



Epidemiology of Pediatric Nonalcoholic Fatty Liver Disease

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DEFINITION

Nonalcoholic fatty liver disease (NAFLD), defined as abnormal hepatic accumulation of macrovesicular fat in the absence of other etiologies, such as infection, autoimmune processes, hepatotoxic drugs, and storage disorders, is the most common cause of liver disease in children and teenagers.¹ NAFLD is also the most common cause of liver transplant in young adults (<50 years) in the United States, surpassing hepatitis C in 2019.² NAFLD is a spectrum of diseases, ranging from isolated steatosis with >5% hepatic steatosis, to nonalcoholic steatohepatitis (NASH), presence of steatosis, hepatocellular inflammation and injury, to fibrosis, and finally, to cirrhosis. There are two distinct histopathological subtypes of pediatric NAFLD: zone 3 and zone 1 NASH.^{3,4} Zone 3 NASH, characterized by pericentral steatosis, lobular inflammation, and ballooned hepatocytes, is consistent with the pattern of injury found in adult NASH. Zone 1 NASH, characterized by periportal steatosis, inflammation, and fibrosis, is twice as common

in children than zone 3 NASH. Differences in histopathological subtypes may be informative in predicting patterns of progression and prognosis of NAFLD in children.

PREVALENCE OF NAFLD IN CHILDREN

NAFLD is a common disease in children. Multiple measures of the prevalence of NAFLD in children exist in the literature. The Study of Child and Adolescent Liver Epidemiology (SCALE) was a histology-based study of children throughout the general population of San Diego, and the prevalence rate of NAFLD was estimated to be 9.6% among children aged 2 to 19 years.¹ In a histology-based study in New York, the prevalence rate of NAFLD in children was estimated to be 4.5%.⁵ Globally, a meta-analysis of pooled data using different methods, including liver chemistry, imaging, and/or histology, estimated the prevalence rate to be 7.6%.⁶ Thus, the prevalence rate of NAFLD in children is likely to be between 5% and 10% in the general population.

Abbreviations: ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SCALE, Study of Child and Adolescent Liver Epidemiology.

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Potential conflict of interest: J.B.S. received grants from Intercept and Genfit.

Received May 13, 2020; accepted August 2, 2020.

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Prevalence of NAFLD in children differs by sex; boys have higher rates of NAFLD than girls. In SCALE,¹ the prevalence rate of NAFLD was 11.1% in boys compared with 7.9% in girls. In the global meta-analysis, among children with normal body mass index, the prevalence rate of NAFLD was 9% in boys and 6.3% in girls.⁶ In a study specifically of children with obesity, NAFLD prevalence rate was also higher in boys than in girls, with a prevalence rate of 29.4% and 22.6%, respectively.⁷

Prevalence of NAFLD in children also varies by race and ethnicity. Children of Hispanic ethnicity (11.8%) and Asian race (10.2%) have a higher prevalence of NAFLD compared with white children (8.6%).^{1,8} In the United States, the prevalence rate of NAFLD in children is lowest in children of African American race with a prevalence rate estimate of 1.5%.¹

Finally, prevalence of NAFLD in children also differs by age. In SCALE,¹ children aged 15 to 19 years had the largest prevalence of NAFLD at 17.3%. Prevalence rate decreased by age group: 11.3% in children aged 10 to 14 years, 3.3% in children aged 5 to 9 years, and 0.7% in children aged 2 to 4 years. Clinically, NAFLD tends to present in the peripubertal period, with an average age of presentation between 12 and 13 years.³ Notably, the mean age at diagnosis has decreased over time. Several studies suggest that NAFLD may be increasing in very young children. It is unknown whether this trend reflects greater screening for disease in younger children or a true increase in the underlying rate of NAFLD in young children. This is evident in a 2014 study in young children where 26% of preschool children aged 2 to 5 years with obesity had elevated alanine aminotransferase (ALT) level.⁹ In addition, in a study in Hispanic children aged 4 to 5 years with obesity, 15% had elevated ALT level.¹⁰

