### Title

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# The Progression and Natural History of Pediatric Nonalcoholic Fatty Liver Disease

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## Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States. Childhood NAFLD is associated with hepatic and non-hepatic morbidity and mortality. Non-hepatic associations included cardiovascular, metabolic, pulmonary and psychological disorders. Cardiovascular conditions observed in childhood include left ventricular dysfunction. Furthermore, childhood obesity is associated with greater odds of having hepatocellular carcinoma as an adult. Evidence suggests that NAFLD may begin in utero in children of diabetic mothers. However, NAFLD typically is diagnosed between the ages of 10–13 years. The actual onset of disease for most children is not known. At diagnosis 10–25% of children can have advanced fibrosis. In the most severe cases, children can progress within a few years to cirrhosis and end-stage liver disease. Quality longitudinal data of the natural history of pediatric NAFLD are limited. Available data suggest that children with NAFLD are at risk for higher mortality rates as young adults. However, NAFLD is a heterogeneous disease and natural history is expected to vary considerably from child to child. Thus rigorous efforts for structured diagnosis and follow-up are a priority to better develop the understanding of outcomes in pediatric NAFLD needed to provide accurate counseling to children and their families.

### Keywords

children; adolescents; nonalcoholic steatohepatitis; obesity; epidemiology; morbidity; mortality; outcomes

## INTRODUCTION

The question of interest this review will address is: What is the progression and natural history of NAFLD in children? The “natural history” of pediatric NAFLD is a complex

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topic, in that there are a paucity of longitudinal data in children with NAFLD. Understanding the natural history is also challenging because it is difficult to properly date the onset of disease. Currently there is insight about the range of disease severity at the time of biopsy diagnosis. With respect to progression over time, however, the data are lacking. One cannot assume that the time point of clinical diagnosis equals the starting point. In fact, for the majority of children with NAFLD, disease onset is unknown. Thus, a better understanding of the severity range, variability, and associations of pediatric NAFLD is important, as children may represent different time points on a history continuum.

In order to answer the broad question of the "natural history" of NAFLD in children, this article is divided into the following series of sub-questions to better address the comprehensive clinical phenotype:

1. When does NAFLD start in children?
2. What is the histologic starting point and severity?
3. What is the associated morbidity?
4. What is the longitudinal hepatic outcome?

## When Does NAFLD Start in Children?

Some data suggest that NAFLD begins in utero. Two studies have used neonatal magnetic resonance spectroscopy (MRS) to assess steatosis in infants born to mothers with gestational diabetes. Hepatic fat fraction (HFF) at 1–3 weeks of age was performed in neonates born to normal weight mothers (n=13) and was compared to those born to obese mothers with gestational diabetes (n=12). In this study, neonates born to obese mothers with gestational diabetes had a mean HFF that was 68% greater than infants born to normal weight mothers [1]. In a study by Modi and colleagues, 105 mother/neonate dyads were studied to determine if maternal body mass index (BMI) influenced neonatal HFF. Their key finding was that maternal BMI at conception was associated with neonatal HFF [2]. Similarly, the presence and severity of fetal hepatic steatosis was assessed in 33 stillborn babies of diabetic mothers compared to 48 stillborn babies of mothers without diabetes [3]. The diabetic mothers were more likely to be obese compared to controls (61% versus 33%). There was a substantially higher rate of hepatic steatosis in neonates born to mothers with diabetes (79%) versus controls (17%). It is not known, however, if the steatosis identified in the neonatal period progresses to the NAFLD that is typically diagnosed in adolescence.

There is evidence that post-natal factors may also have an effect in pediatric NAFLD. Breastfeeding, for example, has also been postulated to be protective for NAFLD. In a study of 191 Italian children with biopsy-proven NAFLD, hepatic steatosis, inflammation and hepatocyte ballooning and fibrosis were worse in children who were not breast-fed compared to breast-fed children [4].

