Published in final edited form as:
J Pediatr. 2022 January ; 240: 280–283. doi:10.1016/j.jpeds.2021.09.033.

The Prevalence of Elevated Alanine Aminotransferase Levels Meeting Clinical Action Thresholds in Children with Obesity in Primary Care Practice

Stephanie J. Wu, MD[1], **Jeanne A. Darbinian, MS, MPH**[2], **Jeffrey B. Schwimmer, MD**[3,4], **Elizabeth L. Yu, MD**[3,4], **Nirmala D. Ramalingam, MPP**[1], **Louise C. Greenspan, MD**[5,6], **Joan C. Lo, MD**[2,6]

[1]Department of Medicine, Kaiser Permanente Oakland Medical Center, 3600 Broadway, Oakland, CA, 94611, USA

[2]Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA, 94612, USA

[3]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, University of California San Diego School of Medicine, La Jolla, California, 92093 USA

[4]Department of Gastroenterology, Rady Children's Hospital, San Diego, California, 92123 USA

[5]Kaiser Permanente San Francisco Medical Center, San Francisco, CA, 94115 USA

[6]The Permanente Medical Group, 1950 Franklin St, Oakland, CA, 94612, USA

Keywords

nonalcoholic fatty liver disease, NAFLD; obesity; children; race, ethnicity; alanine aminotransferase, ALT

Using a clinically actionable threshold for alanine aminotransferase to define suspected nonalcoholic fatty liver disease (NAFLD) in US children with obesity, the risk of suspected NAFLD was highest for Asian and Hispanic race/ethnicity, male sex, and severe obesity.

The incidence of nonalcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in children, is increasing rapidly (1–3). Estimates are that NAFLD is present in 5-10% of all children in the United States (2, 4). The prevalence appears to vary markedly by race and ethnicity. Rates are highest in Hispanic children and lowest in Black children (2). Data for Asian children in the U.S. are limited. NAFLD may progress to end stage liver disease and is now the fastest rising cause of liver transplantation in young adults (5–8). In addition to liver-related morbidity and mortality, NAFLD is associated with multiple extrahepatic comorbidities such as type 2 diabetes, hypertension, dyslipidemia, and mental health conditions (5, 9–12). Because of the long-term complications of NAFLD in children and young adults, pediatric societies recommend screening for NAFLD in all children ages 9-17 years with obesity using serum levels of alanine aminotransferase (ALT) (5). The North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) recommends further evaluation if the screening ALT level is ≥44 U/L in females or ≥52 U/L in males (5). Studies have not evaluated the rate of positive screening tests for NAFLD using these cutoffs in a primary care setting. Moreover, studies have not included settings with Asian American representation. This lack of data has implications on health disparities research, as well as clinical implications when screening among diverse populations in the US. The aim of this study was to evaluate the prevalence of positive screening tests for NAFLD in children with obesity using the society guidelines thresholds with specific attention to differences in prevalence by race and ethnicity.

METHODS

We conducted a cross-sectional study within Kaiser Permanente Northern California (KPNC), using electronic health record data from children aged 9-17 years with body mass index (BMI) ≥95th percentile at well-child visits (2012-2014) and screening ALT measurement within one year of the visit. The study was approved by the KPNC Institutional Review Board and a waiver of informed consent was obtained.

Obesity was defined as BMI percentile ≥95th percentile calculated from well-child height and weight measures and was classified as mild to moderate (BMI 100% to <120% of the 95th percentile) or severe (BMI ≥120% of the 95th percentile) (13). Race and ethnicity data were derived from health plan databases and the electronic health record and categorized as Asian or Pacific Islander, Black, Hispanic, or non-Hispanic White. Asian and Pacific Islanders included those of East, Southeast, and South Asian ethnicity and Native Hawaiians or Pacific Islanders. Less than 5% of children had race classified as other or unknown and they were excluded from multivariable analyses.

