Title

Incidence of Nonalcoholic Fatty Liver Disease in Children: 2009–2018

Journal

Pediatrics, 146(6)

ISSN

0031-4005

Authors

Sahota, Amandeep K

Shapiro, Warren L

Newton, Kimberly P

et al.

Publication Date

2020-12-01

DOI

10.1542/peds.2020-0771

Peer reviewed

Incidence of Nonalcoholic Fatty Liver Disease in Children: 2009–2018

Amandeep K. Sahota, MD,[a,*] Warren L. Shapiro, MD,[a,b,c,*] Kimberly P. Newton, MD,[b,c] Steven T. Kim, DO,[a] Joanie Chung, MPH,[a] Jeffrey B. Schwimmer, MD[b,c]

abstract

BACKGROUND AND OBJECTIVES: In 2007, the American Academy of Pediatrics recommended that children with obesity should be screened for nonalcoholic fatty liver disease (NAFLD). Population epidemiology reveals that NAFLD is common in children; however, little is known about rates of clinical diagnosis. In this study, we aim to determine screening practices, annual incidence, and clinical characteristics of NAFLD in children within an integrated community health system.

METHODS: Using electronic health records, we identified patients newly diagnosed (aged 5–18) with NAFLD on the basis of diagnostic codes from the 9th and 10th revisions of the *International Classification of Diseases*. We calculated screening rates and annual incidence rates of NAFLD from January 1, 2009, to December 31, 2018.

RESULTS: In this study, we evaluated 7 884 844 patient-years. Screening was performed in 54.0% of children with obesity and 24.0% of children with overweight. The results revealed 36 658 children aged 9 to 18 with overweight or obesity and alanine aminotransferase >30 U/L. Of these children, 12.3% received further workup for NAFLD. The incidence of an NAFLD diagnosis significantly increased over time, with 36.0 per 100 000 in 2009 and 58.2 per 100 000 in 2018 ($P < .0001$).

CONCLUSIONS: Our study of a large integrated health care system in southern California revealed that the incidence of NAFLD in children is increasing, although many children may remain undiagnosed.

[a]*Southern California Permanente Medical Group, Pasadena, California;* [b]*Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, School of Medicine, University of California, San Diego, La Jolla, California; and* [c]*Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Rady Children's Hospital, San Diego, California* [*]*Contributed equally as co-first authors*

Dr Sahota obtained funding, conceptualized and designed the study, coordinated data collection, and drafted the initial manuscript; Dr Shapiro conceptualized and designed the study, interpreted data, and drafted the initial manuscript; Dr Newton interpreted data and drafted the initial manuscript; Dr Kim interpreted data; Ms Chung collected data, performed statistical analysis, and drafted the initial manuscript; Dr Schwimmer conceptualized and designed the study, analyzed and interpreted data, drafted the initial manuscript, and supervised the study; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2020-0771

Accepted for publication Sep 9, 2020

Address correspondence to Jeffrey B. Schwimmer, MD, Director, Fatty Liver Clinic, Department of Pediatrics, UC San Diego, 3020 Children's Way, MC 5030 San Diego, CA 92123. E-mail: jschwimmer@ucsd.edu

WHAT'S KNOWN ON THIS SUBJECT: Nonalcoholic fatty liver disease (NAFLD) is reported to be highly prevalent in children; however, there is no information on the incidence of NAFLD and whether the incidence is changing or static. Society guidelines recommend a rigorous diagnostic process and screening for associated comorbidities.

WHAT THIS STUDY ADDS: The incidence of NAFLD increased over time. Half of the children with obesity were screened for NAFLD. Gaps in evaluating positive screening test results were identified. Children diagnosed with NAFLD from a community setting had high rates of diabetes, dyslipidemia, and hypertension.