If NAFLD begins in utero, at birth or soon after, one would expect a meaningful prevalence of NAFLD in very young children. However, in the Study of Child and Adolescent Liver Epidemiology (SCALE) this was not the case in the younger age group, where the prevalence of NAFLD for a ten-year period 1993–2003 was 0.7% in children aged 2–4 years

[5]. As opposed to a general population based study, there may be unique populations of young children with higher rates of NAFLD. In a study of obese preschool age children in Chicago, elevated alanine aminotransferase (ALT) was reported in 26% of obese children aged 2–5 years [6]. In a study of Hispanic children in Houston with a majority of the children being obese, ALT > 35 U/L was reported in 15% of 4–5 year olds [7]. Several gaps remain. In the 2 studies of ALT in pre-school children, it is not known how many actually had NAFLD. Also this population does not typically have symptoms and is well below the age at which guidelines recommend screening for NAFLD. These studies were also conducted more recently than SCALE and it is possible that the prevalence of NAFLD has increased. Notably, in NHANES the rate of elevated ALT in children in the United States nearly tripled from 3.9% in 1988–1994 to 10.7% in 2007–2010 [8].

In the United States, NAFLD is typically diagnosed in children between age 12 and 13 years. Numerous large and multi-center studies consistently report mean ages within this range [9–11]. The largest clinical reports from outside the US are from Italy and it is notable that many such reports have a mean age of 10 to 11 years at diagnosis [12, 13]. Whether there are differences in the age of onset by country or whether the difference in reported ages are due to differences in clinical practice are unknown. Moreover, whether the onset of NAFLD is truly between age 10 and 13 years or whether most of these children have NAFLD that is present earlier but clinically silent is also unknown. In order to answer this query, pre-pubertal should be followed *before* the typical age at diagnosis, to determine if these younger patients may have undiagnosed NAFLD. This was addressed in one study thus far in 123 pre-pubertal children ages 7–9, and those who were of normal weight had lower hepatic lipid load compared to obese children who were at risk for metabolic syndrome [14]. To track the progression of NAFLD that potentially begins during the perinatal period, infants with suspected steatosis born to diabetic mothers should be followed longitudinally for development or ongoing presence of NAFLD. This would be important clinically because if NAFLD onset is in the perinatal period it would have broader implications for pre-conception and pregnancy counseling as well as for earlier screening for NAFLD in infants born to diabetic mothers [15].

When NAFLD begins may also be contingent on genetic risks. Recently, with the advancement of genetic technologies, emerging data have elucidated several genetic risk associations with complex and sporadic diseases such as NAFLD. Genetics is a potential disease modifier, and the natural history of NAFLD and progression of disease may depend on patient specific genetic factors.

Although NAFLD pathogenesis and treatment options have been linked to environmental factors such as diet and physical activity, it is likely that NAFLD has a highly influential genetic component as well. There are two key observations that make a genetic link very plausible: (1) NAFLD has racial and ethnic differences and (2) NAFLD clusters in families. The prevalence of NAFLD varies with respect to race and ethnicity with the highest prevalence in Hispanic children and lowest in black children. In the SCALE study, NAFLD was present in 1.5% of black children, 8.6% of white children, 10.2% of Asian children, and 11.8% of Hispanic children [5]. In a heritability study, 33 obese children with biopsy proven NAFLD, 11 obese children without NAFLD, and 152 of their family members (parents,

siblings, 2nd or 3rd degree relatives) were evaluated. In obese children without NAFLD, 17% of siblings and 37% of parents had MRI HFF ≥ 5% compared to 59% of siblings and 78% of parents of children with biopsy-proven NAFLD. The heritability estimates (with 0 being no heritability and 1 representing a trait that is completely heritable) were 0.85 for the unadjusted dichotomous variable for NAFLD [16]. When HFF was taken as a continuous measure, the heritability was 0.58. Thus, there is an intricate interplay of environment and genetics that requires further investigation.

A NAFLD genome wide association study resulted in the discovery of a single nucleotide polymorphism (SNP) common variant allele in *PNPLA3* that confers susceptibility to NAFLD [17]. This SNP is highly associated with hepatic fat content, as measured by MRS, independent of BMI, diabetes, or alcohol use.