The selection of ALT threshold to use in screening for NAFLD is controversial. In the Screening ALT for Elevation in Today's Youth (SAFETY) study (14), the biological upper limit of normal for ALT was determined to be 22 U/L in females and 26 U/L in males. In a study of children who were screened for NAFLD by their primary care pediatrician and referred to pediatric gastroenterology, having an ALT two times these biological cutoffs was shown to have high sensitivity for NAFLD, nonalcoholic steatohepatitis (NASH) and advanced fibrosis (15). The specificity was low, as repeat measures were needed to demonstrate chronicity and additional evaluation was needed to determine the correct diagnosis. The NASPGHAN guidelines recommended that children who had a screening ALT level above these thresholds should have ALT repeated and if the value remained above these thresholds then should have additional evaluation for the etiology of ALT elevation (5). We therefore defined elevated ALT based on the cutoffs that are recommended to guide clinical action (ALT ≥44 U/L for girls, and ≥52 U/L for boys) (5).

The prevalence of elevated ALT levels, with 95% confidence intervals (CIs), was reported for each demographic subgroup by sex and obesity severity. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% CIs to examine independent associations of race and elevated ALT, adjusting for age, sex, and obesity severity. All analyses were conducted using SAS statistical software (version 9.4, Cary, NC). Statistical tests were two-sided, and statistical significance was defined as $p<0.05$.

RESULTS

This study included 12,945 children with obesity ages 9 to 17 years old receiving care in a Northern California integrated healthcare system. The mean age was 13.5 (± 2.4) years and 54.8% were male. Self-reported race and ethnicity was classified as follows: 16.5% Asian or Pacific Islander (Asian), 10.0% Black, 48.9% Hispanic, and 19.7% non-Hispanic White (White). The distribution of obesity included 7,552 (58.3%) with mild to moderate obesity and 5,393 (41.7%) with severe obesity. Table I shows the demographic characteristics of the population by race and ethnicity.

The overall prevalence of clinically actionable ALT elevation in children with obesity was 7.8%. (95% CI 7.3-8.2%). The prevalence was twice as high in males as it was in females (10.0% vs. 5.0%; $p<0.001$). Children with severe obesity (11.2%, 95% CI 10.4-12.0%) had significantly higher prevalence of elevated ALT levels than children with mild to moderate obesity (5.3%, 95% CI 4.8-5.8%; $P < .001$). The proportion of children with obesity who had elevated ALT varied by race and ethnicity in both males and females (Table 2). For males, the prevalence of ALT elevation was highest in Hispanic children (12.0%) and Asian children (10.4%) and lowest in Black children (3.1%). For females, the overall trend was similar with the highest prevalence of elevated ALT in Asian (7.7%) and Hispanic (6.1%) females. The lowest prevalence of ALT elevation was in Black females (1.7%). In those with severe obesity, the prevalence of ALT elevation was highest in Asian males (16.7%) and Hispanic males (16.3%) with lowest prevalence in Black males (4.3%). For females, the prevalence was also highest in Asian (13.4%) and Hispanic females (9.5%) with the lowest prevalence in Black females (2.3%).

In multivariable analyses adjusting for age, sex and obesity severity, Hispanic ethnicity (OR 1.75, 95% CI 1.44-2.12) and Asian race (OR 1.84, CI 1.46-2.31) were associated with greater odds of elevated ALT, and Black race (OR 0.39, CI 0.26-0.58) was associated with lower odds of elevated ALT compared with children of White race and non-Hispanic ethnicity. In this same multivariable adjusted model, males had nearly twice the odds of ALT elevation compared with females (OR 1.90, 95% CI 1.65-2.20). Obesity severity was also strongly associated with ALT elevation; children with severe obesity had more than two-fold higher odds of ALT elevation compared with children with mild to moderate obesity (OR 2.33, 95% CI 2.03-2.67).

