nutrition policy interventions to limit the consumption of ultra-processed foods, saturated/trans fats and SSB, such as integrated strategies to improve the food environment in childcare and schools, the regulation of food and beverage marketing by revised front-of-package labelling, and the introduction of sweetened beverage taxes are urgently required.[15]

Genetics

The onset of MASLD (*i.e.* presence of hepatic steatosis) is highly heritable, as up to 30% of variation in liver fat is accounted for by common germline polymorphisms.[16] Large-scale genome-wide association studies (GWAS) in adults have identified 17 separate genes (or loci) that are robustly associated with MASLD,[17] including proteins involved in VLDL assembly (*e.g. TM6SF2*), *de novo* lipogenesis (*e.g. GCKR*), regulation of hepatic lipolysis (*e.g*. *PNPLA3*), lipid delivery (*e.g*. *APOE*), and lipid metabolism (*e.g*. *MBOAT7*), though the precise mechanisms for some (*e.g*. *MTARC1*) remain to be formally established.

Because GWAS require a large number of participants to achieve sufficient power to overcome multiple testing, the majority of studies in children have taken candidate gene approaches, selecting variants robustly associated with phenotypes in adults. This approach has been employed to demonstrate that population-level variants in *PNPLA3*, *TM6SF2*, and *HSD17B13* are associated with liver enzymes in 4,018 British children.[18] Stender *et al.* also found that a genome-wide polygenic risk score (derived from adult data) correlated with liver enzymes in children.[18] Similar observations were found in over 3,000 Danish children, where variants in four genes identified in adult GWAS (*PNPLA3*, *TM6SF2*, *GPAM*, *TRIB1*) correlated with liver fat.[19] Collectively, to date, these results have not identified substantial genetic differences between children and adults; however, a formal liver fat GWAS in a large number of children (*e.g*. n >10,000) is required to conclusively establish whether specific paediatric variants are involved. As a case in point, an exome-wide analysis in 229 children (currently in pre-print form) testing for rare coding variants has not yielded significant loci.[20]

In the short term, genetic testing has two main roles in paediatric MASLD: diagnosis and risk stratification. Unlike in adult clinics, it is not uncommon to identify children with rare, genetic causes masquerading as MASLD. Young children (*e.g.* <5 years old) and those who are lean are particularly likely to have an alternative cause for hepatic steatosis.[21] However, whole-exome sequencing analysis can lead to diagnoses of monogenic disease, for instance Wilson's disease,[22] in children who meet diagnostic criteria for MASLD. Still, this is rare and genetic testing is generally reserved for children who do not meet the typical phenotype of MASLD.

Variants in or near *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*, *HSD17B13*, and *MTARC1* have been associated with histological severity of NAFLD in children,[23,24] although studies on clinical outcomes have not been performed. *PNPLA3* rs738409C>G in particular is linked to an odds ratio (OR) of 1.5–2 for the diagnosis of fibrosing steatohepatitis[25] and might in part explain the higher MASLD prevalence and disease severity in children of Hispanic ethnicity. This may be of greater utility in children than adults given the lack of non-invasive risk stratification tools in children. However, genetic variants have not been incorporated into recent risk stratification tools,[26,27] and it has not been established how results should influence management.

Natural history of paediatric MASLD

Short-term data show that the course of MASLD is highly dynamic in children. Two recent studies analysed follow-up data within the non-alcoholic steatohepatitis (NASH) Clinical Research Network, reporting that fibrosis progression, worsening histological NAFLD activity score, and worsening ALT and gamma-glutamyltransferase all occurred in 20-25% of children over a 2-year time window, while roughly 25-50% experienced improvement in these parameters.[28,29] A 5% increase in BMI z-score (OR 1.3, 95% CI 1.1–1.5) or total cholesterol (OR 1.3, 95% CI 1.2–1.5) were the routine clinical measurements associated with worsening MASLD (as defined by increasing ALT and gamma-glutamyltransferase levels).[29] Additionally, worsening glycaemic status was found to predict exacerbation of MASLD in the cohort with sequential histology.[28] It should be noted that these patients were enrolled in placebo arms of clinical trials, potentially biasing results towards improvement. In addition, most children (70–75%) were of Hispanic descent, indicating a potentially high frequency of

PNPLA3 risk variants. A prospective 10-year follow-up study of 51 Dutch adolescents with obesity and MASLD reported fibrosis progression in 16% and advanced fibrosis in 6% based on the ELF (enhanced liver fibrosis) test in young adulthood.[30] Rapid progression from mild fibrosis to cirrhosis within 2 to 3 years has been described in small case series but is rarely encountered in clinical practice.[31] In cross-sectional histopathological paediatric cohorts, which are inherently limited by selection bias, advanced fibrosis is found in 12-14%, while *bona fide* cirrhosis is rare (0.8-1%).[32] Cases of liver failure and hepatocellular carcinoma have also been reported in children.[31] Thus, between 1987-2012, 4% of NASH-cirrhosis-related liver transplants in the US were performed in children and adolescents.[33]

Three recent longitudinal studies provide a more comprehensive picture of the substantial liver-related morbidity and mortality associated with MASLD in adolescents and young adults. In a US-based retrospective cohort from a single tertiary centre (n = 1,079), with a mean follow-up time of 8.5 years, the cumulative incidence of cirrhosis was 4.7% (Fig. 2). The standardized mortality rate was 40 times higher than that of age- and sex-matched controls, with almost half of deaths being liver-related, occurring in 1.6% of patients.[34] In a Swedish cohort of 718 individuals diagnosed with NAFLD before age 25 and followed up for 15 years, liver-related mortality was considerably increased (adjusted hazard ratio [HR] 16.5; 95% CI 2.8-98.4) compared to matched controls.[35] Another Swedish study including over 29,000 individuals in the Swedish Childhood Obesity Treatment Register found that after a median follow-up of 8.3 years, childhood obesity was associated with double the risk of major adverse liver outcomes (MALOs), encompassing decompensation, liver failure and transplantation, compared to controls from the general population. The cumulative prevalence of MALOs was 1.1% at the age of 40 in the paediatric obesity cohort.[36] Alcohol use disorder in adolescence or early adulthood exacerbated the risk of MALOs, stressing the need to swiftly expand efforts to study MetALD in young people and strengthen public health campaigns in this age group.