In adults, the variant PNPLA3 allele is associated with increased hepatic fat as well as histologic severity including fibrosis and cirrhosis [18]. Much remains to be understood in the pediatric population, however, as pediatric histology studies have demonstrated conflicting results. In a study of 223 pediatric patients from the NASH CRN there was no association of the *PNPLA3* locus with the histologic severity of NAFLD [19]. In contrast, in a study of 149 Italian children the *PNPLA3* variant allele was associated with histologic severity and presence of fibrosis [13]. Interestingly, there was an association with age in the NASH CRN cohort. Children carrying the G allele had a younger age at biopsy by 11 months; Hispanic ethnicity was also associated with younger age at biopsy [19], suggesting a more severe phenotype presenting at a younger age in those with a genetic risk. Similarly, in a biopsy study of Italian children with NAFLD, age at first visit was an independent predictor of fibrosis [13]. These data suggest that patients carrying the risk allele of PNPLA3 may benefit from screening at a younger age to capture those with NAFLD. Given the emerging importance of this susceptibility gene and other genes in NAFLD pathophysiology along with the paucity of pediatric data, there is a great need for well-designed studies with biopsy proven NAFLD in large pediatric cohorts. By understanding the genetics of NAFLD, it is possible this knowledge can aid diagnosis, guide treatment, and provide clinicians with tools to help with disease prognosis.

## What is the Histologic Starting Point and Severity?

Although the diagnosis of NAFLD is established at the time of biopsy, disease onset is unclear as this liver histology represents one time point of a chronic disease process. It is currently unknown if the disease begins with steatosis and progresses to NASH or if patients can start with NASH, as there is a lack of data for sequential biopsies over time. There is, however, an observed distribution of histologic severity at time of diagnosis. We performed a study of 347 overweight and obese children who were screened by their primary care providers per prevailing national guidelines and referred to Pediatric Gastroenterology in San Diego for suspected NAFLD based on elevated ALT. The combination of histology, clinical and laboratory features yielded a diagnosis of NAFLD in only 55% of these children. Among the 193 children with NAFLD, 41% had steatohepatitis and 17% had advanced fibrosis [20]. The severity of liver disease depends on the study population, as the distribution of disease severity is shifted in a population selected to have the disease. In the

SCALE study, a careful evaluation of liver histology from 742 children who had autopsies for rapid, unexpected deaths, demonstrated that of those children with NAFLD 23% had NASH and 9% had advanced fibrosis [5]. Two types of histologic patterns have been described in pediatric NASH. Type 1, more common in adults, is characterized by steatosis, ballooning degeneration, and perisinusoidal fibrosis. Type 2, more common in non-Caucasian children, is characterized by steatosis, portal inflammation, and portal fibrosis. Type 1 NASH has an older age of onset, mean age 13.5, while Type 2 NASH is more likely to be present in younger children, mean age 11.5 [21], suggesting these may be different diseases or a different disease process based on individual risk. Adolescents selected for extreme obesity may be biologically different that children with NAFLD who are seen in gastroenterology clinics. In the multi-center Teen LABS Study of adolescents undergoing bariatric surgery, 148 had intraoperative liver biopsies and the prevalence of NAFLD in this cohort was 59%, with only 10% of those with NAFLD having definite NASH and 0.7% having advanced fibrosis [22].

Many children with NAFLD have advanced disease at presentation. In a multi-center study from North America, of 108 children with NAFLD, 20% had advanced fibrosis at presentation [10]. In another US multi-center study in 2015 of biopsy-proven NAFLD, about 24% of children (mean age 13.3 years) had advanced fibrosis or cirrhosis at presentation [23]. When taken in aggregate, for children diagnosed with NAFLD through gastroenterology evaluation, a large number, 10–25%, have advanced fibrosis at initial presentation, and 25–50% have NASH. The data are limited regarding the evolution of NAFLD longitudinally after diagnosis and implications for prognosis in children with advanced stages of disease.

