World Journal of Hepatology

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World J Hepatol 2021 July 27; 13(7): 790-803

DOI: 10.4254/wjh.v13.i7.790

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population

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Institutional review board statement: NHANES protocol was approved by the NCHS Research Ethics Review Board.

Conflict-of-interest statement: The authors declare that there are no any conflicts of interest.

Data sharing statement: NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States, conducted by the National Center for Health

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children and adolescents.

AIM

To determine the prevalence and risk factors of steatosis and advanced fibrosis using transient elastography (TE) in the United States' adolescent population.

METHODS

Using the National Health and Nutrition Examination Survey 2017-2018, adolescent participants aged 13 to 17 years who underwent TE and controlled attenuation parameter (CAP) were included in this study. Forty-one factors associated with liver steatosis and fibrosis were collected. Univariate and multivariate linear regression analysis were used to identify statistically significant predictors.

RESULTS

Seven hundred and forty participants met inclusion criteria. Steatosis (S1-S3), based on CAP, and advanced fibrosis (F3-F4), based on TE, were present in 27% and 2.84% of the study population, respectively. Independent predictors of steatosis grade included log of alanine aminotransferase, insulin resistance, waist-to-height ratio, and body mass index. Independent predictors of fibrosis grade included steatosis grade, non-Hispanic black race, smoking history, and systolic blood pressure.

CONCLUSION

This study demonstrated a high prevalence of steatosis in the United States' adolescent population. Almost 3% of United States' adolescents had advanced fibrosis. These findings are concerning because a younger age of onset of NAFLD can lead to an earlier development of severe disease, including steatohepatitis, cirrhosis, and liver decompensation.

Key Words: Non-alcoholic fatty liver disease; Fatty liver; Metabolic syndrome; Cirrhosis, national health and nutrition examination survey; Pediatric; Adolescents

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Core Tip: Adolescents in the United States were found to have a high prevalence of non-alcoholic fatty liver disease, which was estimated to be 27%. Nearly 3% were found to have advanced fibrosis diagnosed by transient elastography. The severity of steatosis was associated with alanine aminotransferase, insulin resistance, waist-to-height ratio, and body mass index. Risk factors of fibrosis included steatosis grade, non-Hispanic black race, smoking history, and systolic blood pressure.

Citation: Atsawarungruangkit A, Elfanagely Y, Pan J, Anderson K, Scharfen J, Promrat K. Prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population. *World J Hepatol* 2021; 13(7): 790-803
URL: https://www.wjgnet.com/1948-5182/full/v13/i7/790.htm
DOI: https://dx.doi.org/10.4254/wjh.v13.i7.790

INTRODUCTION

With the rise of obesity and metabolic syndrome among younger populations, non-alcoholic fatty liver disease (NAFLD) is a growing concern in adolescents. NAFLD has become the most common cause of chronic liver disease in children and adolescents, with a prevalence previously estimated to be 3%-10% in the global pediatric population[1,2]. The prevalence of NAFLD in children with obesity is exceedingly high at 40%-70%[3]. Unsurprisingly, the rates of NAFLD have grown with the rise of childhood obesity over recent decades. Other established risk factors include insulin resistance, metabolic syndrome, and dyslipidemia. The development of NAFLD in childhood is clinically important because of the progressive nature of the disease. Earlier development of NAFLD increases the risk of earlier-onset fibrosis and frank cirrhosis[4].

Liver biopsy is the gold-standard diagnostic test for NAFLD. It not only confirms the diagnosis of NAFLD, but can also grade the level of inflammation and stage the liver fibrosis. However, this invasive procedure is ill-suited to serve as a general screening tool. Non-invasive alternatives which include a physical exam, biochemical tests, and serum biomarkers for fibrosis are not reliable predictors of fibrosis[5,6]. Because fibrosis is the single most important predictor of long-term mortality in NAFLD, transient elastography (TE) has emerged as a non-invasive, reproducible modality in the assessment of patients with NAFLD. Using ultrasound, TE measures the liver stiffness as a proxy for fibrosis stage. Its accuracy has been demonstrated in adult patients with fibrosis secondary to chronic hepatitis B and C, alcoholic and non-alcoholic liver disease, and biliary disease[7-9]. TE's accuracy however is reduced by active hepatitis, increased waist circumference, recent eating, and liver congestion. In adults with NAFLD, TE has an area under the receiver operating characteristic for detecting advanced fibrosis (bridging fibrosis or cirrhosis) of 0.88[10]. In children and adolescents, TE has been validated for chronic liver disease, including NAFLD with similar accuracy, but the data are limited[11-14]. Further research is needed to confirm the liver stiffness thresholds for fibrosis used in the pediatric population.

In addition to liver stiffness, modern TE is also able to calculate the controlled attenuation parameter (CAP). CAP is a quantitative measurement for steatosis. In adults, significant steatosis is defined by having more than 33% of the hepatocytes on a liver biopsy contain steatotic architecture. This correlates to CAP scores greater than 250 db/m[7]. Cut-offs for CAP of 248 db/m, 268 db/m, and 280 db/m were proposed

Statistics (NCHS). The survey collected multiple data sets, including demographic, interviews, physical examinations, and laboratory testing of biologic samples. It is available to the public.