To cite: Sahota AK, Shapiro WL, Newton KP, et al. Incidence of Nonalcoholic Fatty Liver Disease in Children: 2009–2018. *Pediatrics.* 2020;146(6):e20200771

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in children in the United States, with an estimated prevalence of nearly 10% in the general population.[1–4] Many investigators have speculated that the incidence of NAFLD in children is increasing, but this has not been formally studied. Identification of NAFLD in children is largely dependent on screening for NAFLD. Before the publication of screening guidelines, less than one-third of children with obesity in primary care were screened for NAFLD.[5] Recommendations were made to screen children for NAFLD on the basis of having overweight or obesity.[6] The rate of screening performed in primary care has not been evaluated since these recommendations were published.

Information regarding children diagnosed with NAFLD has been mostly from single-center, tertiary care settings or multicenter specialty networks. Such settings have the potential for referral bias. For example, in patients enrolled in the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network, children with NAFLD have high rates of important comorbid diseases, such as type 2 diabetes, dyslipidemia, and hypertension.[7–9] Whether these rates are representative of pediatric NAFLD or are due to more severely affected children being referred to research centers is unknown. Data regarding children diagnosed with NAFLD in a community setting are needed to better understand the range of the disease.

We studied the screening practices and incidence of NAFLD from 2009 to 2018 in a large health care organization broadly representative of the general population to address the following aims: (1) to determine rates of screening for NAFLD in children in pediatric primary care, (2) to determine the annual incidence of NAFLD in children, and (3) to determine the clinical characteristics of children diagnosed with NAFLD in a community setting.

METHODS

Population

We conducted a multicenter retrospective cohort study using electronic health record data from Kaiser Permanente Southern California (KPSC), which serves 4.8 million members through 12 medical centers with 300 satellite clinics. We identified members aged 5 to 18 years in each calendar year between January 1, 2009, and December 31, 2018. The Kaiser Permanente Institutional Review Board approved this study.

Case Definition for NAFLD

Patients diagnosed with NAFLD by a physician were identified by the *International Classification of Diseases, Ninth Revision* (571.8) and *International Classification of Diseases, 10th Revision* (K76.0 and K75.81) codes for NAFLD or NASH. The date of diagnosis was recorded. Patients were excluded if pregnant within 1 year of the diagnosis of NAFLD.

Data Collection

Data on patient demographics, comorbidities, laboratory, imaging, and vital signs were ascertained from the electronic health record and health plan administrative sources by using diagnoses and procedure codes. Values for alanine aminotransferase (ALT) and aspartate aminotransferase were collected at the time point closest to the date of diagnosis of NAFLD. Other data, including imaging and comorbidities, were captured for 12 months before and after the diagnosis. The method used by the treating physician to diagnose NAFLD was documented (laboratories, imaging, and histology). The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines recommend using ALT to screen children with obesity or overweight with additional risk factors for NAFLD beginning at age 9 years. Therefore, we recorded whether screening with ALT was performed at well-child visits for children aged 9 to 18 with overweight or obesity. The KPSC laboratory upper limit of normal (ULN) for ALT was 54 U/L. The screening result was considered positive at 2 different levels: one result was having an ALT level greater than the institutional ULN, and the other was an ALT level >30 U/L because this has been shown to be a clinically relevant cutoff for detecting NAFLD.[10,11] In patients with NAFLD, the completion of screening for diabetes (fasting glucose), dyslipidemia (lipid panel), and hypertension (blood pressure) was recorded.

Data Analysis

We performed descriptive statistics. Continuous data were reported as mean and SD or median and range. Means of continuous data were compared by using the Student's *t* test. Categorical data were reported in absolute values and percentages. Rates of screening for children with obesity or overweight were calculated, and rates of positive test results were evaluated for an ALT level >54 and an ALT level >30 U/L. A logistic regression model was developed to identify factors associated with children who were screened for NAFLD having additional workup for NAFLD after screening. A χ^2 test was used to test the association of demographic data between patients with NAFLD and the KPSC population. ALT was reported as both a continuous variable and a categorical variable by bins of multiples of the ULN. Analysis of variance was used to compare ALT distribution across the groups. The Cochran-Armitage test for trend was used to test the trend of NAFLD incidence rates over time. Nominal 2-sided *P* values <.05 were considered

to be statistically significant. Statistical analyses were performed by using SAS statistical software version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Participants

We identified all members aged 5 to 18 years on an annual basis from 2009 to 2018. The year-by-year numbers are shown in Table 1 and represent a total of 7 884 844 patient-years.