## What is the Associated Morbidity?

In addition to knowing the distribution of liver disease severity at diagnosis along with hepatic outcomes, it is crucial to also recognize the broader clinical phenotype, which is a key determinant not only of liver disease but also clinical morbidity and mortality. This section will focus on the morbidity associated with NAFLD including: psychosocial, hepatic, cardiovascular, pulmonary, and metabolic.

**Psychosocial—**Although NAFLD can be asymptomatic, children with NAFLD report many symptoms that are only elicited through broad and detailed evaluation. In a study of 239 children with NAFLD enrolled in the NASH CRN, irritability was the most common individual symptom (reported by 73% of children), followed by fatigue (68%), headache (60%), trouble concentrating (55%), and muscle aches or cramps (53%) [24]. Half of these children reported having 5 or more symptoms. Symptoms like pain and fatigue are more common in children with NAFLD, however it is unclear if these symptoms arise from the disease itself or are associated symptoms.

In addition to the physical symptoms associated with NAFLD, NAFLD can also affect the quality of life in children. In a NASH CRN study, 39% of children with NAFLD had impaired quality of life. Fatigue, trouble sleeping, and sadness were the symptoms that accounted for nearly half of the variance in quality of life scores compared to controls [24].

In a study of psychosocial outcomes in children with NAFLD, children with NAFLD had higher levels of depression compared to obese controls [25]. Children with NAFLD may have a substantial psychological burden and disease management should take potential psychosocial co-morbidities into account to provide patient-centered care.

**Hepatic—**In adults NAFLD is an increasingly common cause of hepatocellular carcinoma (HCC). The incidence of HCC in pediatric NAFLD is not known and is likely rare. There is one case report of HCC concurrent with NAFLD in a 7-year-old obese male [26]. However, having NAFLD in childhood may be an important risk factor for HCC in adulthood. In a Dutch study of a cohort of over 280,000 children followed for nearly 30 years, BMI at age 7 and 13 years was evaluated for longitudinal risk of HCC [27]. For every one point increase in BMI z-score at age 13, there was an increased risk of HCC of 33%. As opposed to BMI, there are no data specific to pediatric NAFLD. Although rare, HCC in the young adult is likely to increase given the percentage of children who have severe NAFLD (10–25% with advanced fibrosis). This is a large pool of children who are at increased risk of developing HCC over the next few decades, thereby leading to increased amount of HCC in early adulthood stemming from pediatric NAFLD. This can have a devastating impact as the current estimated 5-year survival rate for HCC is only 15% [28].

**Cardiovascular—**As more children with NAFLD are identified, more data are emerging about the associated cardiac and metabolic risks. NAFLD has been demonstrated to be more frequent in children with metabolic syndrome than in those without [29]. In a case-control study of 300 children, those with biopsy-proven NAFLD had a much higher cardiovascular risk profile including higher total cholesterol, LDL, triglycerides and systolic blood pressure than children with obesity alone. Similarly, in a cohort of 268 Italian children, obese children with ultrasound evidence of steatosis had a higher mean systolic blood pressure than those with obesity alone [30]. In a systematic, longitudinal study of blood pressure in 382 children with NAFLD, the prevalence of hypertension was 36% at the time of diagnosis. At 48-week follow-up, 21% of children with NAFLD had persistent hypertension. More severe steatosis was associated with odds of having hypertension. Of the children with severe steatosis, 45.2% had hypertension vs. 35.1% in the normotensive group [11]. There were higher rates of hypertension in NAFLD cross-sectionally and longitudinally. Hypertension may cause structural and functional cardiac changes in children with NAFLD.

Dyslipidemia is also common in children with NAFLD. In a study of 120 Italian children with NAFLD, 63% had elevated triglycerides and 45% had low HDL. Cali and colleagues evaluated serum lipids in 49 obese children and found that MRI HFF >5.5%, was associated with higher number of small dense LDL and VLDL particles, which denote a more atherogenic lipid profile [31]. Changes in lipids may also track with changes in liver histology. In a secondary analysis of TONIC, 173 children with NAFLD had a follow-up liver biopsy at 2 years and histologic improvement was associated decreases in non-HDL-cholesterol [32].