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Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 4, 2021
Peer-review started: May 4, 2021
First decision: June 4, 2021
Revised: June 10, 2021
Accepted: July 9, 2021
Article in press: July 9, 2021
Published online: July 27, 2021

P-Reviewer: Vignozzi L
S-Editor: Ma YJ
L-Editor: A
P-Editor: Wang LL

to correspond with steatosis ≥ 11%, ≥ 33%, and ≥ 66%, respectively[15]. CAP cut-offs in children are suspected to be similar[16,17], but require additional validation.

In the present study, we reported the prevalence of NAFLD characterized by TE and CAP in United States adolescents. Our study employed novel data from the unselected, general cohort of the 2017-2018 National Health and Nutrition Examination Survey (NHANES). We also assessed risk factors associated with NAFLD in this young demographic.

MATERIALS AND METHODS

Study population and study design

NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States, conducted by the National Center for Health Statistics (NCHS)[18]. The survey collected multiple data sets, including demographic, interviews, physical examinations, and laboratory testing of biologic samples. NHANES protocol was approved by the NCHS Research Ethics Review Board.

Currently, NHANES has been collecting data in a 2-year cycle. The liver ultrasound transient elastography examination was first introduced in NHANES 2017-2018, which has been released in March 2020 along with other data files. Out of 9254 participants in NHANES 2017-2018, there were 740 participants aged younger than 18 years that met inclusion criteria for this study. The exclusion criteria included: (1) Incomplete TE exam status; and (2) Hepatitis B, hepatitis C, or hepatitis E infection. It is worth noting that alcohol consumption data in participants younger than 18 years is not publicly accessible and has not been published by the time of writing this article.

We included 41 factors associated with liver steatosis and fibrosis in this study: demographic (*i.e.*, age , gender, race/ethnicity, and smoking), body measurement (*i.e.*, body mass index (BMI), waist-to-height ratio, and waist-to-hip ratio), physical activities (days of physical active, hours of TV/videos watching, and hours of computer usage), diet (*i.e.*, energy, protein, carbohydrate, sugars, dietary fiber, fat, saturated fatty acids, and cholesterol), blood pressure (*i.e.*, systolic and diastolic), laboratory tests [*i.e.*, triglycerides, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase, alkaline phosphatase, total bilirubin, total protein, albumin, iron, total iron binding capacity, transferrin saturation, ferritin, total cholesterol, direct HDL-Cholesterol, high-sensitivity C-reactive protein, platelet count, HbA1c, fasting glucose, and insulin)]. Additionally, we manually calculated LDL-cholesterol and homeostatic model assessment of insulin resistance (HOMA-IR) from the existing variables.

The above variables were chosen based on the availability of data in NHANES 2017-2018, the usage in clinical practice, and the supporting evidence that demonstrated an association with NAFLD. Additionally, we compared the predictive performance of liver fibrosis indices with the steatosis grade and fibrosis stage. Three liver fibrosis indices used in this study included (1) AST to platelet ratio index (APRI)[19]; (2) Fibrosis-4 (FIB-4) index[20]; and (3) Pediatric NAFLD fibrosis index (PNFI)[21].

Definitions

Assessment by liver ultrasound TE examination resulted in measurement of CAP. CAP is a standardized non-invasive measure for assessment of fibrosis and quantification of steatosis in NAFLD[22]. Cut-off values for median CAP score for different grades of steatosis (S0-S3) were derived from a meta-analysis on CAP technology. S0 was defined as a score of less than 248 dB/m (< 10% steatosis). S1 was defined as a score of 248 to less than 268 dB/m [10% to < 33% steatosis (mild)]. S2 was a defined as a score of 268 to less than 280 dB/m [33% to < 66% steatosis (moderate)]. S3 was defined as a score of 280 dB/m or more [≥ 66% steatosis (severe)][15]. Median CAP scores of 248 dB/m or greater (≥S1) were considered as suspected steatosis.

Participants were also categorized according to stage of hepatic fibrosis. The METAVIR scoring system was used for fibrosis staging (F0-F4)[23]. Stages of hepatic fibrosis ranged from no fibrosis (F0) through intermediate stages of hepatic fibrosis (F1-F3) to end-stage cirrhosis (F4)[24]. The degree of fibrosis was equivalent to the liver stiffness measured in kPa as calculated by liver ultrasound transient elastrography[25]. Stage F0-F1 were defined as a median stiffness < 7 kPa. Stage F2 was defined as a median stiffness of 7 to < 8.6 kPa. Stage F3 was defined as a median stiffness of 8.6 to < 11.5 kPa. Stage F4 was defined as a median stiffness ≥ 11.5 kPa. Participants with a median stiffness of 8.6 kPa or greater (≥F3) were considered to have

advanced fibrosis[26].

BMI was discretized into four classes (1) Underweight, BMI < 5th percentile; (2) Normal, 5th percentile ≤ BMI < 85th percentile; (3) Risk of overweight, 85th percentile ≤ BMI < 95th percentile; and (4) Overweight BMI ≥ 85th percentile[27]. Participants who smoked during the past 30 d or had ever smoked ≥ 100 cigarettes in their entire lives were classified as smokers in this study.

Statistical analysis

Statistical analyses were performed using STATA Release 16 (StataCorp LP, TX, United States). Categorical and ordinal factors were presented in frequency (%). Continuous factors were presented in median (interquartile range). All continuous factors were first tested for skewness; if the distributions were extremely skewed to the right (herein defined as skewness > 3), the factors were log transformed before using them as predictors in regression models. Since the response variables evaluated in this study are the steatosis grade (0 to 3) and the fibrosis score (0 to 4), linear regression model is an appropriate model for determining if predictors are significantly associated with each response variable. The significant factors in univariate level were included as predictors in stepwise regression to determine the significant predictors in multivariate level. The significance level was 0.05.