DISCUSSION

We evaluated nearly 13,000 children ages 9 to 17 in pediatric primary care with obesity who were screened for NAFLD using ALT levels in a large, integrated healthcare delivery system. We found that 7.8% had ALT levels above the threshold for clinical action. Independent of age, race, ethnicity, and level of obesity, males had two times the odds of having elevated ALT compared with females. Asian race and Hispanic ethnicity were most strongly associated with the risk for elevated ALT. In addition, more severe obesity was associated with a higher prevalence of elevated ALT.

Based on these study results, primary care pediatricians can potentially anticipate finding actionable ALT elevation in one of every 13 patients with obesity that they screen for NAFLD. In a large meta-analysis of the global prevalence of NAFLD identified by varying criteria, the pooled prevalence of NAFLD was estimated to be 7.6% in the general population of children and 34.2% in clinical obesity populations (16). A study of 408 children with obesity using liver magnetic resonance imaging (MRI) proton density fat fraction found that the prevalence of NAFLD in children with obesity was estimated to be 26% (17). These latter findings suggest that using the clinical action threshold for ALT likely underestimates the true prevalence of NAFLD in children with obesity. It should be noted that these ALT cut points were not initially selected to identify all cases of NAFLD. Rather, they were selected to identify children for further evaluation and follow-up who were likely to have NAFLD with an increased likelihood of more severe disease such as steatohepatitis and/or fibrosis (5).

Our study provides useful estimates for the prevalence of actionable ALT findings by sex, race and ethnicity, and obesity level in a large community-based primary care practice of children who underwent screening for suspected NAFLD. The finding that males had twice the prevalence of ALT elevation as females is consistent with previous literature. Similarly, the finding that elevated ALT levels were higher in Hispanic children and lower in Black children is also consistent with existing literature. The finding that Asian American children with obesity had a high prevalence of elevated ALT provides new and important information. In the Study of Child and Adolescent Liver Epidemiology (SCALE), we noted a high prevalence of NAFLD in Asian children (10.2%, 95%CI 3.0-17.5) but had limited precision given that only 67 Asian children were studied (2). In a study from Chicago, among 57 Chinese American children with obesity, 33% had an ALT than was greater than the biological upper limit for ALT (22 U/L for girls, 26 U/L for boys), which was half the threshold used in our study (18). Studies from Asia have reported high rates of NAFLD in Asian children with obesity. In a nationally representative study in Korea, among adolescents with obesity, the prevalence of suspected NAFLD based on elevated ALT ≥30 U/L was 24% (19). Asians are now the fastest growing race group in the U.S. with the most common subgroups being Chinese, South Asian, Filipino, Vietnamese, Korean, and Japanese (20, 21). We postulate that Asian American children with obesity are an important risk group for NAFLD. This awareness is particularly important because there are data suggesting that Asian American children with obesity and elevated ALT are less likely to be evaluated for NAFLD than their non-Hispanic White counterparts, despite findings that the elevated ALT levels among Asian children were higher (3).

Our study is limited by lack of data on cause of ALT elevation (including infectious, toxin-mediated, or autoimmune causes) and confirmatory evidence of NAFLD. Furthermore, we did not investigate pubertal status, the degree to which ALT levels were persistently elevated, or other metabolic findings that may vary by race and ethnicity. Finally, these data were derived from a clinical population where it is possible that the presence of other obesity-related conditions influenced the decision to measure ALT, introducing potential selection bias.

Our findings emphasize the importance of screening for NAFLD in minority populations to prevent long-term hepatic and extra hepatic adverse outcomes.

Acknowledgments

Funded by Graduate Medical Education Research with support from the Kaiser Permanente Community Benefit Program. J.S. and E.Y. are supported by the National Institutes of Health (UL1TR001442). The content is solely the responsibility of the authors and does not necessarily represent the official views of Kaiser Permanente Northern California, The Permanente Medical Group, or the National Institutes of Health. J.S. reports grants to the University of California San Diego from Intercept and Seraphina. N.R. owns stock valued at <$20,000 in AbbVie, Inc and previously owned stock in Takeda and Amgen. The other authors declare no conflicts of interest.