Carotid intima-media thickness (CIMT) is a quantifiable cardiovascular phenotype for subclinical atherosclerosis and cardiovascular risk, and has been evaluated in several studies of pediatric NAFLD. In 2 studies of obese children evaluated with liver ultrasonography,

there was higher CIMT in those with suspected hepatic steatosis [33, 34]. However in a study of children with biopsy-proven NAFLD there was no difference in CIMT compared to obese controls [35]. Due to small sample sizes and different methodology the relationship between pediatric NAFLD and CIMT is unsettled. Data regarding alterations in left-ventricular mass (LVM) are most consistent. In a study of 117 Turkish children with ultrasound evidence of liver steatosis, those with liver steatosis and obesity had higher LVM compared to lean children or those with obesity alone [36]. In a study of 14 lean, 15 obese and 15 obese children with MRS HFF > 5.6%, those with suspected NAFLD had significantly higher LV strain compared to children with obesity alone [37]. In a study of 136 Italian children by Pacifico and colleagues, children with obesity and biopsy-proven NAFLD had significantly greater left ventricular dysfunction and higher left ventricular mass [38]. Thus, children with NAFLD may be at increased risk of future heart failure and cardiovascular morbidity and mortality.

**Pulmonary—**Several recent studies have reported an association between NAFLD and obstructive sleep apnea. Obstructive sleep apnea results in a constellation of symptoms including daytime sleepiness, poor school performance and snoring. Apnea can produce hypoxia and oxidative stress, which is speculated to contribute to the progression steatohepatitis and fibrosis due to ischemia-reperfusion injury [39, 40]. There are a few studies of the association between NAFLD and obstructive sleep apnea in children. In a study of 25 obese children with NAFLD, polysomnography demonstrated obstructive sleep apnea in 60% of patients and those with OSA had more hepatic fibrosis [41]. In a study of 65 children with NAFLD, the prevalence of obstructive sleep apnea was also 60%. Obstructive sleep apnea prevalence and severity was associated with NASH and fibrosis stage. In this study, the association with histologic severity was present even for children with NAFLD who were not obese [42]. In contrast, a preliminary report of 53 children with NAFLD, obstructive sleep apnea was again shown to be common, but was not associated with the severity of NAFLD [43]. In order to develop a thorough understanding of sleep and obstructive sleep apnea in children with NAFLD, larger and longitudinal studies are needed. However, clinicians caring for children with NAFLD should be aware of the potential for undiagnosed obstructive sleep apnea.

**Metabolic—**The metabolic co-morbid conditions associated with pediatric NAFLD include metabolic syndrome, type 2 diabetes, low bone mineral density and low vitamin D 25-OH levels.

In a study of obese adolescents, those with MRI HFF > 5.5% were 3 times as likely to have metabolic syndrome compared to those with HFF< 5.5% [44]. In the series of 150 children with NAFLD compared to 150 children with obesity alone, children with NAFLD had higher fasting glucose and insulin [29]. Given that insulin resistance is important in the pathogenesis of NAFLD, the development of type 2 diabetes mellitus in children with NAFLD seems to be a logical progression. About 50% of children with type 2 diabetes have suspected NAFLD based on elevated ALT [45]. There are small studies in which the prevalence of type 2 diabetes is reported in children with NAFLD. Two studies looking at metabolic syndrome in biopsy-proven NAFLD have reported the prevalence of diabetes to

be near 2% [9, 46]. In a study of 43 children with biopsy-proven NAFLD, the prevalence of diabetes was 14% [47]. In a multicenter, retrospective study of patients with biopsy-proven NAFLD, the prevalence of diabetes was near 7%, and did not correlate with presence or absence of fibrosis on biopsy [48]. This is contrary to a study of adolescents undergoing bariatric surgery. In this study 148 children underwent an intraoperative liver biopsy and the detection of liver fibrosis was associated with pre-existing diabetes with an odds ratio of 3.56 [22]. Based on these data, the frequency of type 2 diabetes in children lies somewhere between 2 and 14% and whether diabetes is associated with the severity of NAFLD in children in unknown. Larger studies are needed to allow more stable estimates of prevalence and to clarify the relationship with disease progression.

