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ORIGINAL ARTICLE

Impact of the new definition of metabolic dysfunction–associated fatty liver disease on detection of significant liver fibrosis in US adolescents

Stefano Ciardullo[1,2] | **Marco Carbone**[3,4] | **Pietro Invernizzi**[3,4] | **Gianluca Perseghin**[1,2]

[1]Department of Medicine and Rehabilitation, Policlinico di Monza, Monza, Italy

[2]Department of Medicine and Surgery, University of Milano Bicocca, Milan, Italy

[3]Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

[4]European Reference Network on Hepatological Diseases (ERN RARE-LIVER), San Gerardo Hospital, Monza, Italy

Correspondence
Stefano Ciardullo, Department of Medicine and Surgery, Università degli Studi di Milano Bicocca, Via Modigliani 10, 20900 Monza (MB), Italy.
Email: s.ciardullo@campus.unimib.it or stefano.ciardullo@policlinicodimonza.it

Abstract

Recently, an expert panel proposed diagnostic criteria for metabolic dysfunction–associated fatty liver disease (MAFLD) in the pediatric population. The aim of this study was to evaluate the prevalence of MAFLD among US adolescents and to investigate whether the new MAFLD definition is able to identify individuals with more advanced liver disease. We analyzed data from participants 12–18 years old included in the 2017–2020 cycles of the National Health and Nutrition Examination Survey, a large survey aimed at including individuals representative of the non-institutionalized general US population. Participants with a complete vibration-controlled transient elastography exam were included. Steatosis was evaluated through the median controlled attenuation parameter (CAP) and fibrosis through median liver stiffness measurement (LSM). Recently proposed criteria for the diagnosis of MAFLD were applied. Multivariable logistic regression analysis was performed to evaluate the impact of the new MAFLD definition on the odds of significant liver fibrosis. We included a total of 1446 adolescents (mean age: 14.9 years; 52.0% male; 47.3% overweight or obese). No participant reported a previous history of viral hepatitis. Steatosis (CAP ≥ 248 dB/m) was present in 25.9% (95% confidence interval [CI] 23.3–28.9) of individuals, and among these, 87.7% met the MAFLD criteria. Only 22.9% of patients with steatosis had elevated alanine aminotransferase levels. Among participants with steatosis, prevalence of significant liver fibrosis (LSM ≥ 7.4 kPa) did not differ significantly according to whether they met MAFLD criteria (9.7% vs. 15.2%, $p = 0.276$). In the multivariable model, odds of significant fibrosis did not differ significantly between these two groups. MAFLD criteria are met by most US adolescents with elastographic evidence of steatosis. Nonetheless, these criteria do not appear to improve detection of subjects with more advanced liver disease. Further longitudinal studies are needed to evaluate whether metabolic dysfunction is associated with faster progression toward inflammation, fibrosis, and liver-related events.

INTRODUCTION

Fatty liver disease has been increasing in prevalence among children and adolescents in the United States in the last two decades, and has become the most common cause of chronic liver disease in this age group.[1,2] While estimates vary by method of detection, previous studies reported a prevalence of about 10% in the general US population[3] and up to 29%–38% in obese children.[4,5] Similarly to guidelines directed to adults,[6] the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines define nonalcoholic fatty liver disease (NAFLD) as a diagnosis of exclusion that can be made in the setting of chronic hepatic steatosis in the absence of genetic or metabolic disorders, infections, use of steatogenic medications, ethanol consumption, or malnutrition.[7]

In 2020, an international expert consensus panel suggested a redefinition of adult fatty liver disease and a switch from NAFLD (a diagnosis of exclusion) to metabolic dysfunction–associated fatty liver disease (MAFLD) and provided a set of positive diagnostic criteria.[8] This change aimed to recognize the dominant role of metabolic dysfunction in the development and progression of fatty liver disease[9] and to abandon a notion of a precise threshold for harmful alcohol consumption. The new definition has been endorsed by multiple liver organizations worldwide,[10,11] with some studies showing that it also performs better in identifying patients with significant or advanced liver fibrosis.[12–14]

More recently, Eslam et al. proposed similar (although not identical) criteria for diagnosing MAFLD in children and adolescents, as both similarities and differences exist in the causes, natural history, and prognosis of fatty liver diseases in children compared with adults.[15]

In this context, the current study aims to evaluate the prevalence of MAFLD in adolescents from the general US population, as well as to investigate whether MAFLD criteria are able to identify participants with more advanced liver disease. To achieve these goals, we analyzed data from adolescents who participated in the 2017–2020 cycles of the National Health and Nutrition Examination Survey (NHANES) and were evaluated by vibration-controlled transient elastography (VCTE).

METHODS

Study design and population

The present study represents an analysis of data from the 2017 to 2020 cycles of NHANES, which is conducted in the United States by the National Center for Health Statistics (NCHS), part of the Center for Disease Control and Prevention. NHANES is a cross-sectional survey program that uses a stratified, multistage, clustered probability sampling design to include individuals representative of the general, non-institutionalized population aged ≥2 months. Full methodology of data collection is available at the NHANES website.[16] The survey consists of a structured interview conducted in the participant home, followed by a standardized health examination that includes a physical examination as well as laboratory tests, which are performed at a mobile examination center (MEC). The original survey was approved by the NCHS Research Ethics Review Board; written informed consent was obtained from the guardians of participants <18 years of age; and assent was obtained from those aged 12 to 17 years. The present analysis was deemed exempt by the institutional review board at our institution, as the data set used in the analysis was completely de-identified.