While significant gaps in our understanding of the natural history of paediatric MASLD remain, these data indicate that the disease course can be aggressive, potentially leading to clinical complications in early adulthood and a high number of healthy life years lost. Indeed, a Global Burden of Disease study on adolescents and young adults demonstrated a worsening trend in the proportion of chronic liver disease deaths associated with NAFLD, compared with improving trends for other causes such as hepatitis B or C.[37]

Paediatric disease zonation

Schwimmer *et al.* posited that histopathology in paediatric MASLD exhibits a typical pattern of portal zonation, which is found most frequently in prepubertal boys.[38] While these

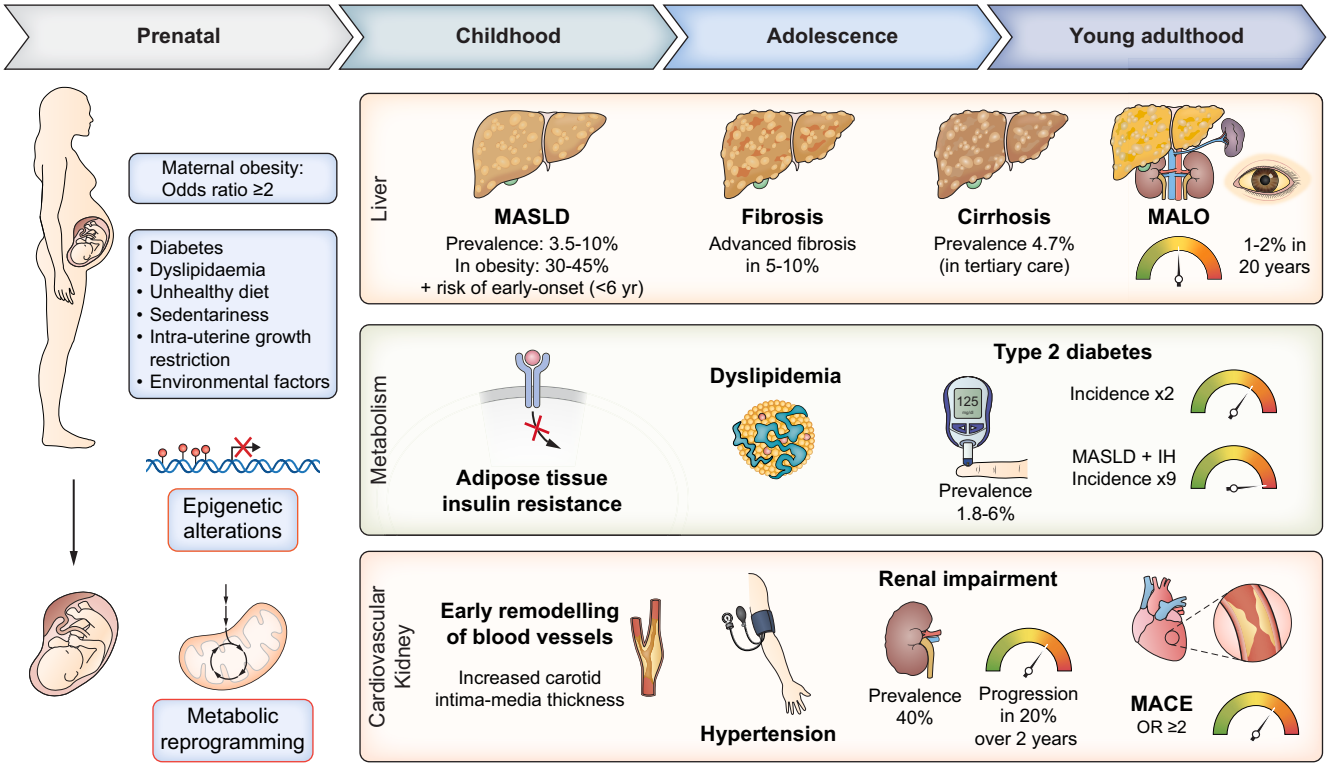

Fig. 2. Potential progression of MASLD and comorbidities over the patients' lifespan. Intrauterine and early life exposures can represent a "first hit" predisposing to MASLD development later in life, mechanistically mediated among others by epigenetic alterations and metabolic reprogramming. Childhood 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.