Children with NAFLD may also be at increased risk for fractures. In a study of 38 children with NAFLD, obese children with NAFLD had significantly lower bone mineral density as measured by DXA compared to age, sex, and adiposity matched obese children without NAFLD [49]. Additionally, the bone mineral density for children with NASH was significantly lower compared to children with steatosis alone. In a cohort of 44 obese children with NAFLD, those with MRI HFF ≥ 5% had significantly lower bone mineral density of the lumbar spine than those with MRI HFF < 5% [50]. A subset of these patients had a liver biopsy and children with NASH had a lower bone mineral density than those without NASH. When to evaluate children with NAFLD for fracture risk is unknown.

Vitamin D insufficiency and deficiency have been associated with obesity and may also have an association with NAFLD in children. Vitamin D deficiency, defined as vitamin D 25-OH levels < 20ng/ml, was present in 50% of 64 children with NAFLD [51]. In a follow-up study of 73 overweight and obese Italian children with NAFLD, vitamin D 25-OH levels were significantly lower in those children with NASH than those without NASH [52]. In contrast, in a study of 102 children in the NASH CRN, although low vitamin D 25-OH levels were common there was no association with the histologic severity of disease [53]. Due to conflicting data, the role of vitamin D in pediatric NAFLD is unclear.

Pediatric NAFLD is a complex disease with potential for multi-organ complications and morbidity. Which of these complications arise directly as a result of liver disease and which are associated is challenging to determine. There are limited data regarding NAFLD and pediatric mortality. One retrospective study in Minnesota found children with NAFLD to be at higher risk for mortality compared to the general population, with a standardized mortality ratio of 13.6 [54]. More studies are needed to assess the long-term outcomes in children with NAFLD in order to reduce the disease burden and associated morbidities that have the potential to significantly reduce life expectancy in these children.

## What is the Longitudinal Hepatic Outcome?

Longitudinal outcomes data are lacking in the pediatric NAFLD population. What is known, however, is that children can present with cirrhosis at diagnosis and that progression from NASH to cirrhosis can be rapid in a subset of patients. This was first detailed in 2002 when Molleston and colleagues reported a 12-year-old child with NASH and mild fibrosis at initial diagnosis who progressed to cirrhosis with variceal bleeding, ascites, and mild encephalopathy by age 14 [55].

There are few longitudinal studies in pediatric NAFLD (Table 1). Several histology studies have a handful of patients with serial liver biopsies from their broader cohort, and some information can be gleaned from these studies. A study from 2008 included 18 patients between the ages of 7–19 years that had a follow-up biopsy at a mean interval of 28 months from initial diagnosis. In this study, 8 patients had no change in fibrosis, 7 patients had progression of fibrosis, and 3 patients had regression or disappearance of fibrosis after losing weight. Children who had resolution of fibrosis decreased their BMI by an average of 13% [56]. In another study from the Mayo Clinic in 2009, 5 children had repeat biopsies. The grade of steatosis and lobular inflammation either worsened or remained the same in all follow-up biopsies and there was progression of fibrosis in 4/5 patients. One patient without fibrosis at initial biopsy developed cirrhosis by 57 months and another without fibrosis at diagnosis progressed to stage 3 fibrosis by 82 months. Two patients with decompensated cirrhosis underwent liver transplant at follow-up. Both allografts had recurrence of NAFLD, and one of those two died after re-transplantation [54]. Recently a preliminary report has described data from UNOS/OPTN (United Network for Organ Sharing/Organ Procurement and Transplantation Network) for liver transplants in patients under the age of 40. There were 330 liver transplants performed for NASH in children and young adults [57]. Although most were not done before age 18, it is possible that many of these cases were the consequence of childhood NAFLD.

Longitudinal histology has been presented in two preliminary reports from the NASH CRN. In one study there were 58 children and in the other there were 102 children [58, 59]. Over a time interval of two years liver histology was stable in most children with NAFLD, however about 25% demonstrated progression in this short timeframe and 20% of children had advanced fibrosis on follow-up liver histology.