Screening

From 2009 to 2018, there were 206 117 children aged 9 to 18 with obesity who had a well-child visit, and an ALT screening was performed in 54.0% (111 207 of 206 117). The rate of a screening test with positive results was 8.9% when using an ALT level >54 U/L (n = 9891) and 28.4% when using an ALT level >30 U/L (n = 31 547). There were 212 710 children aged 9 to 18 with overweight that had a well-child visit, and an ALT screening was performed in 24.0% (50 951 of 212 710). The rate of a screening test with positive results was 2.2% when using an ALT level >54 U/L (n = 1105) and 10.0% when using an ALT level >30 U/L (n = 5111). Among children aged 9 to 18 with overweight or obesity and an ALT level >30 U/L, 12.3% received further workup for NAFLD. Logistic regression was performed to assess what factors were associated with having further evaluation for NAFLD (Table 2). Among children ages 9 to 18 with overweight or obesity who were screened for NAFLD, older age, higher BMI, and higher ALT level were all associated with greater odds of having further evaluation for NAFLD. In addition, among children screened for NAFLD, female patients had twice the odds of having further evaluation for NAFLD (odds ratio: 2.057; 95% confidence interval [CI]: 1.880–2.251). In addition, the odds were 38% greater of having further evaluation for NAFLD in the years 2012–2018 than during the years 2009–2011.

TABLE 1 Annual Membership and Incidence of NAFLD

Year	Members Aged 5–18	Incident Cases of NAFLD	Incidence Rate (Cases per 100c000)	95% CI
2009	776 877	280	36.0	31.9–40.5
2010	766 956	270	35.2	31.1–39.7
2011	773 883	313	40.6	36.1–45.2
2012	783 481	347	44.3	39.8–49.2
2013	773 999	311	40.2	35.8–44.9
2014	774 714	339	43.8	39.2–48.7
2015	793 056	397	50.1	45.3–55.2
2016	805 757	425	52.8	47.9–58.0
2017	816 392	449	55.0	50.0–60.3
2018	819 729	477	58.2	53.1–63.7

Incident NAFLD

There were 3608 children diagnosed with NAFLD from 2009 through 2018. As shown in Table 1, the incidence of NAFLD significantly increased over time ($P < .0001$). The incidence rate was 36.0 per 100 000 in 2009 and 58.2 per 100 000 in 2018.

Demographics and clinical parameters are shown in Table 3. The mean age at diagnosis was 14.1 ± 3.2 years; the distribution by age is shown in Fig 1. Patients with NAFLD were significantly more likely to be male than the general population of patients (59.9% vs 50.8%; $P <$ .0001). The distribution of race and ethnicity was significantly different from the general population, most notable for a higher frequency of children of Hispanic ethnicity (78.3% vs 43.3%; $P <$ .0001). The distribution of BMI classification was underweight (0.4%), normal weight (6.2%), overweight (8.7%), and obesity (84.8%). The distribution of ALT by multiples of the ULN is shown in Fig 2. Children with NAFLD had a mean ALT level of 99 ± 99 U/L.

