Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disorder closely associated with the metabolic syndrome and is the most common cause of abnormal liver function tests (LFTs) in children. NAFLD is set to become the major cause of liver transplantation in adults, and while it is rare for children to develop end-stage liver disease from NAFLD, they may become cirrhotic as adults. Understanding and managing NAFLD in children may represent a method to intervene early and alter the disease process. Furthermore, children with steatosis require careful assessment as it may be secondary to other conditions (e.g., Wilson’s disease [WD]). For these reasons, pediatric NAFLD is of high importance to all gastroenterologists, hepatologists, and pediatricians.

NAFLD refers to a spectrum of diseases, ranging from hepatic steatosis (“simple steatosis” or nonalcoholic fatty liver [NAFL]) to nonalcoholic steatohepatitis (NASH) with or without fibrosis, to end-stage liver disease. Diagnosis requires radiological (or histological) demonstration of steatosis, exclusion of secondary causes, and no significant alcohol intake. Children present in three main ways: incidental abnormal LFT/
imaging, screening in obesity, and during investigation of abdominal pain, the cause of which is not clear.

In this review, we aim to provide an overview of pediatric NAFLD and discuss management in the context of recent guidance.

Epidemiology
Paralleling the dramatic rise in pediatric obesity worldwide, NAFLD has become a leading cause of chronic liver disease during the developmental age, and the main determinant on pediatric liver disease in Western countries. Several studies have demonstrated a prevalence of 3 to 10% in general pediatric populations, which increases up to 60 to 70% in individuals with metabolic comorbidities. However, NAFLD prevalence varies widely depending on geographical area and diagnostic methods used.

Initial population-based studies, which estimated the prevalence of pediatric NAFLD by determining aminotransferases or by ultrasonography in several countries, have indicated a prevalence range of 3 to 7%.

A recent attempt to examine NAFLD prevalence based on a meta-analysis of studies conducted in 76 different populations led to an estimate of 7.6% (95% confidence interval [CI]: 5.5–10.3%) in the general population and 34.2% (95% CI: 27.8–41.2%) in obesity clinics. However, there was a huge heterogeneity ($I^2 = 98$%), which was partly accounted for by sex distribution, difference in body mass index (BMI), and ethnicity, with NAFLD prevalence being higher in males, individuals with more severe adiposity, and Asians. Importantly, use of liver enzymes instead of imaging to diagnose NAFLD led to a significant underestimation of disease prevalence.

Indeed, obesity and metabolic syndrome features are the major risk factors for pediatric NAFLD. The prevalence of this condition is higher in overweight (gender- and age-specific BMI > 85th percentile) or obese (>95th) children as compared with normal weight pairs. However, due to the closest link to insulin resistance, central adiposity, which is accumulation of fat in visceral organs, plays a specific contribution in determining disease risk. Indeed, waist circumference, an easily available index of visceral fat, correlates with NAFLD independently of BMI.

Nutritional factors, such as excessive intake of calories, processed food, and a sedentary lifestyle, play a key role in the predisposition to liver fat accumulation, NAFLD, and progressive liver disease. Fructose intake has emerged as an important determinant of NAFLD risk, independently of total caloric intake, probably due to the ability to stimulate de novo lipogenesis (DNL).

Histology
From a histopathological point of view, NAFLD encompasses a disease spectrum ranging from “simple steatosis” (NAFL) to NASH, which is characterized by the presence of hepatocellular damage under the form of ballooning and mixed lobular inflammation, is associated with the activation of pericellular–perisinusoidal fibrogenesis, and evolves to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) in a variable proportion of cases. Other common features include Mallory–Denk bodies, megamitochondria, acidophili bodies, and iron accumulation.

NASH is associated with faster progression of liver fibrosis as compared with simple steatosis. Importantly, fibrosis stage is the main determinant of the prognosis of patients with NAFLD, concerning both liver-related and overall mortality.