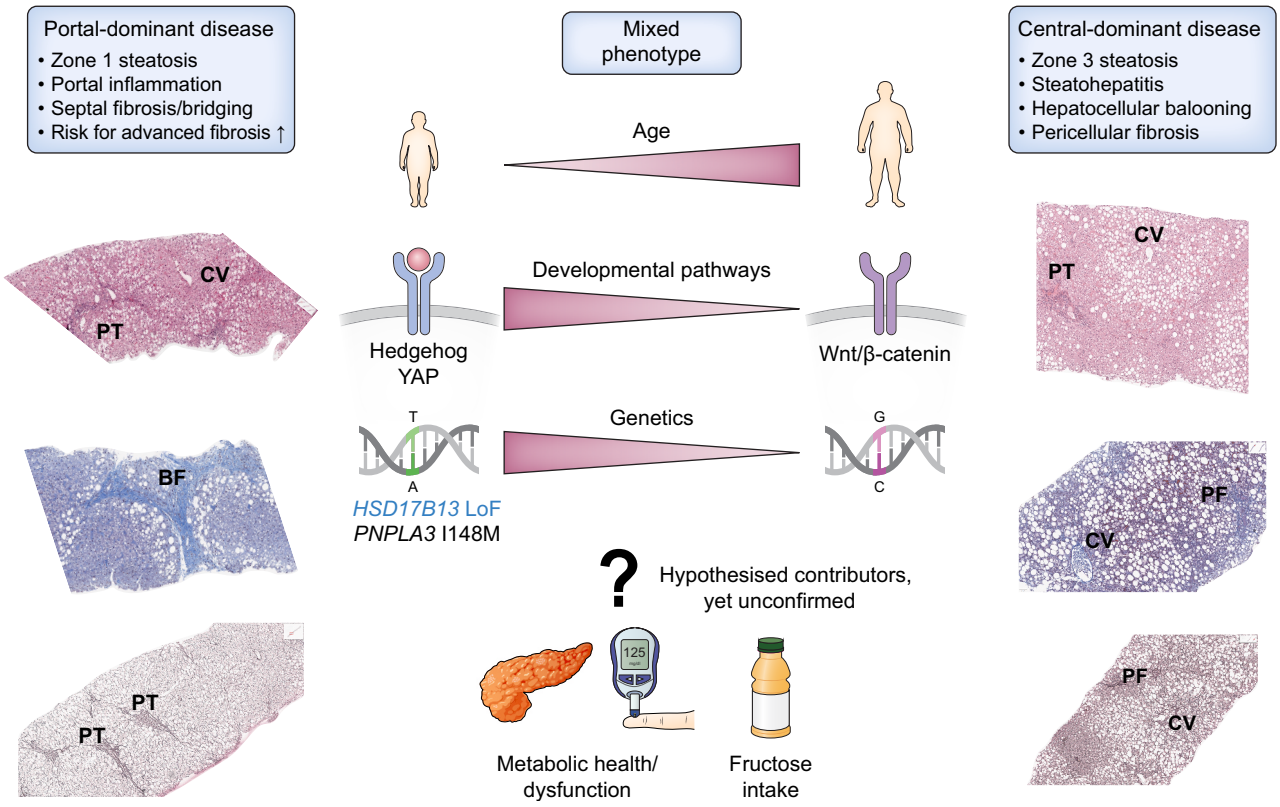

Fig. 3. Zonal phenotypes in paediatric MASLD. On liver histology, paediatric MASLD can present with different phenotypes, the so-called portal-dominant and central-dominant disease, with the former often presenting with severe portal inflammation even without other features of steatohepatitis such as lobular inflammation and hepatocellular ballooning. Demographic and pathophysiological factors, confirmed as well as hypothesized, that impact zonation patterns are depicted. It should be considered that most patients present with a mixed phenotype along a continuum between both extremes. Upper images: H&E staining; middle section: Masson trichrome staining; lower images: silver impregnation. Blue text: protective variant. Blue color indicates the protective role of *HSD17B13* LoF variants against portal inflammation. BF, bridging fibrosis; CV, central vein; LoF, loss of function; MASLD, metabolic dysfunction-associated steatotic liver disease; PF, pericellular fibrosis; PT, portal tract.

findings have since been replicated in multiple independent cohorts,[39,40] it has become evident that the majority of children display a mixed phenotype with disease features of both portal and lobular disease activity, and that a portal-dominant pattern may shift towards a central-dominant phenotype during adolescence.[28] Nonetheless, portal-dominant MASLD, which reflects the distribution of steatosis, inflammatory activity and defined patterns of fibrosis, is of high clinical relevance, given its association with the early development of advanced fibrosis[40,41] (Fig. 3). Histopathologic scoring in paediatric MASLD should therefore account for distinct zonal features[42] such as portal inflammation or zonal distribution of steatosis.

The mechanisms that drive the portal-type MASLD phenotype are incompletely understood. In physiologic conditions, specialised hepatocyte functions are zonated (*e.g.* gluconeogenesis, urea cycle metabolism and lipid beta-oxidation in periportal hepatocytes). Spatial distribution of liver-resident immune cells (*e.g.* predominant periportal distribution of Kupffer cell macrophages) and pattern-recognition receptors also follows zonation. This may account for differential zonal stress with regards to metabolic impairment and microbiota or toxin influx via the gut-liver axis. Additionally, age-dependent activation of evolutionarily conserved developmental signalling pathways may have a superordinate role in conferring zonal disease manifestation. In children, Hedgehog signalling is increased and has been associated with portal-dominant injury, while centrilobular distribution of steatosis has been elegantly linked with WNT/β-catenin signalling in a murine transgenic/knockout model.[43] Finally, genetics might also impact disease zonation patterns. In 822 US children (63% Hispanic), rs738409C>G in *PNPLA3* was associated with both portal and lobular inflammation.[24] However, in 406 European children, this variant in *PNPLA3* was only associated with worse lobular inflammation, while rs72613567T>TA in *HSD17B13* was protective against portal inflammation.[23] It is unclear whether these zonal differences are due to genetic ancestry. Gaining clarity is important given the ongoing development of gene-targeted therapies.[44]

Early-life risk factors

The 'developmental origins of health and disease' paradigm posits that environmental exposures *in utero*, during early life, and even before conception have long-lasting effects on physiology and metabolism, accelerating metabolic disease development. Multiple lines of evidence show that maternal

insulin resistance (IR) and unhealthy dietary patterns can affect placental function, foetal development, and metabolic wiring.[45] This paradigm is relevant given the increasing obesity rates in women of reproductive age.

A systematic review of maternal and perinatal risk factors for paediatric MASLD found the strongest positive association for maternal obesity and, to a lesser extent, maternal overweight, with several studies reporting an OR exceeding 2 (Fig. 2).[46] Most studies agreed that breastfeeding, albeit modestly, reduced the risk of paediatric MASLD. The significant impact of maternal obesity has since been confirmed in recent high-quality cohort studies. An analysis of the Swedish ESPRESSO cohort that included all biopsy-confirmed NAFLD cases in individuals ≤25 years old (84.2% of participants were aged ≤17 years) found that maternal obesity, following adjustment for multiple confounders, increased the risk of NAFLD more than threefold (OR 3.26).[47] This was echoed in a study on approximately 3,000 24-year-olds from the English ALSPAC cohort, which reported an OR of 2.66.[48] Notably, Abeysekera *et al.* undertook the additional step of analysing paternal BMI as a parental negative control for maternal obesity. With this elegant design, they demonstrated that paternal obesity is a risk factor in its own right, albeit with a more limited burden (OR 1.35).[48]

Preclinical studies clearly established how maternal obesity predisposes offspring to MASLD. One of the most translationally relevant models is the feeding of a Western diet to Japanese macaque females for years prior to conception and then throughout pregnancy. Foetuses and 1-year-old offspring, despite weaning onto a control diet, had increased liver collagen deposition that preferentially accrued in the periportal areas.[49] Furthermore, bone marrow-derived macrophages as well as hematopoietic stem and progenitor cells from juvenile macaque offspring were persistently reprogrammed towards a pro-inflammatory phenotype through epigenetic remodelling.[50] Employing a mouse model of multigenerational maternal obesity, impaired mitochondrial function was recently identified as another key mechanism promoting MASLD in offspring.[51] Comparing these data to findings from the Japanese macaque model confirmed oxidative phosphorylation as one of only two differentially regulated pathways by conjoint maternal and offspring Western diet feeding. Conceptually, mitochondria are an attractive target in the setting of maternal obesity, given that these organelles and their DNA are exclusively maternally inherited and obesity is known to impact oocyte mitochondrial quality.