RESULTS

A total of 740 participants were included in the data analysis as shown in Figure 1. General characteristics of the study population are shown in Table 1. The median age was 15 years old with male comprising greater than 50% of the study population (n = 386, 52.16%). The largest race was Non-Hispanic White (n = 229, 30.39%), followed by Non-Hispanic Black (n = 171, 23.11%) and Mexican American (n = 130, 17.57%) respectively. The majority of the study population had a steatosis grade of S0 (n = 538, 72.8%) and fibrosis stages of F0 and F1 (n = 693, 93.65%). Steatosis (S1-S3) was present in 27% of the study population. Advanced fibrosis (F3-F4) was present in 2.84% of the study population. 53.33% (n = 392) of the study population had a normal BMI, while 28.71% (n = 211) were overweight and 0.54% (n = 4) were underweight.

Data concerning social history and physical activity were also analyzed. A smoking history was endorsed by 6 participants (0.84%). The percent of study participants who spent ≥ 5 h per day of watching TV in the past 30 d was 20.63% (n = 150). Similarly, 35.85% (n = 261) of study participants reported spending ≥ 5 h per day on the computer for the past 30 d.

Table 2 is a univariate analysis of participant characteristics stratified according to steatosis grade. Out of the 47 variables, there were 28 significant predictors. Statistically significant variables that were positively associated with steatosis grade in the multivariate analysis were log of ALT (P = 0.001), HOMA-IR (P = 0.006), waist-to-height ratio (P = 0.001), and BMI (P = 0.011) (Table 3).

Similarly, Table 4 is a univariate analysis of participant characteristics stratified according to fibrosis stage. Out of the 48 variables, there were only 9 significant predictors. In the multivariate analysis (Table 5), steatosis grade (P < 0.001), non-Hispanic black race (P = 0.002), a smoking history (P = 0.028), and systolic blood pressure (P = 0.035) were predictors of fibrosis stage that were statistically significant and positively associated with fibrosis stage.

The performance of liver fibrosis indices (APRI, FIB4, and PNFI) were summarized in Table 6. PNFI was the only significant predictor of steatosis grade. However, all liver fibrosis indices had very low positive predictive values (0%-3.26%) for predicting cirrhosis (F4).

DISCUSSION

This study reported the prevalence of steatosis and fibrosis in United States adolescents who participated in NHANES 2017-2018 as diagnosed by TE and CAP. We also identified predictors of steatosis grade and fibrosis stage in this study population. Although there was a recent study on a similar topic that utilized the same database from Ciardullo *et al*[28], the study designs were distinct as follows: (1) The maximum age in this study is 17 since the age 18 and above was used as a cut-off for many adult questionnaires in NHANES (*e.g.*, alcohol use, physical activity, and smoking); (2) We

Table 1 General characteristics of study population

	All participants (*n* = 740)
Age	15 (13-16)
Sex, *n* (%)	
Male	386 (52.16)
Female	354 (47.84)
Race, *n* (%)	
Mexican American	130 (17.57)
Other Hispanic	55 (7.43)
Non-Hispanic White	229 (30.95)
Non-Hispanic Black	171 (23.11)
Non-Hispanic Asian	83 (11.22)
Other race-including multi-racial	72 (9.73)
Smoking, *n* (%)	6 (0.84)
Steatosis grade, *n* (%)	
S0	538 (72.8)
S1	63 (8.53)
S2	39 (5.28)
S3	99 (13.4)
Fibrosis result, *n* (%)	
F0-F1	693 (93.65)
F2	26 (3.51)
F3	12 (1.62)
F4	9 (1.22)
Waist-to-height ratio	0.48 (0.43-0.55)
Waist-to-hip ratio	0.57 (0.53-0.63)
Body mass index, *n* (%)	
Underweight	4 (0.54)
Normal	392 (53.33)
Risk of overweight	128 (17.41)
Overweight	211 (28.71)
Days physically active at least 60 min	4 (2-5)
Hours/day watch TV or videos past 30 d, *n* (%)	
Less than 1 h	107 (14.72)
1 h	121 (16.64)
2 h	166 (22.83)
3 h	105 (14.44)
4 h	78 (10.73)
5 h or more	150 (20.63)
Hours/day use computer past 30 d, *n* (%)	
Less than 1 h	68 (9.34)
1 h	85 (11.68)
2 h	131 (17.99)

3 h	83 (11.4)
4 h	100 (13.74)
5 h or more	261 (35.85)

discretized the steatosis grades and fibrosis levels into 4 Levels each; (3) Advanced fibrosis was defined as ≥F3 (≥ 8.6 kPa) rather than ≥F2 (≥ 7.4 kPa); (4) We included more risk factors that were widely known to be associated with NAFLD (*e.g.*, smoking, physical activity, diet, and insulin resistance); and (5) Linear regression was used instead of logistic regression. For this reason, our results on prevalence and significant predictors are different from the previous study even though we used the same database.