With these data it is clear that NAFLD in children can progress rapidly; it can present with severe cirrhosis and may ultimately require liver transplantation, which has additional implications for morbidity and mortality. Liver transplantation may not be uniformly curative, as data suggest recurrence of NASH and need for re-transplantation in a meaningful subset. Given the lack of larger and more systematic studies it is not known how frequently children with NAFLD should be monitored for progression of disease. What is clear, however, is severe fibrosis and cirrhosis are potential consequences of NAFLD and can occur within a few years of diagnosis in the most severe cases. Another unanswered question is determining which patients are at highest risk of rapid disease progression. Larger study populations are required to assess these outcomes data in pediatric NAFLD.

## CONCLUSIONS

NAFLD is the leading cause of chronic liver disease in children, thus more rigorous study of children with NAFLD over time is required in order to understand outcomes. Current observations and data can help elucidate portions of the natural history of NAFLD in children as we have data on the spectrum of histologic disease severity at diagnosis, evidence of multi-organ morbidity and a few longitudinal studies, but much about the progression of disease remains unanswered (Table 2). NAFLD typically is a disease of peri-puberty and adolescence because that is when children are diagnosed, however disease onset

is unknown. Does it start in utero for some and adolescence for others, and does genetics modify this age at presentation? Is it different diseases at different age groups?

With present data the field cannot accurately answer the question: What is the progression and natural history of pediatric NAFLD? In order to address this complicated question, studies with the following parameters would be needed: (1) very large sample size, (2) age, sex, racial, and geographic diversity, (3) per protocol follow-up histology, (4) standardized pathology evaluation, and (5) detailed phenotyping evaluation of BMI, liver transaminases, and NAFLD co-morbidities at each biopsy time point.

NAFLD is not exclusively a liver disease; rather, it is a systemic disorder in which the liver acts with many other organ systems, and understanding those phenotypes and outcomes are critical to understanding NAFLD. Children with NAFLD need to be followed at regular and frequent intervals to watch for advancement of their liver and associated diseases, and to determine need for repeat biopsies depending on the clinical situation. However, the timing of this interval is unknown. Much remains to be uncovered about the natural history and progression of this disease spectrum as currently biopsy only provides one time point in the chronic disease process. It is with additional longitudinal pediatric data that the clinician can accurately anticipate prognosis, determine length of follow-up and need for repeat liver biopsies, and provide informed counseling to patients regarding their chronic disease.

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## Abbreviations

| | |
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| **NAFLD** | nonalcoholic fatty liver disease |
| **NASH** | nonalcoholic steatohepatitis |
| **HCC** | hepatocellular carcinoma |
| **HFF** | hepatic fat fraction |
| **BMI** | body mass index |
| **NASH CRN** | nonalcoholic steatohepatitis clinical research network |
| **MRS** | magnetic resonance spectroscopy |
| **ALT** | alanine aminotransferase |
| **LDL** | low density lipoprotein |
| **VLDL** | very low density lipoprotein |
| **CIMT** | carotid intima media |

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| **UNOS/OPTN** | United Network for Organ Sharing/Organ Procurement and Transplantation Network |
| **DXA** | dual energy X-ray absorptiometr |

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**Key Points**

- Evidence suggests NAFLD may begin in the perinatal period in children of diabetic mothers.
- Pediatric NAFLD is typically diagnosed between 10–13 years of age.
- At diagnosis, among children with NAFLD, 25–50% of children have NASH and 10–25% have advanced fibrosis.
- Cardiovascular derangement in the form of left ventricular dysfunction and increased left ventricular strain and mass is observed in adolescents with NAFLD raising concern for premature cardiovascular morbidity and mortality.
- Obesity in childhood is a known risk factor for hepatocellular carcinoma in adulthood.