Thus, maternal obesity might be a targetable risk factor for prevention. The PREMEDI trial investigated the effect of serial counselling promoting a Mediterranean diet during pregnancy. While maternal weight gain was not affected, offspring at 2 years of age had a significantly lower rate of overweight/obesity compared with controls.[52] These thought-provoking data warrant further validation in larger studies.

Paediatric MASLD – a multisystem disease

Metabolism

IR appears to be a prerequisite for the development of MASLD, independently of *PNPLA3* genotype.[53] In the physiologic state, transient IR occurs during puberty independently of BMI and body fat mass, which may further promote the onset of MASLD in this age group.[54] The impact of adipose tissue IR was recently investigated in a prospective cohort of 200 children with severe obesity, revealing an association with liver fat content. Both adipose tissue IR and liver fat content were associated with visceral fat mass and waist circumference, as markers of central obesity, but not with total body fat percentage.[55]

Several longitudinal studies have recently reported the bidirectional association between type 2 diabetes mellitus (T2DM) and MASLD, and their impact on overall morbidity and mortality in children and young adults. In a cohort of 122 children with NAFLD and paired biopsies, Xanthakos *et al.* found that concurrent prediabetes or incident T2DM increased the risk of steatohepatitis and fibrosis progression, and that histological progression correlated closely with worsening HbA1c and new-onset T2DM.[28] Though T2DM did not mediate adverse liver outcomes in a Swedish paediatric obesity cohort during the median 8.3 years follow-up period.[36]

Two prospective cohort studies further corroborate a substantial detrimental effect of MASLD on the risk of T2DM development even in childhood. In a multicentre North American study,[32] the prevalence of T2DM in 955 children with biopsy-proven NAFLD was 6.6%. Over 3.8 years follow-up, 10.9% of children (mean BMI z-score 2.3) with NAFLD but without T2DM at baseline developed T2DM, resulting in an incidence rate of 3,000 new cases per 100,000 person-at-risk years. Risk factors for the development of T2DM were female sex, higher BMI z-score, and more severe liver disease on histology at baseline, with both steatosis and fibrosis independently increasing odds (HR 1.3 each). A large longitudinal study from Sweden[56] looked at incident youth-onset T2DM over a median period of 8.1 years in 10,364 children receiving obesity treatment compared to 59,336 children from the general population. Baseline prevalence in the MASLD group was 1.8%. Incident T2DM was highest in children with obesity and MASLD (median BMI z-score 2.9; 131/10,000 person-years, HR 2.7), while additional intermediate hyperglycaemia further raised T2DM risk (HR 9.0) (Fig. 2). Critically, obesity treatment decreased the risk of diabetes: every 0.1 BMI z-score decrease, a rather modest outcome, was associated with a 9% relative risk reduction, while patients who achieved at least a 0.25 BMI z-score reduction saw their risk reduced by 43%.[56]

Of note, despite the widely different genetic ancestry between the two studies (73% Hispanic in Newton *et al.* and 69% Nordic in Putri *et al.*), a similar increase in HR for incident T2DM was observed in girls compared to boys (1.8 *vs*. 1.7).

Cardiovascular and renal comorbidities

In adults, MASLD increases the risk of developing cardiometabolic risk factors as well as of cardiovascular morbidity and mortality. However, it remained unclear whether similar associations held true for liver fat content in children.

Important data were generated by analysing more than 3,000 liver MRI scans of 10-year-old children participating in the Generation R study, a prospective birth cohort based in Rotterdam, The Netherlands.[57] Higher liver fat was associated with elevated blood pressure, insulin resistance and serum lipids, which remained the case after adjusting for either BMI or visceral fat mass. Notably, not only overt liver steatosis but even low levels of liver fat were associated with higher odds of