We found that significant steatosis was present in over a fifth of the adolescents studied as indicated by a median CAP ≥ 248 dB/m and that advanced fibrosis (F3-F4) was present in 2.84% of the adolescents studied. Log of ALT, waist-to-height ratio, HOMA-IR, and BMI were significant predictors of steatosis in multivariate level. These four factors can be categorized into three groups that are commonly known as risk factors of NAFLD: liver chemistry (ALT), insulin resistance (HOMA-IR), and body fat (BMI and waist-to-height ratio). North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines suggested using ALT as a screening test for NAFLD with the cutoff levels of 22 mg/dL for girls and 26 mg/dL for boys[29]. BMI, waist-to-height ratio, and insulin resistance have been heavily documented as risk factors for hepatic steatosis in obese children[30,31]. In fact, insulin resistance plays a central role in the pathogenesis of non-alcoholic fatty liver disease[32].

Identifying predictors of fibrosis in adolescents is important because fibrosis has been shown to be a strong predictor of liver related complications and overall mortality[33]. Having sensitive and specific predictors of fibrosis allows us to effectively prevent and manage associated liver-related complications such as hepatocellular carcinoma and cirrhosis. In our study, multivariate stepwise regression revealed that the independent predictors of fibrosis were steatosis grade, non-Hispanic black race, smoking, and systolic blood pressure.

Non-Hispanic black race as an independent predictor of fibrosis that may be a proxy for other socioeconomic and environmental factors not collected in the research effort. Although the pathogenesis of NAFLD is not fully understood, NAFLD is widely accepted to be a genetic-environment-metabolism-related disease[34]. Consumption of refined carbohydrates and sugar-sweetened beverages have been associated with NAFLD[35]. In a study that documented self-reported sugar-sweetened beverage intake among college students, black undergraduates were found to have a higher intake of sugared beverages than compared to their contemporaries[36]. Additionally, non-Hispanic blacks are reported to have suboptimal diet quality and to not meet national dietary recommendations with lower intakes of total vegetables, milk, and whole grains than whites[37]. Our findings may reflect the dietary and environmental differences among black adolescents and requires further investigation.

Smoking has been identified as an independent risk factor of NAFLD in adult patients[38,39]. The presumed pathogenesis is through the consumption of toxins in cigarettes that affect the antioxidant system, which includes cytochrome P450 and inflammatory cytokines[35]. Our smoking sub-group was adolescents and underpowered with a sample size of 6, so further investigation is needed to confirm smoking as a specific predictor for fibrosis.

Previous animal model study showed that the steatosis of any cause was associated with hepatic inflammatory changes and fibrosis by causing oxidative stress and mitochondrial dysfunction[40]. However, there were limited clinical evidence on the association between steatosis and fibrosis in general pediatric or adolescent population. Systolic hypertension is known as a primary clinical feature of metabolic syndrome, which were previously reported as independence risk factor of NAFLD[41].

Additionally, we compared the performance of three liver fibrosis indices for predicting steatosis (S1-S3) and cirrhosis (F4). PNFI was the only liver fibrosis index having a PPV and sensitivity greater than zero. Although it was only index that can be used to predict NAFLD, the performance on this dataset was moderately high with an accuracy of 85.6%. The superior performance of PNFI could derive from the fact that it is the only index developed by using the liver biopsy in the pediatric population[21] while other two indices (APRI and FIB4) were originally developed from the adult population[19,20], which could perform poorly in pediatric or adolescent population.