TABLE 2 Odds of Further Evaluation for NAFLD for Children With Obesity Aged 9–18 Who Were Screened for NAFLD

Effect	Odds Ratio	95% CI
Age, y	1.11	1.10–1.13
Female sex	2.06	1.89–2.25
Race and ethnicity		
White, non-Hispanic	Reference	—
Asian, non-Hispanic	0.76	0.60–0.95
Black, non-Hispanic	0.53	0.39–0.72
Hispanic	0.87	0.76–1.01
BMI	1.03	1.02–1.04
ALT ULN		
≤1	Reference	—
>1–<2	4.63	4.20–5.11
2–<3	13.83	11.98–15.95
3–<4	29.73	23.77–37.18
4–<5	21.71	15.32–30.76
≥5	27.90	21.13–36.85
Years		
2009–2011	Reference	—
2012–2018	1.38	1.25–1.52

Age and BMI were continuous variables. ALT was evaluated in multiples of the ULN. The ULN for ALT was 54 U/L. ALT ≤ 1 × ULN (54 U/L) was the reference group, compared to >1–<2 × ULN (55–108 U/L), 2–<3 × ULN (109–162 U/L), 3–<4 × ULN (163–216 U/L), 4–<5 × ULN (217–270 U/L), and ≥5 × ULN (≥270 U/L). —, not applicable.

TABLE 3 Demographics and Clinical Characteristics of Children With NAFLD

Characteristic	All Cases (N = 3608)	ALT Level ≤54 U/L (n = 894)	ALT Level >54 U/L (n = 2714)	P
Age, y, mean (SD)	14.1 (3.2)	14.2 (3.1)	13.8 (3.2)	<.001
Sex, n (%)				<.001
Male	2162 (59.9)	419 (46.9)	1743 (64.2)	
Female	1446 (41.1)	475 (53.1)	971 (35.8)	
Race, n (%)				<.001
Asian American	181 (5.0)	26 (2.9)	155 (5.7)	
Black	71 (2.0)	26 (2.9)	45 (1.7)	
Hispanic	2825 (78.3)	667 (74.6)	2158 (79.5)	
Other	99 (2.7)	29 (3.2)	70 (2.6)	
Pacific Islander	27 (0.7)	6 (0.6)	21 (0.8)	
White	405 (11.2)	140 (15.7)	265 (9.8)	
Weight, kg, mean (SD)	85.5 (26.9)	86.3 (26.9)	86.8 (27.3)	.61
Height, cm, mean (SD)	161.1 (14.0)	161.6 (14.3)	161.3 (12.3)	.70
BMI, mean (SD)	32.2 (7.0)	32.2 (7.0)	32.5 (7.1)	.26
BMI percentile, mean (SD)	95.0 (13.3)	94.6 (14.4)	95.5 (12.8)	.13
BMI z score, mean (SD)	2.07 (0.73)	2.05 (0.75)	2.11 (0.69)	.06

Among children with NAFLD, 24.8% had an ALT level that was less than the laboratory ULN (ie, ≤54 U/L) and, as shown in Table 3, were significantly older (14.2 ± 3.1 vs 13.8 ± 3.2 years; $P < .001$) and more likely to be female (53.1% vs 35.8%; $P < .001$). The distribution of race and ethnicity was also significantly different between these 2 groups.

Diagnostic Approach

Patients were mainly diagnosed with NAFLD by imaging (61.1%; 2205 of 3608). Among those with an imaging-based diagnosis, ultrasonography was most common at 79.2% (1747 of 2205), followed by computed tomography (CT) scan at 17.4% (385 of 2208) and MRI at 3.3% (73 of 2205). A diagnosis was made by liver histology in 1.4% of patients. In the remaining 37.5% (1352 of 2205) of patients, NAFLD was diagnosed by the presence of elevated liver chemistry in the appropriate clinical context, with the exclusion of other potential etiologies. The distribution of ALT was significantly ($P < .0001$) different by the modality used to diagnose NAFLD. Children diagnosed with NAFLD by liver histology had the highest ALT level, and children diagnosed with NAFLD by CT scan had the lowest ALT level (median [interquartile range]: histology 141 U/L [80–227], ultrasound 84 U/L [51–129], laboratories only 73 U/L [41–109], MRI 55 U/L [30–107], and CT scan 38 U/L [24–72]). The distribution of age, sex, and BMI z score did not differ by diagnostic modality.