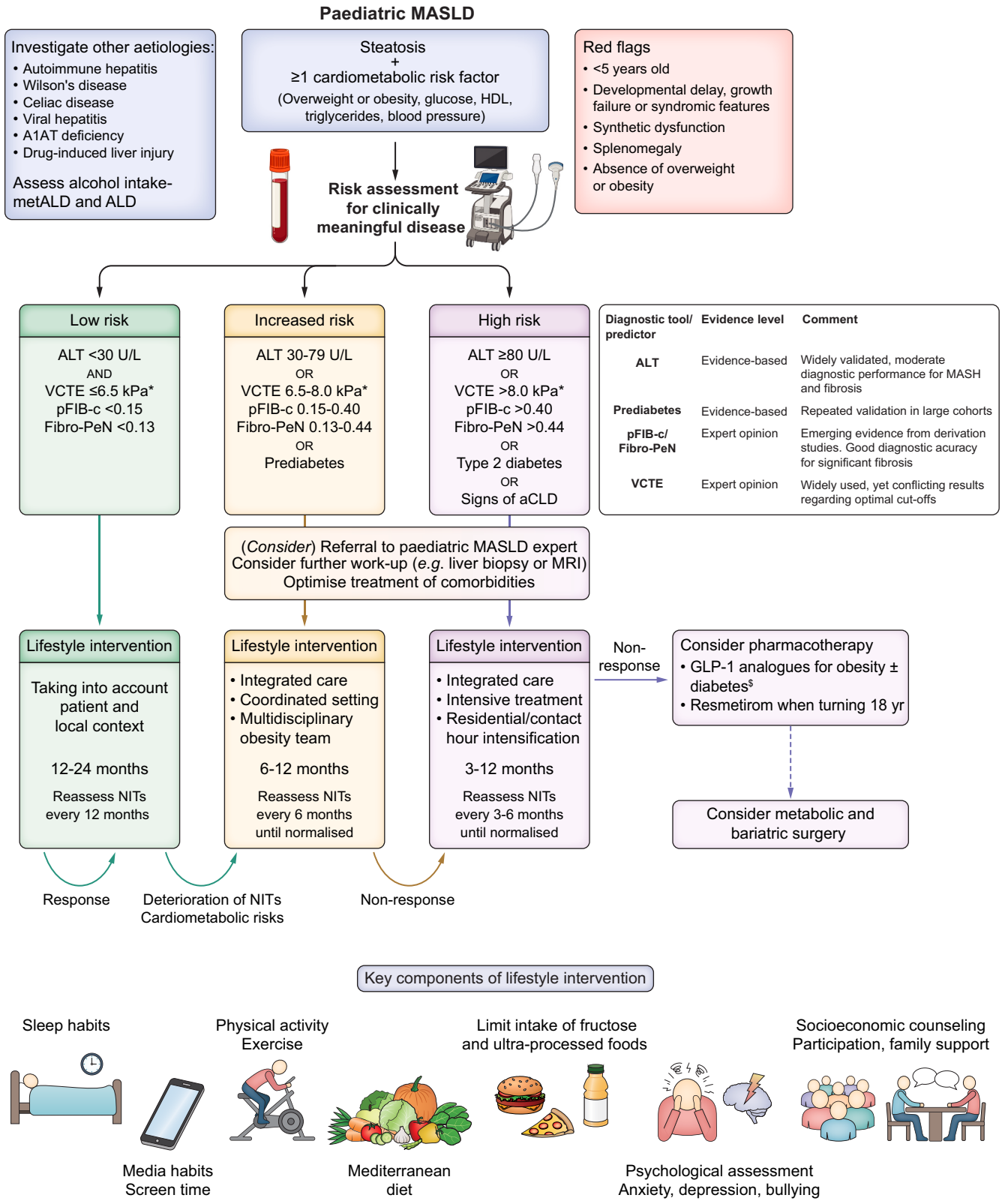

Fig. 4. Proposed expert opinion-based algorithm for the diagnosis, risk stratification and treatment of MASLD in children and adolescents. A diagnosis of paediatric MASLD should prompt exclusion of concurrent aetiologies, including assessing alcohol intake. Based on various NITs, we propose patients can be stratified as low, increased, and high risk. The suggested cut-offs for the Fibro-PeN score were the optimal ones in the original publication, whereas those for the pFIB-c score correspond to values with high negative (0.94) and positive (0.65) predictive values in the derivation cohort, respectively.[26,27] Multicomponent lifestyle intervention is the cornerstone of treatment, with its intensity increasing with patient risk. Periodic reassessment of body weight and NITs is critical. If lifestyle

cardiovascular risk factors. This association was evident from a liver fat fraction ≥2.0%, compared with <2% as the reference. These associations were significant for children with a healthy weight but became stronger in children with overweight or obesity.[57] In a Chinese cohort of 1,081 children with a mean age of 12.1 years, persistent or incident MASLD over a 2-year follow-up period was associated with markers of subclinical cardiovascular damage, such as elevated carotid intima-media thickness.[58]

Whether this translates into a higher cardiovascular risk in (early) adulthood was subsequently investigated in a Swedish nationwide study using the histological ESPRESSO cohort. Over a median follow-up time of 16.6 years, starting at an index age of 17.4 years, 33 major adverse cardiovascular events occurred in 699 patients with MASLD. Compared to age-, sex-, and geographically matched controls, risk was increased with an adjusted OR of 2.33. In the subset of patients with steatohepatitis, the OR further increased to 5.27[59] (Fig. 2). Analysing individual outcomes, the risk of ischaemic heart disease and congestive heart failure, but not stroke, was increased, although the low number of events for each outcome precludes drawing strong conclusions. Time-varying covariate analysis suggested that MASLD, in part, increases the risk of major adverse cardiovascular events by promoting diabetes, hypertension and other cardiovascular risk factors.[59]

Kidney injury is another cardiometabolic comorbidity which can be aggravated by paediatric MASLD. Two recent studies with large sample sizes (>1,000 children) have demonstrated that chronic kidney disease is common in paediatric patients with MASLD, especially in those with significant fibrosis. However, there is no data on hard outcomes, and questions remain concerning the progression rate of renal injury over time, the linkage between liver and kidney disease progression, and whether the *PNPLA3* I148M variant, independent of MASLD, promotes kidney injury.[60,61]

Therapeutic strategies in paediatric MASLD

MASLD is not an isolated liver disease, but the hepatic manifestation of a metabolic multisystem disorder closely associated with obesity and insulin resistance. Consequently, clinical management of MASLD in children should take a holistic approach, addressing the full spectrum of mechanistic factors and comorbidities. This requires substantial coordination among public health services, primary care, general paediatricians, multiprofessional obesity care teams, and paediatric hepatologists. The principles for treating obesity and the metabolic syndrome in children lie at the very core of MASLD management,[62] with recent evidence indicating that successful paediatric obesity treatment protects against the development of T2DM, hypertension, and dyslipidaemia, while also improving survival in young adulthood.[63] Lifestyle interventions should go beyond diet and exercise to incorporate an assessment of and intervention in sleep habits, screen time and media habits, as well as psychological factors and mental wellbeing. The care for the individual child with obesity should also encompass a broader socioeconomic evaluation and counselling of family and caregivers regarding a healthy lifestyle (Fig. 4).

One randomised controlled trial (RCT) demonstrated that restricting free sugar intake, for even just 8 weeks, decreased liver fat content as well as hepatic *de novo* lipogenesis.[64] Beyond this, multiple dietary interventions have shown efficacy in small-scale clinical trials, though effect sizes were generally small. For the Mediterranean diet, which has been studied most extensively, a recent meta-analysis of two RCTs and three quasi-experimental studies found that liver enzymes were modestly improved in the treatment groups, with small but non-significant ameliorations in insulin resistance, body weight and lipid metabolism.[65]

Underpinning the central role of obesity management, data in children recapitulate the findings in adults that clinically significant weight loss may improve liver disease (in a pre-cirrhotic condition). This is illustrated by three studies that employed an intensive inpatient lifestyle treatment,[66] the glucagon-like peptide 1 (GLP-1) receptor agonist semaglutide,[67] and metabolic and bariatric surgery[68] (Table 1). In all three studies, a BMI reduction of >20% was accompanied by a significant improvement in liver steatosis and fibrosis after 1 year.

The metabolic and bariatric surgery study by Manco *et al.* reported resolution of steatohepatitis in a small cohort of 20 patients. In line with these findings a recent study from the US reported statistical improvements in all histological hallmarks of MASLD in 23 adolescents who underwent repeat liver biopsy 1 year after surgery.[69]

In the semaglutide RCT, adolescents with obesity – but not MASLD specifically – experienced ALT reductions despite normal baseline values. Extrapolating from the phase III ESSENCE trial in adults,[70] we might postulate similar benefits for paediatric MASLD, although efficacy remains unproven. As a first set of real-world data, a single-centre retrospective study in 42 children reported a mean ALT decrease of 37%, starting from 118 U/L at initiation of GLP-1 receptor agonists.[71] These early paediatric findings are encouraging but preliminary. The field of incretin mimetics is rapidly evolving. In adults, the GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonist tirzepatide and the glucagon/GIP/GLP-1 triple receptor agonist retatrutide have been shown to further enhance body weight loss, approaching levels observed with metabolic and bariatric surgery, with associated resolution of steatohepatitis on histology and reduction of steatosis on MRI-PDFF, respectively.[72,73] For all these drugs, efficacy in paediatric MASLD remains to be demonstrated and is eagerly awaited.