ABBREVIATIONS:

NAFLD	Nonalcoholic fatty liver disease
ALT	alanine aminotransferase
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
KPNC	Kaiser Permanente Northern California
BMI	body mass index
NASH	nonalcoholic steatohepatitis
CI	confidence interval
OR	odds ratio

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. [PubMed: 23084707]
2. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics. 2006;118(4):1388–93. [PubMed: 17015527]
3. Sahota AK, Shapiro WL, Newton KP, Kim ST, Chung J, Schwimmer JB. Incidence of Nonalcoholic Fatty Liver Disease in Children: 2009-2018. Pediatrics. 2020.
4. Fernandes DM, Pantangi V, Azam M, Salomao M, Iuga AC, Lefkowitch JH, et al. Pediatric Nonalcoholic Fatty Liver Disease in New York City: An Autopsy Study. J Pediatr. 2018;200:174–80. [PubMed: 29903531]
5. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, 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):319–34. [PubMed: 28107283]
6. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. Clin Gastroenterol Hepatol. 2019;17(4):748–55 e3. [PubMed: 29908364]

7. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology. 2014;59(6):2188–95. [PubMed: 24375711]

8. Doycheva I, Issa D, Watt KD, Lopez R, Rifai G, Alkhouri N. Nonalcoholic Steatohepatitis is the Most Rapidly Increasing Indication for Liver Transplantation in Young Adults in the United States. J Clin Gastroenterol. 2018;52(4):339–46. [PubMed: 28961576]

9. Harlow KE, Africa JA, Wells A, Belt PH, Behling CA, Jain AK, et al. Clinically Actionable Hypercholesterolemia and Hypertriglyceridemia in Children with Nonalcoholic Fatty Liver Disease. J Pediatr. 2018;198:76–83 e2. [PubMed: 29661561]

10. Newton KP, Hou J, Crimmins NA, Lavine JE, Barlow SE, Xanthakos SA, et al. Prevalence of Prediabetes and Type 2 Diabetes in Children With Nonalcoholic Fatty Liver Disease. JAMA Pediatr. 2016;170(10):e161971. [PubMed: 27478956]

11. Noon SL, D'Annibale DA, Schwimmer MH, Shiels J, Arin J, Durelle J, et al. Incidence of Depression and Anxiety in a Cohort of Adolescents With Nonalcoholic Fatty Liver Disease. J Pediatr Gastroenterol Nutr. 2021;72(4):579–83. [PubMed: 33346572]

12. Schwimmer JB, Zepeda A, Newton KP, Xanthakos SA, Behling C, Hallinan EK, et al. Longitudinal assessment of high blood pressure in children with nonalcoholic fatty liver disease. PLoS One. 2014;9(11):e112569. [PubMed: 25419656]

13. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689–712. [PubMed: 24016455]

14. Schwimmer JB, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology. 2010;138(4):1357–64, 64 e1–2. [PubMed: 20064512]

15. Schwimmer JB, Newton KP, Awai HI, Choi LJ, Garcia MA, Ellis LL, et al. Paediatric gastroenterology evaluation of overweight and obese children referred from primary care for suspected non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2013;38(10):1267–77. [PubMed: 24117728]

16. Anderson EL, Howe LD, Jones HE, Higgins JP, 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. [PubMed: 26512983]

17. Yu EL, Golshan S, Harlow KE, Angeles JE, Durelle J, Goyal NP, et al. Prevalence of Nonalcoholic Fatty Liver Disease in Children with Obesity. J Pediatr. 2019;207:64–70. [PubMed: 30559024]