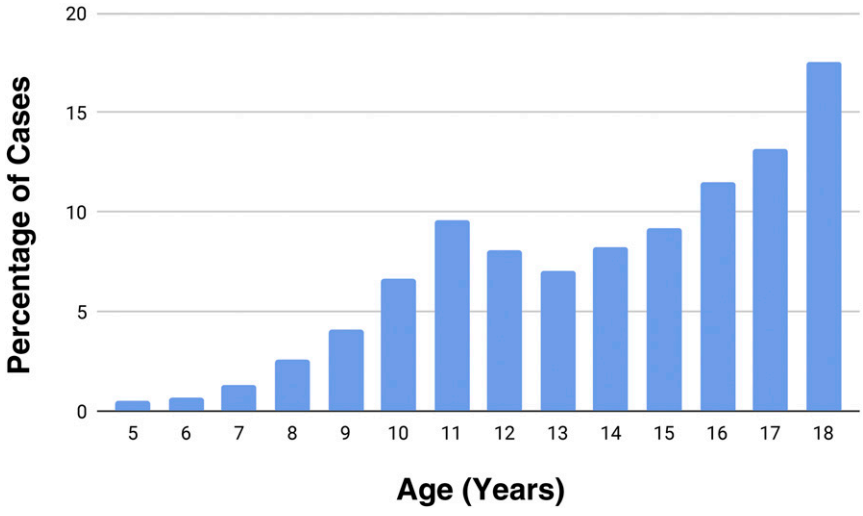

FIGURE 1
Age distribution of children with NAFLD at diagnosis. During the study period, there were 3608 children newly diagnosed with NAFLD. The histogram reveals the percentage of these patients by their age at the time of diagnosis.

Comorbidities

Among children with NAFLD, screening rates for diabetes, dyslipidemia, and hypertension were 47.3%, 14.4%, and 100%, respectively. Among those screened for diabetes, 10.9% (186 of 1706) had glucose ≥126 mg/dL, and 67.2% of these were diagnosed with diabetes. The overall rate of diabetes was 3.5% in children with NAFLD (125 of 3608). Of those children with diabetes, 19% (24 of 125) were classified as type 1 diabetes, and 81% (101 of 125) were classified as type 2 diabetes by their treating pediatric endocrinologist. Among those who were screened for dyslipidemia, clinically actionable, elevated low-density lipoprotein cholesterol was present in 15.4% (79 of 512) of patients, and clinically actionable hypertriglyceridemia was present in 73.5% (381 of 518). Systolic blood pressure of 130 to 139 mm Hg was observed in 13.3% (481 of 3608) of patients and ≥140 mm Hg in 6.2% (224 of 3608). Diastolic blood pressure of ≥80 mm Hg was observed in 10.3% (373 of 3608). Medication to treat hypertension was prescribed for 7.2% (260 of 3608) of patients.

DISCUSSION

We evaluated the screening practices and annual incidence of NAFLD in children within a large health