Metabolic and bariatric surgery is the most effective and sustained treatment for severe obesity and can improve comorbidities including dyslipidaemia, hypertension, diabetes and MASLD, but it is invasive and irreversible.[74,75] A

management fails, pharmacotherapy or, in specific cases, metabolic and bariatric surgery, can be considered. Risk stratification factors with most evidence are underlined. *Suggested cut-offs for post-pubertal children; current evidence is insufficient to propose specific cut-offs for younger children. $Approved for adults with MASH and F2/3 fibrosis; approved for treatment of obesity in adolescents from 12-years-old, not currently indicated for the treatment of MASH in adolescents. A1AT, alpha-1 antitrypsin deficiency; aCLD, advanced chronic liver disease; GLP, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NITs, non-invasive tests; VCTE, vibration-controlled transient elastography.

Table 1. Comparison of recent studies on different weight loss interventions and effects on pediatric MASLD.

	Intensive (residential) lifestyle management	Pharmacotherapy GLP-1 agonists	Metabolic and bariatric surgery
Author, year	Lefere, 2022[66]	Weghuber, 2022[67]	Manco, 2017[68]
Study design	Prospective cohort	Randomized, placebo-controlled trial	Prospective cohort
Intervention	Dietary intervention, physical activity, psychological support in residential setting	2.4 mg semaglutide weekly SC	Sleeve gastrectomy
Control group	None	Placebo + lifestyle management	Lifestyle management
Study duration	Up to 1 year (individualised)	68 weeks	1 year
MASLD assessment method	Ultrasound, FibroScan with CAP, ALT	ALT	Biopsy, ultrasound, ALT
Prevalence of MASLD	69.6%	N/A	100%
Prevalence of significant fibrosis (≥F2)	35.4%	N/A	100%
Sample size (n)	79 (at 1 yr timepoint)	134 (semaglutide group)	20 (surgical group)
Age (years)	14 (12-16)	15.5 (1.5)	16.7 (1.44)
Sex (female)	50.9%	62.7%	65.0%
ALT (U/L)	39 (25-66)	23	38 (15)
BMI z-score	2.9 (2.5-3.2)	3.39 (0.92)	2.99 (0.37)
Waist circumference (cm)	121 (106-129)	111.9 (16.9)	119.5 (11.9)
BMI change (%)	-27.2 (-22.0; -31.7)	-16.1	-20.6
Waist circumference change (cm)	-22	-12.7	-15
ALT	16 (13-25)	-18.3% (no absolute values given)	24 (10)
Resolution of MASLD	78.2%	N/A	75.0%
Resolution of significant fibrosis	85.7%	N/A	90.0%
Limitations	No histological outcome No long-term outcomes after discharge Residential programme not widely available	Mean ALT normal, thus low MASLD prevalence No histology or imaging. MASLD not evaluated as an outcome measure	No long-term efficacy and safety outcomes in paediatric MASLD Small study population

ALT, alanine aminotransferase; CAP, controlled attenuation parameter; MASLD, metabolic dysfunction-associated steatotic liver disease.
Continuous data are presented as median (interquartile range) (Lefere) or mean (standard deviation) (Weghuber, Manco).

recent prospective 8-year follow-up of the Teen-LABS (Teen-Longitudinal Assessment of Bariatric Surgery) study reported that the prevalence of alcohol-related harm and alcohol-related problems (*i.e.* harm and/or dependence) significantly increased to 16%, and 19%, respectively, 8 years post-operatively.[76] Given that the developing brain of adolescents and young adults is particularly vulnerable to the harmful effects of alcohol, and that there is often social pressure to consume alcohol, the findings from this study are cause for concern. Still, the absence of a non-surgical control group limits strong causal inferences. GLP-1 receptor agonists have been shown to decrease alcohol consumption and craving in adults with alcohol use disorder;[77] whether such effects extend to adolescents is unknown.

Collectively, the studies presented here should be interpreted as hypothesis-generating signals rather than definitive proof of MASLD treatment response in paediatric populations. It should also be noted that included patients were not representative of those seen in tertiary paediatric hepatology clinics, and therefore provide limited guidance for the treatment of the most severe MASLD cases. Thus, an urgent need remains for controlled studies to determine the efficacy and safety of therapies with proven effect in adult MASLD. Nevertheless, the reported resolution of fibrosis and steatohepatitis is noteworthy, and supports the conjecture that paediatric MASLD may be a highly dynamic condition, which might not only progress rapidly to advanced fibrosis in some cases but also be more responsive to therapeutic interventions.

Therapeutic guidance for body weight change in paediatrics should reflect change in BMI z-score, especially in younger children still growing in stature. Recently, a reduction in BMI z-score >0.25 has emerged as predictive for clinical improvement of liver disease, being associated with higher odds of resolution of NASH[28] and significant reduction in ALT in children with NAFLD.[78]

Risk stratification

Liver biopsy remains the gold standard for diagnosis and risk stratification. A recent survey of paediatricians treating children with MASLD found that approximately 25% of paediatric gastroenterologists and 50% of paediatric hepatologists performed liver biopsy in these patients, although 75% reported using biopsy in ≤10% of paediatric patients with MASLD.[79] Liver biopsy retains a critical role in cases of diagnostic uncertainty, upon findings of more advanced liver disease, and for exact phenotyping and staging of MASLD. In addition, liver histology may inform treatment strategies and the monitoring of therapeutic response, which will become increasingly important as new pharmacological options emerge.

The diagnostic role of imaging for fibrosis assessment is equally debated. While vibration-controlled transient elastography (VCTE) correlates with fibrosis in children,[80,81] defining cut-offs is a point of contention. A meta-analysis of 650 children found the upper limit of normal to be 5.56 kPa.[82] However, children with diabetes, elevated ALT or – critically – obesity were excluded from the analysis. Therefore, it is

challenging to define a VCTE cut-off suggestive of fibrosis in children with obesity, and *a fortiori* in MASLD. Notably, a recent study suggested that VCTE values in children without fibrosis (Ishak stage 0) are higher in those with NAFLD than in those with other liver disease aetiologies (mean 6.2 kPa *vs*. 5.2 kPa).[80] For the detection of advanced fibrosis in children with histologically confirmed MASLD, two recent studies reported a modest to moderate diagnostic performance (AUC 0.67–0.76), with cut-offs of 8.0 and 8.5 kPa, respectively.[83,84] In addition, recent adult data demonstrate significant short-term variability in liver stiffness measurements (>2.0 kPa in 33% of patients), especially in patients with severe fibrosis.[85] These limitations mandate caution, and we suggest repeating VCTE examinations when stiffness is elevated to validate the results.