**Table 1**

Longitudinal Studies in Pediatric NAFLD

| Study | Year | Population | N | Age (y) | Follow-up (y) | Results |
|---|---|---|---|---|---|---|
| **Peer Reviewed Publications** | | | | | | |
| Molleston et al. [55] | 2002 | Single Site Pediatric Hepatology Clinic | 2 | 10 and 14 | N/A | • Patient 1 - initial biopsy with cirrhosis<br>• Patient 2 - initial biopsy with NASH, within 2 years with portal hypertension, ascites, esophageal varices and cirrhosis |
| A-Kader et al. [56] | 2008 | | 18 | Range 7–19 | 2.3 | • 8 patients - no change in fibrosis<br>• 7 patients - progression of fibrosis<br>• 3 patients - regression of fibrosis after losing weight<br>• 2 patients with complete resolution of steatosis and fibrosis after decrease in BMI (23.9 to 19kg/$m^2$ and 24.4 to 22.8kg/$m^2$) |
| Feldstein et al. [54] | 2009 | | 5 | mean 13.9 | 6.4 | • Grade of steatosis and lobular inflammation either worsened or remained the same in all follow-up biopsies.<br>• Progression of fibrosis in 4/5 patients<br>• 2 underwent liver transplant at follow-up - they presented with cirrhosis - one of those 2 died after re-transplantation |
| **Preliminary Reports** | | | | | | |
| Lavine et al. [59] | 2012 | NASH CRN | 58 | Range 8–17 | 1.8 | • Histologic improvement associated with improvement in ALT, insulin resistance, alkaline phosphatase, and BMI.<br>• 26% with progression of fibrosis on follow-up |
| Brunt et al. [58] | 2014 | NASH CRN | 102 | Range 11–17 | 2.2 | • 20% of patients with advanced fibrosis on follow-up biopsy |
| Alkhouri et al. [57] | 2015 | UNOS/OPTN database for 1987–2010 | 330 | Range 4–40 | N/A | Transplants for NASH:<br>• 14 children<br>• 20 patients between ages 18–25.<br>• 13 patients required re-transplantation for NASH recurrence |

Legend: NASH CRN – Nonalcoholic Steatohepatitis Clinical Research Network; UNOS – United Network for Organ Sharing; OPTN – Organ Procurement and Transplant Network

## Table 2

Current Understanding about the Progression and Natural History of Pediatric NAFLD

| What is Known | What is Unknown |
|---|---|
| **When Does NAFLD Start in Children?** | |
| Data support perinatal onset for some children of diabetic mothers | Does perinatal disease progress to adolescent NAFLD or is it a different disease? |
| Uncommon in children under 5 yrs | What is the disease process in younger children (perinatal and preadolescence)? |
| Average age at diagnosis in the U.S. between 12–13 yrs | Is the PNPLA3 gene associated with histologic severity in children? |
| PNPLA3 gene is associated with presence of NAFLD. | Does PNPLA3 risk allele modify disease (i.e. younger age of onset)? |
| **What is the Histologic Starting Point?** | |
| 25–50% of children with NASH at time of diagnosis | Is there a linear progression from steatosis to NASH or can NASH be a starting point of disease? |
| 10–25% of children can present with advanced fibrosis and cirrhosis | |
| **What is the Associated Morbidity?** | |
| NAFLD may be symptomatic: pain, fatigue and lower quality of life | Are these symptoms associated with or caused by liver disease? |
| NAFLD can lead to hepatocellular carcinoma. | Risk of hepatocellular carcinoma is unknown in pediatric NAFLD. |
| Higher cardiovascular risk profiles including hypertension, carotid intima media thickness, left ventricular dysfunction and dyslipidemia. | Need more data on pediatric mortality and NAFLD. |
| Metabolic co-morbid conditions include type 2 diabetes, low bone mineral density and low vitamin D 25-OH levels. | Is OSA associated with histologic severity or presence of NAFLD? |
| **What is the Longitudinal Hepatic Outcome?** | |
| Progression from NASH to cirrhosis in a subset of patients can be rapid. | Who is at risk for rapid disease progression? |
| Liver transplant is a potential outcome. | How frequently should patients be biopsied to monitor disease progression? |
| Liver transplant is not uniformly curative; recurrence of NAFLD can occur. | Very few longitudinal data exist with serial liver biopsies in the pediatric NAFLD population to make accurate conclusions about hepatic outcomes. |