Table 2 Univariate Analysis of participant characteristics and steatosis grade

	Steatosis grade				Coefficient	*P* value
	S0 (*n* = 538)	S1 (*n* = 63)	S2 (*n* = 39)	S3 (*n* = 99)		
Age	14 (13-16)	14 (13-16)	15 (14-16)	15 (14-16)	0.0562	0.016[a]
Sex						
Male	273 (50.74%)	29 (46.03%)	20 (51.28%)	64 (64.65%)	0.1747	0.027[a]
Female	265 (49.26%)	34 (53.97%)	19 (48.72%)	35 (35.35%)		
Race						
Mexican American	82 (15.24%)	11 (17.46%)	7 (17.95%)	30 (30.3%)	0.3542	< 0.001[a]
Other Hispanic	42 (7.81%)	5 (7.94%)	1 (2.56%)	7 (7.07%)	-0.0903	0.549
Non-Hispanic White	178 (33.09%)	18 (28.57%)	13 (33.33%)	20 (20.2%)	-0.2008	0.019[a]
Non-Hispanic Black	128 (23.79%)	10 (15.87%)	11 (28.21%)	21 (21.21%)	-0.0440	0.640
Non-Hispanic Asian	60 (11.15%)	8 (12.7%)	4 (10.26%)	11 (11.11%)	-0.0026	0.983
Other Race-Including Multi-Racial	48 (8.92%)	11 (17.46%)	3 (7.69%)	10 (10.1%)	0.0666	0.618
Smoking	4 (0.77%)	1 (1.59%)	0 (0%)	1 (1.04%)	0.0732	0.868
Waist-to-height ratio	0.45 (0.42-0.51)	0.54 (0.47-0.59)	0.57 (0.48-0.62)	0.6 (0.55-0.66)	6.5565	< 0.001[a]
Waist-to-hip ratio	0.56 (0.52-0.6)	0.6 (0.57-0.65)	0.63 (0.57-0.68)	0.64 (0.61-0.69)	6.6835	< 0.001[a]
Body mass index					0.6128	< 0.001[a]
Underweight	4 (0.75%)	0 (0%)	0 (0%)	0 (0%)		
Normal	349 (65.48%)	22 (34.92%)	10 (25.64%)	10 (10.1%)		
Risk of overweight	97 (18.2%)	14 (22.22%)	8 (20.51%)	9 (9.09%)		
Overweight	83 (15.57%)	27 (42.86%)	21 (53.85%)	80 (80.81%)		
Days physically active at least 60 min	4 (2-6)	3.5 (1-5)	4 (2-5)	4 (2-5)	-0.0167	0.348
Hours/day watch TV or videos past 30 d	2 (1-4)	2 (1-4)	3 (1.75-5)	2 (1-4.25)	0.0421	0.070
Hours/day use computer past 30 d	3 (2-5)	4 (2-5)	5 (2-5)	4 (2-5)	0.0560	0.014[a]
Diet						
Energy (1000 kcal)	1.82 (1.43-2.45)	1.75 (1.26-2.28)	1.62 (1.33-2)	1.71 (1.34-2.38)	-0.0732	0.145
Protein (mg)	63.59 (48.32-86.06)	63.15 (40.29-77.27)	53.38 (37.92-80.78)	64.1 (49.36-87.48)	-0.0732	0.145
Carbohydrate (mg)	230.94 (180.54-301.73)	233.36 (154.21-296.51)	213.08 (169.63-253.71)	219.06 (173.09-290.58)	-0.0005	0.178
Total sugars (mg)	94.74 (67.04-133.77)	89.84 (54.32-140.86)	75.37 (51.43-97.67)	90.5 (63.35-127.21)	-0.0008	0.224
Dietary fiber (mg)	12.85 (9.25-17.36)	12.2 (8.77-18.3)	12.5 (9.24-16.79)	12.2 (8.8-16.4)	-0.0051	0.368
Total fat (mg)	75.09 (55.41-97.52)	66.13 (43.61-93.44)	62.68 (45.53-83.34)	71.58 (47.42-95.31)	-0.0016	0.143
Total saturated fatty acids (mg)	25.07 (17.39-35.43)	24.43 (11.47-32.25)	18.7 (11.7-30.89)	22.91 (14.97-31.11)	-0.0044	0.122
Cholesterol (mg)	197 (132.88-320.5)	165 (90.25-305.5)	162 (72.38-283.63)	199 (134-279.25)	-0.0003	0.254
Systolic blood pressure (mm Hg)	106 (100-114)	108 (103.5-114.5)	112 (104-120)	112 (104-120)	0.0254	< 0.001[a]
Diastolic blood pressure (mm Hg)	62 (54-68)	60 (51.5-68)	62 (55.5-70)	60 (54-66)	-0.0038	0.222
Triglycerides, refrig serum (mg/dL)[1]	74 (57-98)	79 (62-103)	78.5 (70-105.5)	98 (68-159)	0.0051	< 0.001[a]
Uric acid (mg/dL)	4.7 (4-5.6)	5.1 (4.15-6.05)	5.45 (4.65-6.15)	5.75 (4.7-6.7)	0.1984	< 0.001[a]
Aspartate aminotransferase (IU/L)[1]	18 (16-22)	18 (15.25-21.75)	16.5 (15-21)	20.5 (18-27)	0.0151	0.002[a]
Alanine aminotransferase (IU/L)[1]	12 (10-15)	15 (11.25-19)	14 (10-17.5)	20.5 (14-34)	0.0372	< 0.001[a]
Gamma glutamyl transferase (IU/L)[1]	12 (10-15)	12 (10-18.75)	15.5 (10-19)	18 (12-24)	0.0375	< 0.001[a]

Alkaline phosphatase (ALP) (IU/L)	130 (87-225.75)	121 (86.75-235)	135 (75.5-188)	126.5 (99-188)	-0.0003	0.537
Total bilirubin (mg/dL)[1]	0.4 (0.3-0.6)	0.3 (0.23-0.48)	0.4 (0.3-0.5)	0.4 (0.3-0.4)	-0.3419	0.009[a]
Total protein (g/dL)	7.3 (7-7.5)	7.3 (7-7.5)	7.35 (7.15-7.6)	7.35 (7.2-7.6)	0.3620	0.002[a]
Albumin, refrigerated serum (g/dL)	4.3 (4.1-4.5)	4.3 (4.1-4.5)	4.25 (4.05-4.45)	4.2 (4-4.4)	-0.5553	< 0.001[a]
Iron frozen, serum (μg/dL)	85 (61-113)	86 (58.25-105.75)	69 (49.5-85.75)	75 (56-103)	-0.0027	0.013[a]
Total iron binding capacity (μg/dL)	348 (317.5-382)	366 (342-392.25)	360 (326.25-406.5)	356 (322-385)	0.0015	0.092
Transferrin Saturation (%)	24 (17-33)	23 (15.25-30.75)	19 (13.5-26)	22.5 (15-30)	-0.0104	0.004[a]
Ferritin (ng/mL)	39.2 (24.85-59.85)	35.25 (18.75-57.5)	30.85 (14.65-60.15)	59.2 (35-93.12)	0.0038	< 0.001[a]
Total cholesterol (mg/dL)	150 (134-168)	158 (132.75-174)	152 (139.5-166.25)	157 (139.25-178.75)	0.0032	0.035[a]
Low-density lipoprotein cholesterol (mg/dL)	78.8 (64.8-94.6)	85.8 (69.15-107.45)	82.5 (70.1-97.8)	87 (70.6-103.6)	0.0041	0.019[a]
Direct high-density lipoprotein cholesterol (mg/dL)	53 (46-61)	50 (46-56)	48 (41.5-55)	44 (39-51)	-0.0238	< 0.001[a]
HS C-reactive protein (mg/L)[1]	0.49 (0.32-1.01)	0.72 (0.35-1.51)	0.95 (0.43-1.89)	1.76 (0.87-3.74)	0.0448	< 0.001[a]
Platelet count (1000 cells/uL)	258 (228-292)	269 (228.5-318.5)	273 (239-307)	282 (248-313)	0.0026	< 0.001[a]
Hemoglobin A1c (%)[1]	5.3 (5.1-5.5)	5.3 (5.1-5.45)	5.3 (5.1-5.6)	5.4 (5.2-5.5)	0.2280	0.054
Fasting glucose (mg/dL)	97 (93-101)	98 (93.25-101.75)	101 (94-103)	99.5 (96-103)	0.0219	0.017[a]
Insulin (pmol/L)	54.96 (39.84-79.38)	101.1 (71.58-130.8)	88.32 (62.28-118.14)	129.63 (75.66-185.46)	0.0086	< 0.001[a]
Homeostatic model assessment for insulin resistance	2.23 (1.58-3.32)	4.08 (2.96-5.47)	3.56 (2.64-4.96)	5.34 (3.08-7.78)	0.1976	< 0.001[a]