Non-invasive tests (NITs) are widely available and used for risk stratification of MASLD in adults; however, this area represents a clinically important unmet need in children, as existing risk scores for adults perform poorly in the paediatric setting. A European-wide biopsy-controlled study showed that existing NITs for the detection of fibrosis in paediatric MASLD did not perform better than a single measurement of serum ALT and thus lack the accuracy for use in clinical practice.[86] Therefore, the current paediatric guidelines recommend screening and management based on ALT levels.[87] However, ALT also lacks accuracy for fibrosis and may remain normal in a subset of children with significant disease. In one histological study, the prevalence of advanced fibrosis in children with normal ALT, mildly elevated ALT and highly elevated ALT was 12%, 9% and 15%, respectively.[88,89]

Novel algorithms for paediatric MASLD fibrosis, the Fibro-PeN and pFIB scores, have recently been developed. An online calculator for the latter is available on MDCalc (link: https://www.mdcalc.com/calc/10615/pediatric-fibrosis-score-continuous-pFIB-c). The incorporation of measures of glucose metabolism, lipid metabolism and hypertension together with anthropometric parameters and liver biochemistry[26,27] importantly reflects the greater risk of MASLD fibrosis in children with cardiometabolic comorbidities, as discussed above, and can thereby explain the scores' improved performance. These scores can be readily incorporated into clinical practice, as they are composed of routinely obtained clinical and biochemical variables.

In conclusion, no single marker for diagnosing or risk-stratifying paediatric MASLD is optimal, and all require further validation. Efforts to validate scoring systems and develop novel biomarkers or non-invasive tests (NITs) with high diagnostic accuracy are critically important. To facilitate the latter, international multicentre collaborations will be crucial to overcome key challenges – namely, low biopsy rates (and the resulting lack of a gold standard comparator and reduced statistical power) as well as cohort bias (*e.g*. ethnicity, *PNPLA3* carrier status).

Clinical management

Clinical guidance for paediatricians on the management of children and adolescents with MASLD has been issued by multiple national and international societies, the most recent being the AASLD clinical practice statement (CPS) by Xanthakos *et al.*[87] In this comprehensive work, an integrated approach to screening, diagnosis and management for children with suspected MASLD is proposed, with hepatology referral being triggered by (repeated) abnormal sex-specific ALT or clinical signs of acute liver disease.

In the following section, we propose a pragmatic, expert opinion-based framework to support longitudinal risk assessment that can guide care escalation. It diverges on aspects of the AASLD CPS, reflecting differences in healthcare organisation, referral capacity, clinical pathways and expert opinion between North America and Europe (Fig. 4). The proposed framework is applied after a diagnosis of MASLD has been established using standard clinical, biochemical, and imaging criteria. Its purpose is to assist clinicians in identifying children who may warrant closer monitoring, intensified lifestyle intervention, specialist input, or consideration of advanced diagnostics. We defined three clinical pathways, for patients at low, increased or high risk of clinically meaningful MASLD. Given the absence of a single, highly discriminative and validated non-invasive risk stratification tool for identifying the severity of paediatric MASLD, concordant abnormalities in several tools are likely more informative than any single cross-sectional measurement (Fig. 4). Conversely, discordant results should prompt repeat measurement and consideration of liver biopsy.

The guidelines agree that an ALT below the upper limit of normal corresponds to a low risk of significant fibrosis; although the exact value is debated, it is likely around 30 U/L in European cohorts.[4] A mildly elevated ALT (>30 U/L), abnormal NITs, and particularly their combination, support an increased-risk designation. Periodic reassessment of ALT and risk scores is warranted to refine stratification over time.

Patients with significant metabolic comorbidities should be considered at least at increased risk, even in the absence of abnormal NITs, given their increased likelihood of disease progression (discussed above). Importantly, the risk appears to be most pronounced with high ALT values (≥80 U/L),[88] youth-onset diabetes or clearly abnormal NITs, especially when more than one marker is concordantly abnormal. These patients can be stratified as high risk, unless there are mitigating clinical considerations. Some children with significant liver fibrosis might present with lower ALT levels;[88,89] in such cases, persistent mild abnormalities in ALT and/or NITs despite lifestyle interventions could warrant referral and re-stratification to a higher risk category.

This proposed framework differs from the recent AASLD CPS.[87] In many European settings, applying low ALT-based referral thresholds would result in a volume of specialist referrals that is not feasible. We therefore advocate a strategy of risk enrichment and longitudinal reassessment, taking into account regional variability in healthcare organisation and resource capacity. We explicitly propose this framework as a testable model; prospective cohort studies are required to evaluate its predictive value, clinical utility, and cost-effectiveness.

Consistent with the AASLD CPS,[87] we view multicomponent lifestyle intervention as the foundation of treatment for paediatric MASLD. The intensity and modalities of treatment should be guided by patients' risk stratification and response to treatment (Fig. 4). Whereas paediatric hepatologists or gastroenterologists provide most of the MASLD care in some

countries, in Europe, paediatric obesity care is commonly led by paediatricians with expertise in obesity or by paediatric endocrinologists. In addition, the organisation and setting (*e.g.* regional *vs*. university hospitals) of multidisciplinary obesity clinics in Europe vary considerably across health systems and countries. The proposed algorithm is intended to highlight where liver-focused expertise is essential – acknowledging that, depending on local context and resources, access to and availability of dedicated hepatology care may be limited.