RISK FACTORS FOR NAFLD IN CHILDREN

The largest risk factor for NAFLD is obesity. Obesity and NAFLD in children are often associated; however, they are not concomitant. In a 2019 study in 408 children with obesity using whole liver magnetic resonance imaging–proton density fat fraction, the prevalence rate of NAFLD was 26.0%, or roughly one in every four children.⁷ In the Teen LABS study of adolescents with obesity severe enough to warrant weight loss surgery, the prevalence rate of NAFLD was higher at 59%.¹¹ NAFLD also occurs in children without obesity. In a nationally representative sample of

adolescents with normal body mass index percentile, 8% had unexplained liver chemistry elevation that was interpreted as suspected NAFLD.¹²

Studies have also demonstrated that a child's *in utero* environment influences development of NAFLD. Compared with children with normal birth weight, children with low birth weight and high birth weight may have increased risk for development of NAFLD.¹³

In addition, NAFLD is heritable. A 2009 heritability study¹⁴ evaluated the families of children with and without NAFLD matched for overweight and obesity, and showed that 39% of the variability of liver fat from person to person is attributable to heritability.

PREVALENCE OF NASH/FIBROSIS

In addition to the prevalence of NAFLD itself, it is important to know the extent of disease severity. Prevalence estimates of NASH in children also vary based on population. In SCALE, nearly one-fourth of children with NAFLD had NASH in the general population.¹ In a 2013 study in a tertiary gastroenterology clinic, 54% of patients with biopsy-proved NAFLD had NASH.¹⁵ In a 2018 multicenter study of 623 children with NAFLD, 26% had definite NASH and 46% had borderline NASH.¹⁶ Thus, when studies are aggregated, approximately 20% to 50% of patients with NAFLD had NASH at the time of diagnosis.

Advanced fibrosis was demonstrated in 11.7% of children in a 2009 NASH Clinical Research Network study.¹⁷ Advanced fibrosis was demonstrated in 17% of children with NAFLD in a 2013 study of children from a tertiary gastroenterology clinic.¹⁵ In a 2016 study in 169 children with biopsy-proved NAFLD, 18% had advanced or bridging fibrosis.¹⁸ In a 2018 study of children with NAFLD, 15% of children aged 9 to 18 years had advanced fibrosis.¹⁶ Thus, approximately 10% to 20% of children with NAFLD in tertiary care have advanced fibrosis.

RISK FACTORS FOR NASH/FIBROSIS

Multiple factors also play a role in severity of NAFLD. In a study of 675 children with biopsy-proved NAFLD, 30% had prediabetes or type 2 diabetes.¹⁹ Prediabetes and type 2 diabetes are risk factors associated with more severe histological disease and greater odds of NASH among those with NAFLD. The prevalence rate of NASH was 34.2%

in patients with prediabetes and NAFLD compared with 43.2% in patients with type 2 diabetes and NAFLD. Birth weight is another risk factor because high birth weight is associated with higher odds for NASH and low birth weight is associated with higher rates of advanced fibrosis. Age also factors into severity of disease, with younger children more likely to have portal pattern of disease, which is associated with fibrosis.⁴

In addition, dysbiosis of the microbiome is a risk factor for development of NASH or more severe fibrosis. In a 2019 study of 87 children with biopsy-proved NAFLD compared with 37 children with obesity, but not NAFLD, the fecal microbiomes of children with NAFLD had lower diversity than controls. Patients with NASH had the lowest diversity in their microbiome.^{20,21}

Hypothalamic dysfunction and panhypopituitarism are also known risk factors for development of progressive NASH and advanced fibrosis.^{22,23} Patients with panhypopituitarism have increased leptin levels, which leads to increased tumor necrosis factor-alpha levels and a proinflammatory and fibrotic environment.

Finally, obstructive sleep apnea and hypoxemia are associated with greater stages of hepatic fibrosis.^{24,25}

CONCLUSION

NAFLD is a common disease in children, with a prevalence rate between 5% and 10%. Prevalence is higher in older children, boys, and children of Hispanic ethnicity or Asian race compared with younger children, girls, or children of black race. Obesity is one of the strongest risk factors for NAFLD in children, but most children with obesity do not have NAFLD. The prevalence rate of NASH and advanced fibrosis in children with NAFLD is ~20% to 50% and between 10% and 20%, respectively.

CORRESPONDENCE

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