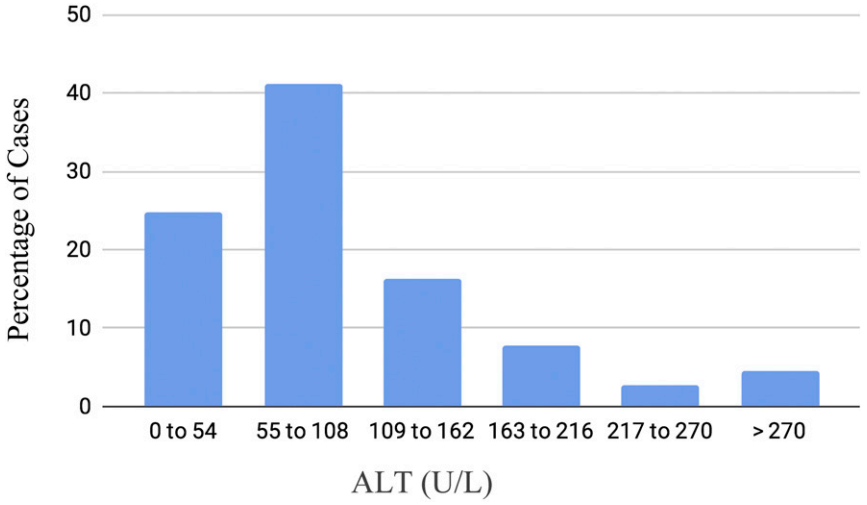

FIGURE 2
Distribution of ALT in children with NAFLD. For children with NAFLD, the distribution for ALT is shown by multiples of the ULN used in the clinical laboratory. The ULN for ALT was 54 U/L.

maintenance organization. The incidence of NAFLD increased significantly over the 10-year observation period. Despite this, a majority of children with NAFLD likely went undiagnosed. We performed screening in more than half of the children with obesity. However, most patients with a positive screening test result did not have further evaluation for NAFLD, perhaps because of the complexity of evaluating elevated ALT levels. Because of this, the approach to diagnosis was not standardized. In this study, liver imaging was the most common diagnostic modality used to confirm NAFLD. These children diagnosed with NAFLD in a community setting had high rates of associated comorbidities of diabetes, dyslipidemia, and hypertension.

In our study, the incidence rate of NAFLD in children increased by 62% from 36.0 per 100 000 in 2009 to 58.2 per 100 000 in 2018. Although authors of many studies have assessed the prevalence of NAFLD, to our knowledge, there have been no studies in which authors evaluate the annual incidence. We, therefore, cannot compare our findings of incidence directly to other studies. Although the absolute number of patients in our study is much larger than that of any other clinical series of pediatric NAFLD, the number of patients who would be expected on the basis of available prevalence data is higher. Prevalence estimates in children with NAFLD in the United States range from 4.5% to 9.6%.[4,12,13] On the basis of these rates, if all children were diagnosed with NAFLD, we would have expected 40 000 to 90 000 cases of NAFLD. In our study, we observed a higher rate for screening than previously reported; screening was done in more than half of the children with obesity and a quarter of the children with overweight. Although many children went unscreened, the number of children identified with an elevated ALT level >30 U/L (36 658) approached the predicted prevalence estimate range. Thus, although the incidence rate of NAFLD in children increased, we conclude that screening was underused, and it is likely that many children with NAFLD went undetected.

In addition to underscreening, a barrier to diagnosing NAFLD is the complexity of interpreting ALT values once obtained. There was a substantial gap between the number of positive screening test results and the number of children who received a diagnosis of NAFLD. This may be due to confusion in ALT interpretation based on differences between laboratory normal reference ranges and biologically based normal values for ALT. The median ALT ULN used for children nationally is 53 U/L, which is similar to what is used by KPSC (54 U/L). However, this is approximately twice the biological ULN for ALT, as determined by the SAFETY study: 26 U/L for boys and 22 U/L for girls.[5] Notably, in the later portion of our study, the odds of a child with overweight or obesity and an elevated ALT level receiving a full workup and being diagnosed with NAFLD increased. Additionally, there may be certain patient characteristics that influence interpretation of ALT values, because children with an older age, higher BMI, and higher degree of ALT elevation were more likely to receive an NAFLD diagnosis. The interpretation of ALT screening results by primary care pediatricians and resulting diagnostic decision-making were a large determinant as to whether NAFLD was ultimately diagnosed.

The evaluation necessary to confirm a diagnosis of NAFLD in a child who has an elevated ALT level is controversial and not straightforward.[14] The definitive diagnosis of NAFLD requires exclusion of other causes of steatosis by clinical history, laboratory studies, and histology. In clinical practice, the extent of the evaluation based on the degree and duration of an elevated ALT level and the decision of when to perform a liver biopsy is not standardized.[15,16] In the current study, a majority of children were diagnosed with NAFLD via abdominal ultrasound, and this is likely the most common method used to support a diagnosis of NAFLD at other

institutions as well. However, ultrasound does not measure hepatic steatosis directly. The relationship between changes on ultrasound-derived images and liver fat is inferred, thus making it subjective and nonquantitative.[17] How to balance these limitations of ultrasound with the limitations of more expensive or invasive diagnostic tools remains a work in progress for the field. The current data from a large, real-world integrated health system reveal that there is a gap between guidelines that is based largely on expert opinion and pragmatic decisions in patient care that needs to be addressed to better understand the true scope of this problem and inform optimal diagnostic and management strategies.