[1]Skewness > 3.
[a]$P < 0.05$. HS: High sensitivity.

Table 3 Predictors of steatosis grade in multivariate level

Predictors	Coefficient (standard error)	*P* value
Alanine aminotransferase (IU/L)[1]	0.3912 (0.1159)	0.001
Homestatic model assessment for insulin resistance	0.0684 (0.0247)	0.006
Waist-to-height ratio	3.2299 (0.0912)	0.001
Body mass index	0.2335 (0.0912)	0.011

[1]Log-transformed predictor. Number of observations = 307; Adjusted $R^2 = 0.37$;

There are several limitations of this study. Our study population is of United States adolescents and may not be reflective of non-American populations. Alcohol was not measured in the study population and also presumed to be zero because the population was United States adolescents. The legal age to drink in the United States is 21 but for some people drinking alcohol begins in adolescence[42]. Another limitation is subgroup sample size which was seen subgroups such as smoking, F3, and F4. Low statistical power reduces the chance of detecting a true effect[43]. Some variables not available in the NHANES include hormonal levels and Tanner stages of the participants. Hypogonadism and low testosterone level are associated with an increased risk for NAFLD and NASH[44]. Additionally, low sex hormone binding globulin (SHBG) can be viewed as a marker for NAFLD in women with oligomenorrhea and/or hirsutism[45]. Since these variables were not included in the NHANES database, they were not accounted for. Lastly, though seeing increasing utility in diagnostic value, TE has not been traditionally studied in adolescents.

Table 4 Univariate Analysis of participant characteristics and fibrosis stage

	Fibrosis stage				Coefficient	*P* value
	F0 - F1 (*n* = 693)	F2 (*n* = 26)	F3 (*n* = 12)	F4 (*n* = 9)		
Age	15 (13-16)	15 (13-17)	14 (13-15)	15 (14.75-17)	0.0106	0.276
Sex						
Male	356 (51.37%)	17 (65.38%)	6 (50%)	7 (77.78%)	0.0533	0.105
Female	337 (48.63%)	9 (34.62%)	6 (50%)	2 (22.22%)		
Race						
Mexican American	123 (17.75%)	4 (15.38%)	0 (0%)	3 (33.33%)	-0.0049	0.909
Other Hispanic	53 (7.65%)	1 (3.85%)	1 (8.33%)	0 (0%)	-0.0535	0.393
Non-Hispanic White	222 (32.03%)	3 (11.54%)	2 (16.67%)	2 (22.22%)	-0.0685	0.054
Non-Hispanic Black	148 (21.36%)	13 (50%)	8 (66.67%)	2 (22.22%)	0.1309	< 0.001[a]
Non-Hispanic Asian	78 (11.26%)	4 (15.38%)	0 (0%)	1 (11.11%)	-0.0222	0.669
Other Race-Including Multi-Racial	69 (9.96%)	1 (3.85%)	1 (8.33%)	1 (11.11%)	-0.0230	0.679
Smoking	5 (0.75%)	0 (0%)	0 (0%)	1 (11.11%)	0.3967	0.032[a]
Waist-to-height ratio	0.48 (0.43-0.55)	0.49 (0.44-0.61)	0.49 (0.4-0.61)	0.5 (0.42-0.68)	0.3746	0.042[a]
Waist-to-hip ratio	0.57 (0.53-0.62)	0.59 (0.54-0.69)	0.6 (0.52-0.64)	0.59 (0.5-0.7)	0.2804	0.215
Body mass index					0.0330	0.079
Underweight	4 (0.58%)	0 (0%)	0 (0%)	0 (0%)		
Normal	370 (53.78%)	11 (42.31%)	6 (50%)	5 (55.56%)		
Risk of overweight	126 (18.31%)	2 (7.69%)	0 (0%)	0 (0%)		
Overweight	188 (27.33%)	13 (50%)	6 (50%)	4 (44.44%)		
Days physically active at least 60 min	4 (2-5)	4 (2-5)	2.5 (0.5-6)	5 (2.5-6)	-0.0039	0.597
Hours/day watch TV or videos past 30 d	2 (1-4)	2 (1-4)	2.5 (2-4.5)	2 (0-3.5)	-0.0027	0.779
Hours/day use computer past 30 d	3 (2-5)	5 (3-5)	4 (2.5-5)	3 (0.75-5)	0.0062	0.519
Steatosis grade					0.0757	< 0.001[a]
S0	518 (74.86%)	13 (50%)	3 (25%)	4 (44.44%)		
S1	57 (8.24%)	2 (7.69%)	3 (25%)	1 (11.11%)		
S2	35 (5.06%)	2 (7.69%)	2 (16.67%)	0 (0%)		
S3	82 (11.85%)	9 (34.62%)	4 (33.33%)	4 (44.44%)		
Diet						
Energy (1000 kcal)	1.8 (1.4-2.42)	1.5 (1.37-2.11)	1.62 (1.4-1.75)	1.75 (1.32-2.4)	-0.0225	0.282
Protein (mg)	63.69 (46.81-85.41)	50.66 (42.74-94.29)	59.33 (45.9-76.55)	68.03 (49.61-73.78)	-0.0004	0.405
Carbohydrate (mg)	230.55 (174.26-299.84)	202.56 (152.11-255.23)	204.26 (177.87-238.7)	242.27 (186.12-305.52)	-0.0001	0.671
Total sugars (mg)	92.59 (64.25-133.63)	87.43 (58.07-120.32)	75.76 (62.31-94.74)	94.74 (85.8-123.02)	-0.0001	0.697
Dietary fiber (mg)	12.7 (9.25-17.1)	10.8 (7.62-17.64)	10.4 (9.02-14.29)	12.85 (10.8-16.96)	-0.0018	0.461
Total fat (mg)	74.07 (52.04-97.34)	55.7 (45.07-79.29)	65.98 (50.43-78.07)	69.09 (45.95-97.94)	-0.0007	0.091
Total saturated fatty acids (mg)	24.72 (16.8-34.81)	21.06 (14.84-29.88)	23.04 (18.87-27.64)	22.84 (18.35-28.35)	-0.0020	0.083
Cholesterol (mg)	197 (129.13-317.63)	150.5 (85-213.25)	162.5 (118.38-228.88)	146.5 (124.75-310.25)	-0.0002	0.065
Systolic blood pressure (mmHg)	106 (102-114)	108 (103.5-126.5)	108 (100.5-120)	116 (113-122)	0.0066	< 0.001[a]
Diastolic blood pressure (mmHg)	62 (54-68)	64 (53-71)	56 (50.5-65.5)	60 (56-68)	-0.0001	0.967