Pediatric NAFLD displays some peculiar histological features compared with the adult form and, unlike the adult disease, is rarely influenced by some secondary lifestyle factors (e.g., alcohol and drugs), whereas others may have a more prominent role (e.g., fructose intake). Indeed, two different types of histological damage have been described in children with NAFLD: “type 1” NAFLD and “type 2” NAFLD. Type 1 NAFLD refers to the histological features classically associated with NASH in obese adults. These are represented by steatosis, that is, accumulation of neutral lipids within intracellular lipid droplets, which is generally more severe in the centrilobular area. This is accompanied by hepatocellular damage in the form of ballooning, lobular inflammation, and/
or perisinusoidal fibrosis. In contrast, type 2 NAFLD has been described more frequently during the developmental age and is characterized by steatosis with portal inflammation and/or periportal fibrosis. This form is more commonly observed in males and in children of Hispanic or Asian ethnicity as compared with Europeans. However, in the majority of series, it was found that although type 2 features are more frequent, most pediatric patients display overlapping features of type 1 and type 2 NAFLD, which can be considered the two extremes of a pathological spectrum. Importantly, portal inflammation, which is typical of type 2 NAFLD, has been associated with more severe fibrosis stage.

In a recent series of 440 Caucasian children with histological NAFLD, 12% had type 1, 22% had type 2, and 66% had overlapping features. Remarkably, those with type 2 had a more severe metabolic phenotype, with higher central adiposity and dyslipidemia. Furthermore, the presence of portal inflammation, a feature of type 2 NAFLD, was independently associated with waist circumference and clinically significant fibrosis, suggesting that this histological feature is involved in mediating faster progression of the disease.

Pathogenesis of Nonalcoholic Fatty Liver Disease in Children

The pathogenesis of NAFLD in adults has been well-defined. In contrast, the pathogenesis of NAFLD in children has not been the object of comparable attention, and thus its contributing factors have yet to be mapped comprehensively and fully understood. In the following sections, we describe the key pre- and postnatal factors that have been shown to affect the pathogenesis of NAFLD in children.

Prenatal Factors

Recent evidence has shown that there are some prenatal factors that are responsible for the pathogenesis of pediatric NAFLD, such as maternal obesity, metabolic syndrome during pregnancy, gestational diabetes, and low birth weight. This is supported by a series of well-conducted in vitro and in vivo mechanistic studies. It is a multifactorial process that results from a combination of biochemical factors (fetal insulin, lipid profile) and epigenetic modification, which influences hepatic DNL, mitochondrial function, and oxidative stress in hepatocytes, macrophages, and adipocytes. It is generally agreed that a "second hit" is required to initiate development of NAFLD as an adolescent or adult, for which the most important is a positive energy balance in the form of a high-fat/high-carbohydrate (Western) diet. Recent human studies showed that there is an association between maternal prepregnancy BMI and infant ectopic fat deposition in the liver and in the intra-abdominal cavity (Table 1). Magnetic resonance imaging (MRI) has been used to measure adiposity and hepatic liver fat in newborns of obese mothers and women with gestational diabetes. In one of these studies, a correlation was shown between gestational BMI and offspring hepatic lipid accumulation. Though it is unclear whether these same newborns go on to develop progressive NAFLD, a possible explanation for the ectopic hepatic fat deposition in these newborns may be that immature fetal adipocytes are not sufficiently developed to accommodate and store lipids crossing the placenta in excess, throughout pregnancy. Consequently, in the presence of maternal obesity or gestational diabetes mellitus (two states where nonesterified fatty acid concentrations might be expected to be increased), excess transference of maternal lipid will result in accumulation of fetal ectopic fat as the fetus is not able to expand adipose depots to buffer the increased transplacental lipid delivery. The presence and persistence of liver fat after birth have also been shown by us in a mouse model developed to investigate developmental programming of offspring NAFLD. In this study, we showed that increased dietary maternal fat intake in the mother from before conception primed the development of increased liver fat in the offspring mice in adulthood, even if the offspring mice had only ever eaten a normal chow (carbohydrate-rich, low-fat) diet from weaning until adulthood. Furthermore, adult mice that had been exposed in utero to increased dietary maternal fat intake in the mother from before conception, coupled with only consuming the same high-fat diet from weaning until adulthood, developed a florid form of NASH, which was a considerably more severe form of NAFLD than comparator mice who had only been exposed to the high-fat diet from weaning until adulthood. Additionally, mice exposed to gestational high-fat diet had decreased mitochondrial electron transport chain function, suggesting that a stressor in early life caused dysfunctional mitochondria that are less efficient at preforming mitochondrial β-oxidation, predisposing the mouse to hepatic fat accumulation and programming the development of NAFLD in adulthood. Another interesting prenatal factor associated with the pathogenesis of pediatric NAFLD is the perturbation of intrauterine environment during pregnancy. According to the "thrifty phenotype" hypothesis, intrauterine growth retardation can lead to several chronic conditions and metabolic disorders (such as NAFLD) later in life. We have shown that the "small for gestational age" state was significantly associated with severe liver steatosis (NAFLD Activity Score > 5) in childhood. Moreover, in a large epidemiological study, Sandboge et al have also shown that body weight at 2 years was negatively associated with NAFLD after adjusting for age, sex, and gestational age. Thus, the current evidence to date suggests that the intrauterine environment has the potential to have a powerful effect on the offspring’s future risk of developing NAFLD later in life.