Screening of children with NAFLD for comorbidities was high for hypertension, moderate for type 2 diabetes, and low for dyslipidemia. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends that all children with NAFLD should be screened for type 2 diabetes, dyslipidemia, and hypertension.[18] Nationally, pediatric gastroenterologists report that 80% screen for type 2 diabetes, 72% screen for dyslipidemia, and 56% screen for hypertension.[19]In our study, the rate of screening for hypertension was much higher. This shows the value of universal blood pressure measurement within a large health care system. In previous studies, authors have reported that up to one-third of children with NAFLD have elevated blood pressure.[7,20] In the current study, the rate of overt hypertension requiring treatment with medication was 7.2%, which is much higher than the rate of 2.4% for the general pediatric population.[21] Unlike hypertension, less than half of the children with NAFLD were screened for diabetes. In our cohort, if all children with NAFLD had been screened for diabetes, the prevalence of type 2 diabetes would have been close to 6%. This is similar to the rate in a national multicenter study of children with biopsy-proven NAFLD, which reported that the prevalence of type 2 diabetes was 6.5%.[8] Although the rate of screening for dyslipidemia was low at 14.4%, the rate of detection of clinically actionable low-density lipoprotein cholesterol observed was once again similar to that observed in national multicenter data: 15.4% at KPSC and 14% in the NASH Clinical Research Network.[9] The comorbidities of hypertension, type 2 diabetes, and dyslipidemia are an important component of the morbidity and mortality associated with NAFLD. These data reinforce the high prevalence of these conditions in children with NAFLD and support the importance of screening as recommended in clinical guidelines.

To our knowledge, this study is the first to evaluate the incidence of NAFLD in children. Our study was strengthened by evaluating the incidence annually for a decade. An additional strength was the use of the KPSC database. Using the database, we studied nearly 8 million patient-years that were broadly representative of the general population. The prevalence of patients of Hispanic ethnicity within KPSC was similar to that of southern California and the southwestern United States but higher than in other areas of the nation. Therefore, the rates of NAFLD observed may differ elsewhere. The database also allowed us to carefully document comorbidities. The study was limited by the realities of clinical practice. We were able to document children who were diagnosed with NAFLD but observed that many children may have remained undiagnosed. We further observed that the reference standard diagnosis of NAFLD to include liver histology was infrequently used; thus, some diagnoses may have been inaccurate, and we are not able to comment on what fraction of the population with NAFLD had NASH and/or fibrosis.

The number of children diagnosed with NAFLD each year increased over a decade, and the annual rate rose faster in the more recent years. Health care systems and physicians will need to prepare for these growing numbers of children with chronic liver disease. The identification of all children with NAFLD would require improvement in screening practices as well as the evaluation of elevated ALT levels uncovered by screening. Notably, children diagnosed with NAFLD in a large, community-based health maintenance organization setting have similar rates of important comorbidities, as previously reported in tertiary care centers. Physicians caring for children with NAFLD should be prepared to identify and address type 2 diabetes, dyslipidemia, and hypertension. Optimal recognition and management of NAFLD and its associated comorbidities will require systematic coordination between primary care pediatrics and subspecialty pediatrics, including pediatric gastroenterology.