Triglycerides, refrig serum (mg/dL)[1]	78 (61-104)	67.5 (50-111)	88 (61.75-161)	88.5 (56.5-121.5)	0.0276	0.471
Uric acid (mg/dL)	4.9 (4.1-5.8)	5 (3.7-6)	4.7 (3.3-5.98)	5.75 (4.2-7.45)	0.0079	0.560
Aspartate aminotransferase (IU/L)[1]	18 (16-22)	18 (15-25)	15 (14-23)	29 (20-32)	0.0882	0.137
Alanine aminotransferase (IU/L)[1]	13 (10-17)	14 (9-20)	12 (9.5-15)	20.5 (15-37.5)	0.0738	0.046[a]
Gamma glutamyl transferase (IU/L)[1]	13 (10-17)	12 (9-16)	12 (10-19.5)	20.5 (14-32.5)	0.0047	0.018[a]
Alkaline phosphatase (IU/L)	129 (88-222.5)	121.5 (81-205)	187 (127.75-242.75)	113 (105-129.5)	-0.0001	0.470
Total bilirubin (mg/dL)[1]	0.4 (0.3-0.5)	0.3 (0.2-0.6)	0.4 (0.3-0.5)	0.45 (0.35-0.7)	0.0178	0.577
Total protein (g/dL)	7.3 (7-7.5)	7.15 (6.8-7.3)	7.3 (7-7.63)	7.2 (7.15-7.45)	-0.0156	0.745
Albumin, refrigerated serum (g/dL)	4.3 (4.1-4.5)	4.05 (3.8-4.4)	4.2 (4.03-4.3)	4.3 (4.1-4.65)	-0.0744	0.229
Iron frozen, Serum (μg/dL)	83 (59-112)	80.5 (47-88)	88 (68-106)	67.5 (58-120.5)	0.0001	0.777
Total iron binding capacity (μg/dL)	352 (322-387)	346 (314-378)	355 (315.25-375.25)	314 (310-327.5)	-0.0009	0.018[a]
Transferrin saturation (%)	23 (17-32)	22 (15-26)	28 (19.25-31.5)	20 (18-39)	0.0013	0.377
Ferritin (ng/mL)	39.3 (24.5-62.1)	45.55 (24.45-61.85)	56.25 (29-71)	102.35 (35.75-141)	0.0009	0.030[a]
Total cholesterol (mg/dL)	151 (134-171)	140.5 (136-156)	161 (143-175)	131 (119-147.5)	-0.0010	0.102
Low-density lipoprotein cholesterol (mg/dL)	81 (66.2-97.6)	77.5 (64.2-92.6)	88.2 (71.6-91.4)	57.2 (55.5-80.1)	-0.0013	0.082
Direct high-density lipoprotein cholesterol (mg/dL)	51 (44-59)	49.5 (44-58)	50 (46-62)	49.5 (39-56)	-0.0012	0.426
HS C-reactive protein (mg/L)[1]	0.57 (0.35-1.39)	0.83 (0.34-1.34)	0.72 (0.37-1.12)	0.97 (0.53-7.09)	0.0240	0.134
Platelet count (1000 cells/uL)	262 (230-297.5)	275.5 (242-302.5)	262.5 (226-277)	262.5 (234-275)	-0.0001	0.769
Hemoglobin A1c (%)[1]	5.3 (5.1-5.5)	5.3 (5.25-5.6)	5.45 (5.25-5.65)	5.35 (5.15-5.6)	0.4629	0.098
Fasting glucose (mg/dL)	98 (94-102)	99 (94-103)	101 (95.5-104.25)	92 (89.75-95.75)	-0.0031	0.490
Insulin (pmol/L)	64.83 (43.38-99)	70.26 (45.87-183.17)	87.06 (59.28-160.28)	51.42 (27.29-127.14)	0.0005	0.291
Homeostatic model assessment for insulin resistance	2.61 (1.71-3.96)	2.66 (1.96-7.9)	4.08 (2.34-6.66)	1.95 (1.1-4.95)	0.0101	0.383