Postnatal Factors

The postnatal factors predisposing to pediatric NAFLD are similar to those for adult NAFLD and include common factors such as obesity, hyperinsulinemia, and insulin resistance. In the presence of obesity, the potential for good adipose tissue expansion is fundamental for maintaining lipid homeostasis and insulin sensitivity and for protecting the lipid from increased lipid and inflammatory fluxes that have the potential for promoting development and subsequent progression of NAFLD. When the process of the adipose tissue expansion fails, there is an associated low-grade inflammation
associated with adipocyte autophagy and adipokine production. In this low-grade inflammatory state, there is increased flux of free fatty acids from the adipose tissue to the liver together with increased proinflammatory cytokines causing the recruitment of macrophages in adipose tissue, stimulating the production of TNF-α, IL-6, and reactive oxygen species, and increasing adipocyte lipolysis. In the liver, the combined effect of free fatty acids and adipokines coming from the adipose tissue increases endoplasmic reticulum stress with consequent activation of Kupffer cells, and this triggers liver inflammation, potentially promoting development of NASH. This inflammatory state triggers a cascade of hepatocyte injury and increases oxidative stress and mitochondrial dysfunction with consequent impairment of liver metabolic capacity. Hyperinsulinemia and insulin resistance also contribute to the development of NAFLD in adolescence as during puberty, children experience a physiological state of insulin resistance. In a large cross-sectional study, Moran et al studied 357 healthy children and adolescents who underwent hyperinsulinemic–euglycemic clamps. They showed that there are significant differences in insulin resistance between boys and girls and that insulin resistance increases significantly at Tanner stages 2, 3, and 4 but decreases to near prepubertal levels at Tanner stage 5.

Furthermore, while insulin resistance was related to BMI and anthropometric measures of fatness, these factors did not completely explain the insulin resistance that occurs during the Tanner stages of puberty. Moreover, in further work, the authors showed there were sex-related developmental changes in insulin resistance, which are independent of changes in adiposity. During the transition from late childhood through adolescence, insulin resistance in males increased in association with increased triglyceride concentrations and decreased high-density lipoprotein cholesterol levels. This phenomenon was noted despite a concurrent reduction in body fatness in male children, whereas the opposite effect was observed in female children. It is interesting to speculate that these sex-related developmental changes in insulin resistance may underpin not only differences in NAFLD prevalence between males and females in adulthood but also differences in cardiovascular risk between males and females in adult life.

In childhood, a physiological state of insulin resistance plus a sedentary lifestyle and the consumption of unhealthy food may increase obesity, decrease skeletal muscle oxidation of lipids, and promote hepatic DNL. In the presence of hyperinsulinemia that is associated with insulin resistance, acetyl-CoA carboxylase is activated by insulin, and acetyl-
CoA is converted into malonyl-CoA, which is the committed step in hepatic fatty acid synthesis. There are two important transcription factors that regulate DNL: sterol regulatory element-binding protein-1 (SREBP-1c) and carbohydrate response element-binding protein (ChREBP). These transcription factors regulate enzymes involved in fatty acid and triacyl glycerol synthesis. In addition, a high-carbohydrate diet, particularly one that contains high levels of dietary fructose, can increase hepatic DNL by increasing substrate supply and promoting the expression of SREBP-1c and ChREBP.