18. Malespin M, Sleesman B, Lau A, Wong SS, Cotler SJ. Prevalence and correlates of suspected nonalcoholic fatty liver disease in Chinese American children. J Clin Gastroenterol. 2015;49(4):345–9. [PubMed: 24667593]

19. Kim JW, Lee KJ, Yang HR, Chang JY, Moon JS, Khang YH, et al. Prevalence and risk factors of elevated alanine aminotransferase among Korean adolescents: 2001-2014. BMC Public Health. 2018;18(1):617. [PubMed: 29751750]

20. Budiman A, Ruiz NG. Key facts about Asian Americans, a diverse and growing population: Pew Research Center; 2021 [updated April 29, 2021. Available from: https://www.pewresearch.org/fact-tank/2021/04/29/key-facts-about-asian-americans/.

21. Hoeffel EM, Rastogi S, Kim MO, Shahid H. The Asian Population: 2010. 2010 Census Briefs [Internet]. 2012. Available from: http://www.census.gov/prod/cen2010/briefs/c2010br-11.pdf.

Table 1.

Demographic and Clinical Characteristics of Children with Obesity

	All Groups* N = 12,945	Asian/PI N = 2136	Black N = 1293	Hispanic N = 6336	White N = 2552
Age, mean ± SD)	13.5 ± 2.4	13.2 ± 2.4	13.6 ± 2.4	13.4 ± 2.4	13.8 ± 2.4
Sex					
Male	7087 (54.8%)	1412 (66.1%)	515 (39.8%)	3451 (54.5%)	1328 (52.0%)
Female	5858 (45.3%)	724 (33.9%)	778 (60.2%)	2885 (45.5%)	1224 (48.0%)
Obesity Severity					
Moderate	7552 (58.3%)	1441 (67.5%)	614 (47.5%)	3591 (56.7%)	1557 (61.0%)
Severe	5393 (41.7%)	695 (32.5%)	679 (52.5%)	2745 (43.3%)	995 (39.0%)
Elevated ALT‡	1003 (7.8%)	203 (9.5%)	29 (2.2%)	591 (9.3%)	138 (5.4%)

PI = Pacific Islander; ALT = alanine aminotransferase activity level

*Includes 628 (4.9%) of other or unknown race/ethnicity

‡Clinically actionable elevated ALT level was defined according to the NASPGHAN guidelines: ≥44 U/L for girls and ≥52 U/L for boys (5)

Table 2.

Prevalence (and 95% confidence intervals) of clinically actionable elevated alanine aminotransferase (ALT) level in children with obesity

	All Groups	Asian/PI	Black	Hispanic	White
Males	10.0% (9.3-10.7)	10.4% (8.8-12.0)	3.1% (1.6-4.6)	12.0% (10.9-13.1)	7.3% (5.9-8.7)
Moderate Obesity	6.9% (6.1-7.7)	7.1% (5.5-8.8)	1.7% (0.0-3.4)	8.4% (7.2-9.7)	4.9% (3.4-6.4)
Severe Obesity	14.1% (12.9-15.3)	16.7% (13.4-20.0)	4.3% (1.9-6.6)	16.3% (14.5-18.2)	10.7% (8.1-13.3)
Females	5.0% (4.4-5.5)	7.7% (5.8-9.7)	1.7% (0.8-2.6)	6.1% (5.2-7.0)	3.4% (2.3-4.4)
Moderate Obesity	3.4% (2.8-4.0)	5.4% (3.5-7.4)	1.0% (0.0-2.1)	3.8% (2.9-4.7)	2.6% (1.5-3.7)
Severe Obesity	7.4% (6.3-8.4)	13.4% (8.8-18.0)	2.3% (0.8-3.7)	9.5% (7.8-11.2)	4.7% (2.8-6.7)

Clinically actionable elevated ALT level was defined according to the NASPGHAN guidelines: ≥44 U/L for girls and ≥52 U/L for boys (5)

PI = Pacific Islander