Within this framework, we propose that patients at low risk of meaningful liver disease, barring other indications, can be evaluated and receive lifestyle intervention support by dedicated paediatricians. For patients at increased risk, an integrated, multidisciplinary care setting involving specialists in nutrition, physical activity and behaviour management is advised (where available). At this stage, beyond lifestyle management, further diagnostic work-up and staging of MASLD and related comorbidities is essential and should be guided by a paediatrician with expertise in MASLD. Finally, in addition to the aforementioned measures, we propose that patients at high risk, or those in whom previous approaches did not improve NITs despite weight loss, receive intensive treatment with more contact hours. Pharmacotherapy with an incretin mimetic (or other pharmacotherapies), approved for paediatric obesity but not MASLD specifically, may be considered when lifestyle management fails. Metabolic and bariatric surgery should be reserved for adolescents with severe obesity and liver disease for whom other therapeutic options have failed, and for whom waiting until adulthood or extended adolescent approval of resmetirom is not feasible. In these patients, a rigorous multidisciplinary work-up should be performed, as recommended in the AASLD CPS.[87]

Important areas for future research and advances in clinical management

Despite the recent advances in our knowledge on paediatric MASLD outlined in this paper, many clinical questions remain unsolved (Table 2). First, the field is hampered by a lack of validated NITs for steatosis, and especially, fibrosis. The novel pFIB and Fibro-PeN scores are promising and can be integrated into clinical practice, yet they also require further validation in diverse cohorts. An important need is the prospective validation of risk stratification pathways, such as the one we proposed here based on expert opinion. Moreover, it remains an open question whether novel NITs also possess prognostic value for liver-related events or cardiometabolic comorbidities. Direct biomarkers for fibrosis and steatohepatitis are equally unavailable; their identification requires translational efforts from promising markers in adults or, preferably, unbiased omics-based analysis on large sets of paediatric samples.

Second, despite emerging data from large natural history studies, gaps remain. In contrast to adult MASLD, the risk of MALOs might be as high as, or higher than, the cardiovascular risk, though this requires substantiation.

Third, several risk factors and novel pathophysiological concepts in adult steatotic liver disease have not yet been extensively investigated in the paediatric population. Alcohol consumption and even harmful drinking are prevalent in adolescents.[90] WHO data from a 2024 report indicate that one in five 15-year-olds experienced lifetime drunkenness, including 15% in the last 30 days.[91] Nevertheless, there are almost no data on MetALD in youth: the prevalence, prognostic impact, interaction with genetic risk factors, potential interventions and utility of alcohol biomarkers in this setting are largely unknown. In a similar vein, emerging evidence indicates that in the context of obesity, myosteatosis pathophysiologically underlies sarcopenia, a well-established risk factor for poor outcomes in liver disease. It has been posited that myosteatosis causes muscle IR and dysregulates myokine secretion, which through a muscle-liver axis can ultimately drive MASLD progression.[92] However, high-quality studies on myosteatosis, muscle strength and MASLD in children are currently lacking.

Last, as discussed in the previous section, specific pharmacological treatments are not available for minors, and the

Table 2. Important areas for future research and advances in clinical management – and our opinion on these.

Important areas for future research and advances in clinical management	Our opinion
Validation of NITs for steatosis and fibrosis	Coordinated efforts in international multicentre biopsy-proven cohorts will be necessary to validate and establish cut-offs for NITs for steatosis (*e.g.* CAP) and fibrosis (*e.g.* pFIB, Fibro-PeN, elastography). These studies should include sub-analyses for age, sex and anthropometrics and longitudinal follow-up measures. Ideally, long-term observations will be able to determine correlations with clinical outcomes, similar to NITs in adult patients with MASLD.
Prospective validation of clinical risk stratification pathways	Clinical frameworks for risk stratification, such as the proposed algorithm in this publication, need to be critically evaluated in real-world settings, and tested for their feasibility in diverse care settings and impact on long-term clinical outcomes.
Understanding the prevalence, distinct pathophysiological mechanisms and clinical relevance of MetALD in adolescents	Limited data exist on MetALD in adolescents, an entity that is likely underdiagnosed to date. Besides the need to deepen the understanding of liver-specific aspects, we believe areas of focus should be the study of psychosocial factors (*e.g.* depression, interaction of obesity and substance use disorder) and strengthening of prevention.
Conducting paediatric studies for drugs licensed for the treatment of MASH in adults	Compared to adult trials, these studies should account for the paediatric phenotype on histology (including scoring of portal inflammation).
Identification of zonation-specific pharmaceutical targets to address paediatric portal-type MASH	Future pharmacologic treatment of MASH should be personalised and tailored to the specific patient phenotype. This is of particular importance with regards to the higher risk of progression of portal-dominant disease.

CAP, controlled attenuation pattern; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic- and alcohol-related liver disease; NIT, non-invasive test.

number of clinical trials performed is relatively low. While semaglutide has been approved by the FDA and EMA for obesity treatment in adolescents, its effectiveness on MASLD in this age group has not been demonstrated. Overall, the evidence supporting therapeutic responses in hepatology-referred paediatric populations is very limited. High-quality, MASLD-focused paediatric interventional trials, for instance with liver-directed therapies such as the thyroid hormone receptor-β agonist resmetirom, are eagerly awaited. There is equally a pressing need to identify phenotype-specific regulators of (portal) inflammatory or fibrogenic programmes in paediatric MASLD and develop additional liver-specific drugs to complement life-style intervention.

Affiliations

[1]*Hepatology Research Unit, Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium;* [2]*Liver Research Center Ghent, Ghent University Hospital, Ghent, Belgium;* [3]*Department of Pediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands;* [4]*Department of Immunology & Immunotherapy, School of Infection, Inflammation and Immunology, College of Medicine and Health, University of Birmingham, UK;* [5]*Liver Unit (including small bowel transplantation), Birmingham Women's and Children's NHS, Foundation Trust, Birmingham, UK;* [6]*Department of Pediatric Gastroenterology, Nephrology and Metabolic Diseases, Charité – Universitätsmedizin Berlin, Berlin, Germany;* [7]*German Center for Child and Adolescent Health (DZKJ), partner site Berlin, Berlin, Germany;* [8]*Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ghent University Hospital, Ghent, Belgium*

Abbreviations

ALT, alanine aminotransferase; CAP, controlled attenuation pattern; CPS, clinical practice statement; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GWAS, genome-wide association studies; IR, insulin resistance; HR, hazard ratio; MALOs, major adverse liver outcomes; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic- and alcohol-related liver disease; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NIT, non-invasive test; OR, odds ratio; RCT, randomized controlled trial; SSB, sugar-containing beverages; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

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Conflicts of interest

Work in the lab of SL has received grants from Inventiva and Agomab. BK has consulted for Boehringer Ingelheim and Inventiva. The other authors do not report any conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SL, RDB and CAH conceptualized the review, wrote and edited the manuscript. SL and CAH produced the figures and tables. JPM, BGPK and PB wrote, reviewed and edited the manuscript.

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Supplementary data

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Author names in bold designate shared co-first authorship

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