DNL is an energy-expensive process consuming 7 ATPs and 14 NADPH to generate each palmitate from acetyl-CoA. Consistent with this, fructose causes hepatic ATP depletion with resultant oxidative stress and potential for mitochondrial dysfunction.

Softic et al investigated the differential effects of glucose and fructose in a mouse model and showed that the addition of fructose to a high-fat diet was associated with increased expression of SREBP-1c and ChREBP and increased fatty acid synthesis, as well as hepatic insulin resistance. In contrast, when glucose was added to the high-fat diet, the authors found an increase in total ChREBP and liver triglyceride accumulation but not insulin resistance. In the same study, Softic et al studied hepatic expression of ketohexokinase (KHK), an enzyme that catalyzes the first step of intracellular fructose metabolism, in both mice and obese adolescents with NAFLD who were undergoing bariatric surgery. The authors found that KHK expression was increased twofold in mice whose high-fat diet was supplemented with fructose. This finding contrasted with their observations in mice whose high-fat diet was supplemented with glucose, where KHK expression did not increase significantly. In the adolescents, KHK expression was twofold higher in obese patients with NASH compared with obese patients without fatty liver. Thus, these data suggest that dietary fructose is associated with an increased expression of KHK favoring the production of acyl-CoA that contributes to the development of NAFLD through increased DNL. The high activity of KHK contributes to reduced cellular ATP by rapid phosphorylation of fructose, and, through regeneration of ATP in oxidative phosphorylation, hepatocytes become depleted in inorganic phosphate. The net effect is elevated uric acid production, which has been independently associated with advanced NASH histology in children.

Hepatic Outcomes

The long-term hepatic outcomes of pediatric NAFLD are not clear due to a lack of prospective natural history data, and few children undergo paired biopsies. The outcomes of NAFLD in adults are more defined, where data demonstrate that after over 30 years of follow-up, NAFLD is associated with increased all-cause mortality (hazard ratio [HR]: 1.3) and HCC in (OR: 6.6). Overall, liver-related events occur in < 10% of patients with NAFLD, but there is a strong correlation with fibrosis stage and outcome. In addition, it has been suggested that...
there is a group of “rapid progressors” who may develop severe fibrosis within 5 years, though it remains to be established whether this is due to sampling variability on repeat biopsy. Liver-related causes of death are third after cardiovascular disease and nonhepatic malignancy.

There are no robust data to determine whether this natural history holds true for pediatric NAFLD. It is also not well established what proportion of children with NAFLD continue to have NAFLD as adults. It is known that around a third of obese adolescents will become obese adults, but a follow-up study from pediatric to adult transition in NAFLD has not yet been reported.

Feldstein et al reported a retrospective cohort of 66 children with NAFLD in which 2 children underwent transplant for decompensated cirrhosis. This study has the longest follow-up, but its retrospective design and lack of data on method of diagnosis for children limit its conclusions. There have been other case series to suggest that severe fibrosis is possible while still a child; however, it is generally regarded that end-stage liver disease while under 16 years of age is unlikely to be secondary to NAFLD alone and should prompt a search for alternative diagnoses. It is worthy to mention that there are some specific circumstances, particularly acquired hypothalamic–pituitary insufficiency, that may be associated with rapid progression of fibrosis.

In adults, fibrosis is the sole predictor of long-term liver-related events. This finding has been reproduced in multiple cohorts, and noninvasive fibrosis scores (NAFLD fibrosis score, Fibrosis 4, BARD [BMI ≥28 kg/m², an AST/ALT ratio ≥0.8 and diabetes]) correlate with mortality. While similar scores exist in pediatric NAFLD (e.g., the pediatric NAFLD fibrosis index), it is not known whether they correlate with long-term outcome.

Data from randomized controlled trials demonstrate that stage 1 and 2 fibroses are readily reversible within 2 years. It is not known to what extent advanced fibrosis can regress in pediatric NAFLD.

Therefore, to accurately determine the long-term hepatic outcomes in pediatric NAFLD, natural history studies are required. These have recently been established on both sides of the Atlantic and are likely to require more than 20 years follow-up to quantify rates of HCC development and liver failure.