[1]Skewness > 3.
[a]$P < 0.05$. HS: High sensitivity.

Table 5 Predictors of fibrosis stage in multivariate level

Predictors	Coefficient (standard error)	*P* value
Steatosis grade	0.0730 (0.0172)	< 0.001
Race: Non-Hispanic Black	0.1352 (0.0430)	0.002
Smoke	0.4065 (0.1845)	0.028
Systolic blood pressure (mmHg)	0.0040 (0.0019)	0.035

Number of observations = 643; Adjusted R^2 = 0.0598.

CONCLUSION

In conclusion, this study showed steatosis and advanced liver fibrosis in 27.2% and 2.7% of United States adolescents, respectively. ALT, BMI, HOMA-IR, and waist-to-height ratio were predictors of steatosis, while steatosis grade, smoking, non-Hispanic black race, systolic blood pressure were predictors of fibrosis. Environmental, dietary, and social history are important information to gather from adolescents as these factors can contribute to a risk of steatosis and fibrosis. Given the progressive nature of chronic liver disease, the evidence of steatosis or advanced fibrosis in younger age could lead to increased steatohepatitis and cirrhosis in young adults.

Table 6 Predictive performance of liver fibrosis indices

Liver fibrosis indices (Predictor)		Outcome	Predictive performance				
Index	Cutoff		Accuracy	PPV	NPV	Sensitivity	Specificity
APRI	0.7	F4	98.45%	0%	98.8%	0.0%	99.7%
FIB4	1.3	F4	98.61%	0%	98.8%	0.0%	99.8%
PNFI	9	F4	85.31%	3.26%	99.1%	37.5%	85.9%
PNFI	3	S1-S3	85.60%	83.33%	86.2%	59.7%	95.5%

APRI: Aspartate aminotransferase to platelet ratio index; FIB4: Fibrosis-4 index; NPV: Negative predictive value; PNFI: Pediatric non-alcoholic fatty liver disease fibrosis index; PPV: Positive predictive value.

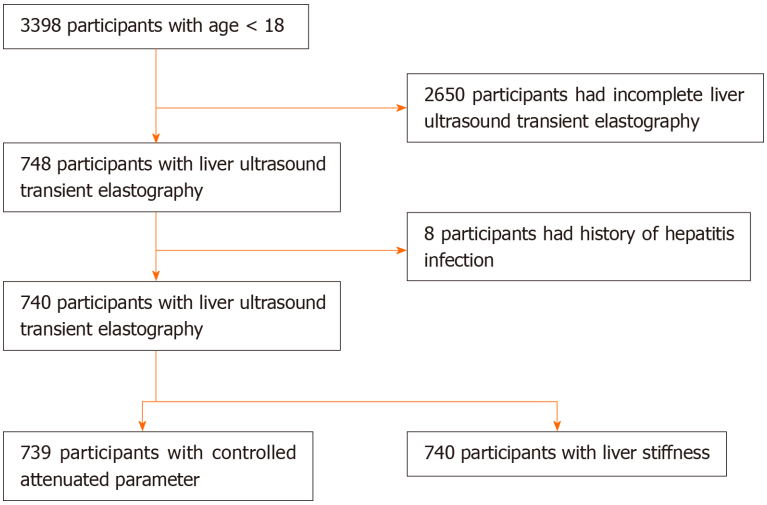

Figure 1 Study design flow chart.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children and adolescents.

Research motivation

With the rise of obesity and metabolic syndrome among younger populations, NAFLD is a growing concern in adolescents.

Research objectives

The authors aimed to determine the prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States' adolescent population.

Research methods

The authors studied adolescent participants aged 13 to 17 years who underwent TE and controlled attenuation parameter using the National Health and Nutrition Examination Survey 2017-2018.

Research results

There is a high prevalence of steatosis (27.2%) in the United States' adolescent population, with 2.84% having advanced fibrosis. Risk factors of steatosis grade included alanine aminotransferase, insulin resistance, waist-to-height ratio, and body mass index. Steatosis grade, non-Hispanic black race, smoking history, and systolic blood pressure were significant predictors of fibrosis.

Research conclusions

Adolescents with steatosis or advanced fibrosis could progress to increased steatohepatitis and cirrhosis in young adults.

Research perspectives

Environmental, dietary, and social history are important information to gather from adolescents as these factors can contribute to a risk of steatosis and fibrosis. Given the progressive nature of chronic liver disease, the evidence of steatosis or advanced fibrosis in younger age could lead to increased steatohepatitis and cirrhosis in young adults.

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