ABBREVIATIONS

ALT: alanine aminotransferase
CI: confidence interval
CT: computed tomography
KPSC: Kaiser Permanente Southern California
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis
ULN: upper limit of normal

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Sahota has clinical trial agreements with Allergan and Bristol Myers Squibb. Dr Schwimmer has grant funding from Galmed Pharmaceuticals, Intercept Pharmaceuticals, and Genfit; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by grants from the Regional Research Committee of Kaiser Permanente Southern California (grant KP-RRC-20190403) and the National Institutes of Health (grant UL1TR001442). The funders did not participate in the conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation of the article. The content is solely the responsibility of the authors and does not necessarily represent the official views of Kaiser Permanente Southern California or the National Institutes of Health. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *J Pediatr*. 2013;162(3):496–500.e1
2. Temple JL, Cordero P, Li J, Nguyen V, Oben JA. A guide to non-alcoholic fatty liver disease in childhood and adolescence. *Int J Mol Sci*. 2016;17(6):947
3. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006;118(4):1388–1393
4. Fernandes DM, Pantangi V, Azam M, et al. Pediatric nonalcoholic fatty liver disease in New York City: an autopsy study. *J Pediatr*. 2018;200:174–180
5. Riley MR, Bass NM, Rosenthal P, Merriman RB. Underdiagnosis of pediatric obesity and underscreening for fatty liver disease and metabolic syndrome by pediatricians and pediatric subspecialists. *J Pediatr*. 2005;147(6):839–842
6. Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(suppl 4):S164–S192
7. Schwimmer JB, Zepeda A, Newton KP, et al.; Nonalcoholic Steatohepatitis Clinical Research Network. Longitudinal assessment of high blood pressure in children with nonalcoholic fatty liver disease. *PLoS One*. 2014;9(11):e112569
8. Newton KP, Hou J, Crimmins NA, et al.; Nonalcoholic Steatohepatitis Clinical Research Network. Prevalence of prediabetes and type 2 diabetes in children with nonalcoholic fatty liver disease. *JAMA Pediatr*. 2016;170(10):e161971
9. Harlow KE, Africa JA, Wells A, et al.; Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). Clinically actionable hypercholesterolemia and hypertriglyceridemia in children with nonalcoholic fatty liver disease. *J Pediatr*. 2018;198:76–83.e2
10. Schwimmer JB. Clinical advances in pediatric nonalcoholic fatty liver disease. *Hepatology*. 2016;63(5):1718–1725
11. Yu EL, Golshan S, Harlow KE, et al. Prevalence of nonalcoholic fatty liver disease in children with obesity. *J Pediatr*. 2019;207:64–70
12. Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology*. 2005;42(3):641–649
13. Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *PLoS One*. 2015;10(10):e0140908
14. Kohli R, Sunduram S, Mouzaki M, et al. Pediatric nonalcoholic fatty liver disease: a report from the Expert Committee on Nonalcoholic fatty Liver Disease (ECON). *J Pediatr*. 2016;172:9–13
15. DeVore S, Kohli R, Lake K, et al. A multidisciplinary clinical program is effective in stabilizing BMI and reducing transaminase levels in pediatric patients with NAFLD. *J Pediatr Gastroenterol Nutr*. 2013;57(1):119–123
16. Hegarty R, Deheragoda M, Fitzpatrick E, Dhawan A. Paediatric fatty liver disease (PeFLD): all is not NAFLD - pathophysiological insights and approach to management. *J Hepatol*. 2018;68(6):1286–1299
17. Awai HI, Newton KP, Sirlin CB, Behling C, Schwimmer JB. Evidence and recommendations for imaging liver fat in children, based on systematic review. *Clin Gastroenterol Hepatol*. 2014;12(5):765–773
18. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of pediatric gastroenterology, Hepatology and nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr*. 2017;64(2):319–334
19. Shapiro WL, Yu EL, Arin JC, et al. Clinical practice approach to nonalcoholic fatty liver disease by pediatric gastroenterologists in the United States. *J Pediatr Gastroenterol Nutr*. 2019;68(2):182–189
20. Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Circulation*. 2008;118(3):277–283
21. Bell CS, Samuel JP, Samuels JA. Prevalence of hypertension in children. *Hypertension*. 2019;73(1):148–152