**Dangerous Liaisons**

There are several potential pitfalls in the diagnosis, monitoring, and management of pediatric NAFLD, which will be discussed in this section.

The most important point about diagnosing NAFLD in children is to exclude conditions masquerading as fatty liver. It is recognized that a variety of liver and systemic disorders may cause secondary steatosis, including those listed in Table 2. Schwimmer et al presented strong evidence for liver biopsy in children with suspected NAFLD. Out of 374 children referred from primary care, 255 underwent biopsy and 61 had a diagnosis other than NAFLD, most frequently autoimmune hepatitis. Children and adults with “lean” NAFLD, with BMI and waist circumference < 95 percentile, are more likely to have secondary causes for steatosis or NAFLD-associated polymorphisms. In very lean children with severe insulin resistance, lipodystrophy should be considered.

Differentiating between WD and NAFLD may be very challenging, and some pediatricians would argue that biopsy is the only method to truly exclude WD. Ceruloplasmin is a good screening test for WD and, depending on the threshold used, may have a negative predictive value of 99% (Table 3). However, a subset of patients may have normal ceruloplasmin, and missing the diagnosis can result in permanent neurologic damage. Therefore, a liver biopsy with dry weight copper improves the reliability of diagnosis, but can give a false-positive result (for WD) as cholestatic disorders can cause copper accumulation. Molecular genetics can be used to make a diagnosis of WD, but ATP7B can be affected by a variety of mutations; therefore, genetics cannot exclude the diagnosis.

Lysosomal acid lipase deficiency (LAL-D), also known as cholesterol ester storage disease, is a potential differential diagnosis.

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**Table 2** Some secondary causes of hepatic steatosis that should be excluded before making a diagnosis of pediatric NAFLD

<table>
<thead>
<tr>
<th>Secondary causes of NAFLD</th>
<th>Test</th>
<th>Abnormality</th>
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<tr>
<td>Hepatitis B and C, EBV, CMV</td>
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<td>IgG or IgM serology positive</td>
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<td>Wilson’s disease</td>
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<td>Increased IgG</td>
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<td>Alpha-1-antitrypsin deficiency</td>
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<td>Hereditary hemochromatosis</td>
<td>Serum iron studies</td>
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<td>Lipodystrophy and other insulin-resistance syndromes</td>
<td>Clinical examination</td>
<td>Reduced subcutaneous adipose</td>
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<td></td>
<td>Serum fasting insulin</td>
<td>Greatly elevated</td>
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<tr>
<td>LAL deficiency</td>
<td>Dry blood spot assay</td>
<td>Reduced LAL activity</td>
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</table>

Abbreviations: ANA, antinuclear antibodies; ASMA, antismooth muscle antibodies; CMV, cytomegalovirus; EBV, Epstein–Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; LAL, lysosomal acid lipase; NAFLD, nonalcoholic fatty liver disease.
diagnosis for NAFLD. This rare, autosomal recessive lysosomal disorder has a wide spectrum of clinical presentation.\textsuperscript{87} Wolman disease is the most severe form, with rapidly progressive liver failure in infants. A milder form presents in childhood or adults with hepatic steatosis, raised aminotransferases, raised low-density lipoprotein, and low high-density lipoprotein. Diagnosis is theoretically important because of the potential for treatment with sebelipase alfa.\textsuperscript{88} However, despite the possibility of misdiagnosis of LAL-D as NAFLD, or a role of LAL in NAFLD,\textsuperscript{89} to date there are no reports of identification of LAL-D in cohorts of children with fatty liver; therefore, its relevance to routine clinical practice remains to be established.

It is not clear how best to monitor pediatric NAFLD, but it is well established that aminotransferases are a poor marker of disease activity. Alanine aminotransferase (ALT) and aspartate aminotransferase fluctuate throughout the disease course and do not correlate with fibrosis,\textsuperscript{90} though they may show some correlation with NAFLD activity score.\textsuperscript{38} Blood often becomes most abnormal during the relatively insulin-resistant state of adolescence;\textsuperscript{91} therefore, a reduction of ALT without evidence of weight loss should not be relied upon as a reassuring finding.

Though the long-term cardiovascular and metabolic outcomes of pediatric NAFLD have yet to be formally quantified, these are likely to be the main burden of disease for patients in adult life.\textsuperscript{29,32} Therefore, hepatologists must remember that weight loss and improvement of insulin resistance are the most important management goals. Apart from therapies, targets at improving liver disease activity are discussed below.

### Management Program

The treatment of pediatric NAFLD can be divided into conservative, medical, and surgical approaches. As alluded to above, the determinants of successful management are not clear as the natural history of the condition is uncertain. The goals are multidimensional: improve the metabolic health of children to reduce their long-term cardiovascular risk and reduce liver-related clinical events, presumably by targeting fibrosis. Results from the major controlled trials in pediatric NAFLD are summarized in Table 4.

Weight loss is the core therapy for pediatric NAFLD and for all children with obesity.\textsuperscript{92} This may be achieved by dietary modification and/or physical activity. A variety of diets have been used in randomized and nonrandomized clinical trials. The most frequently used diet is a “low-fat” hypocaloric diet with 25 to 30 kcal/kg, 50 to 60% carbohydrate and 23 to 30% fat (with one-third saturated fat).\textsuperscript{80,93,94} A recent systematic review of dietary and physical activity interventions found that there was insufficient evidence to suggest any single method of weight loss, but that greater weight loss gave a larger improvement in noninvasive markers of NAFLD.\textsuperscript{95} In studies with biopsy endpoints, a reduction in age- and sex-corrected BMI is associated with an improvement in features of NAS and fibrosis.\textsuperscript{80}

There is recent physiological evidence to suggest that fructose restriction improves the metabolic profile of obese children and potential for treatment of fatty liver.\textsuperscript{12} Low-carbohydrate\textsuperscript{96} or low-fructose\textsuperscript{97} diet has only been used in pilot studies on pediatric NAFLD; however, there are several larger studies planned.\textsuperscript{98}

However, it must be remembered that even with close follow-up in well-conducted clinical trials, there is a relatively poor response to dietary and physical activity in childhood obesity.\textsuperscript{99} Compliance is poor, and participants with low uptake of advice have greater increases in aminotransferases.\textsuperscript{99} Therefore, NAFLD should ideally be managed in a multidisciplinary clinic that includes a dietitian, clinical nurse specialist, and clinical psychologist to give the best chance of achieving weight loss.

There are no approved pharmacological therapies of pediatric NAFLD.\textsuperscript{100} The main groups of agents that have been tested to date are antioxidants, metformin, polyunsaturated fatty acids (PUFAs), probiotics, and vitamin D.

The American Association for the Study of Liver Diseases (AASLD) guidance recommends vitamin E as the only therapy that is potentially efficacious in pediatric NAFLD.\textsuperscript{92} This is primarily based on data from the Treatment of NAFLD in Children (TONIC) trial that demonstrated an improvement in ballooning and overall NAS with vitamin E use, without any major adverse events.\textsuperscript{79} Other studies have used vitamin E in a variety of doses and durations but have been limited by not using protocolled paired biopsies,\textsuperscript{93,101} combination treatment,\textsuperscript{80,102} or differing weight loss between intervention arms.\textsuperscript{103} Overall, vitamin E is probably safe and may improve NASH activity, though it remains to be established if this translates into improved liver-related outcomes.

Results from a randomized trial of cysteamine bitartrate delayed release (CBDR) have recently shown modest improvements in lobular inflammation, and there was overall improvement in histology in participants weighing under 65 kg.\textsuperscript{104} It acts by increasing intracellular glutathione,
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Abbreviations: CBDR, cysteamine bitartrate delayed release; DHA, docosahexaenoic acid; DHA-Cho-VE, docosahexaenoic acid with choline and vitamin E; EPA, eicosapentaenoic acid; IGWLD, intragastric weight loss device; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PUFA, polyunsaturated fatty acids; US, ultrasound; VSL#3, a probiotic mixture.
which then scavenges oxygen free radicals. The evidence body for CBDR is smaller than that for vitamin E, and it is likely that further studies will be required before it is incorporated into guidelines.

Metformin has had more modest results, with some reports of improved radiological evidence of steatosis, but randomized biopsy data are limited than those from the TONIC trial. However, aside from its effects on the liver, metformin may be used by pediatric endocrinologists in children with insulin resistance and thus at a risk of type 2 diabetes. At this time, consensus guidelines do not recommend metformin as a primary treatment for NAFLD or NASH.

PUFAs, mostly docosahexaenoic acid (DHA) and eicosapentaenoic acid, are given with the aim of alerting the composition of the hepatic lipidome and reducing lipotoxicity. Noninvasive data are encouraging, where use of at least 250 mg per day for 6 months may result in reduction of radiological steatosis, but there are no biopsy data available to confirm these findings.

The evidence of use of probiotics is similar; a variety of regimens have been used in trials for pediatric NAFLD, but there are no studies with biopsy endpoints to date. Although there is a large body of evidence that confirms the association of intestinal dysbiosis with obesity and NAFLD, there are little data to support modulation of the microbiome as a primary treatment strategy.

The association of vitamin D deficiency with pediatric obesity, NAFLD, and NASH is relatively well established, and the use of replacement therapy in deficient children is logical. Indeed, in children deficient in vitamin D, replacement in combination with DHA does improve histology. However, it remains to be demonstrated whether children with acceptable 25-OH-D$_3$ (>20 ng/L) benefit from supplementary vitamin D. In addition, the risk of hypervitaminosis and resulting renal impairment must be considered.

Finally, bariatric surgery is a treatment option for severe pediatric obesity with comorbidities. Expert consensus recommends that NAFLD should not be a primary indication for weight loss surgery; however, evidence does suggest it to be of use, with potential for reversal of fibrosis. These findings are consistent with data from adults, though there were insufficient unbiased studies for a Cochrane review to recommend it as a primary treatment. However, the long-term data are clear that bariatric surgery improves the metabolic and cardiovascular outcomes for obese individuals, and therefore it may be part of the care for patients with NAFLD. The psychological effects of bariatric surgery are not to be underestimated, and there are emerging data on the impact that such operations have on patients later in adult life.

Therefore, weight loss is the primary treatment of pediatric NAFLD, and it appears that the method by which this is achieved does not affect the outcome. Vitamin E is the only drug treatment that may be a direct hepatic benefit, but pharmacological management of the liver is a small component of the overall care for children with the metabolic syndrome.

### Implications and Future Directions

The implications of these data are that pediatric NAFLD is increasing, and that these patients will become adults with end-stage liver disease or HCC in 10 to 30 years’ time. Weight loss is the only intervention demonstrated to have significant efficacy. Further investigation into the pathogenesis of pediatric NAFLD is needed to complement translational studies, with an aim to develop novel therapeutic strategies. There are only a few agents in trials in children, and drug development is progressing at a much slower rate than in adults.

Future directions must focus on establishing and expanding our understanding of NAFLD pathogenesis with a translational therapy in mind, for example, determining the microbiome phylogeny associated with less severe fibrosis and trialing probiotic therapy. It may also involve exploring whether recent advances in adult hepatology are also applicable to pediatrics, such as the role of VAP-1 in gut–liver axis, which has not yet been investigated in children. There is much heterogeneity in investigations of NAFLD, particularly in regard to the use of biopsy, and establishing biomarkers that correlate with histology progression and clinical outcomes remains a major target. Finally, despite weight loss being the primary treatment for NAFLD, minimal progress has been made in guidance on determining the optimal regimen of lifestyle changes.

In conclusion, despite major advances in understanding, research in pediatric NAFLD has not yet translated into patient benefit. It is an important condition with unmet scientific and clinical needs that requires urgent attention to slow the future epidemic of end-stage liver disease in adults.

### Abbreviations

- NAFLD = nonalcoholic fatty liver disease
- NAFL = nonalcoholic fatty liver
- NASH = nonalcoholic steatohepatitis

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All authors declare that there is no conflict of interest that could be perceived as affecting the impartiality of the reported research.

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### Authors’ Contribution

All authors equally participated to the manuscript, approved the final version as submitted, and agreed to be accountable for all aspects of the work.

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