The coronavirus disease 2019 pandemic required suspension of the NHANES 2019–2020 field operations in March 2020. Therefore, the partial 2019–2020 data were combined with the full data set from the previous cycle (2017–2018) to create nationally representative 2017–March 2020 pre-pandemic data files. All analyses reported in this study were performed according to specific guidance from the NCHS.[17]

A total of 15,560 individuals participated in the 2017–2020 NHANES cycles. The study population for the current analysis consisted of adolescents aged 12–18 (n = 1774). Participants who did not attend a MEC examination (n = 115) or who did not have a reliable VCTE exam (n = 213) were excluded from the analysis, leading to a final study sample of 1446 subjects (Figure 1).

Laboratory tests and clinical data

Participants (or proxies for participants <16 years) self-reported age, sex, race-ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or other), and previous medical history. Body measurements including height (centimeters), weight (kilograms), and waist circumference (centimeters) were ascertained during the MEC visit; body mass index

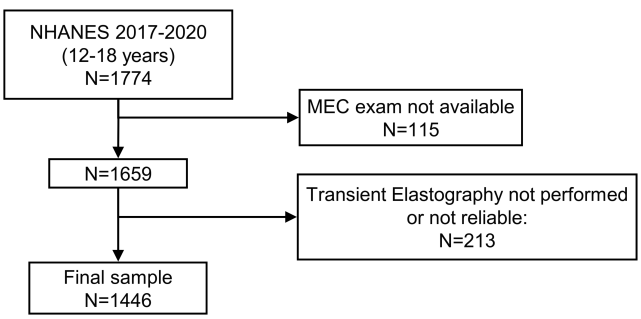

FIGURE 1 Flow chart of the study participants. Abbreviations: MEC, mobile examination center; NHANES, National Health and Nutrition Examination Survey

(BMI) was calculated as weight in kilograms divided by height in meters squared.

Following the new MAFLD diagnostic criteria,[15] presence of overweight or obesity was defined as a BMI > 1 SD above the World Health Organization growth reference median (which translates into a BMI > 25 kg/m^2 in adults[18]) or as a waist circumference >90th percentile for age and sex.[19]

After measuring upper-arm circumference to guide selection of cuff size and resting quietly in a seated position for 5 min, three consecutive blood pressure (BP) measurements were taken 60 s apart using a digital upper-arm electronic measurement device (Omron HEM–907X)L. A previous study performed on the 2017–2018 cycle showed high concordance between measurements obtained with this device compared with a mercury sphygmomanometer.[20] The mean of the three measurements was considered the representative value for the current study.

Elevated BP was defined as a systolic BP (SBP) > 130 mm Hg and/or a diastolic BP (DBP) > 85 mm Hg.[15] Prediabetes and diabetes were defined as follows, in accordance with international guidelines[21]: (1) a previous diagnosis of diabetes; (2) a Hemoglobin A1c (HbA1c) level ≥ 5.7% (48 mmol/mol); or (3) a fasting plasma glucose ≥ 100 mg/dl.

Laboratory methods for measurements of HbA1c, glucose, lipid profile, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are reported in detail elsewhere.[22] ALT levels were considered elevated if ≥22 IU/L in females and ≥26 IU/L in males, as suggested by the NASPGHAN guidelines.[7]

Presence of viral hepatitis was reported by participants or proxies. In adolescents from the 2017–2018 cycles, hepatitis B surface antigen and hepatitis C virus antibodies were also measured. No participants self-reported or tested positive for either hepatitis B or hepatitis C.[23]

VCTE

In the 2017–2020 cycles, VCTE was performed by NHANES technicians after a 2-day training program with an expert technician, using the FibroScan model 502 V2 Touch (Echosens, Paris, France) equipped with medium (M) and extra-large (XL) probes. Interrater reliability between health technicians and expert FibroScan technicians (tested on 32 subjects) was 0.86 for stiffness (mean difference 0.44 ± 1.3 KPa) and 0.94 for controlled attenuation parameter (CAP) (mean difference 4.5 ± 19.8 db/m). The M probe was used initially unless the machine indicated use of the XL probe. All participants aged 12 years and over were eligible with the exception of those who were unable to lie down, were currently pregnant, had an implanted electronic medical device, or had lesions where measurements would be taken. Only patients with complete exams (i.e., fasting time of at least 3 h, 10 or more complete stiffness [E] measurements, and a liver stiffness interquartile range/median E < 30%) were included in the present analysis. In the absence of a clear indication from international guidelines, a median CAP score ≥ 248 dB/m was considered indicative of steatosis, as it showed a good performance in a recent individual patient meta-analysis.[24]

Cutoffs for liver stiffness were obtained from previous studies. A cutoff of 7.4 KPa showed good performance in identifying ≥ F2 fibrosis in a previous study by Nobili et al. when compared with liver biopsy.[25] The same group later reported a higher cutoff of 8.6 KPa.[26] Finally, we also applied the cutoff of 8.0 kPa, derived from a large study performed in adults.[27]

MAFLD definition

In accordance with the recent consensus, MAFLD was diagnosed in the presence of steatosis (evaluated by CAP) plus at least one of the following criteria: overweight/obesity (as previously specified), prediabetes or diabetes (as previously specified), and at least two metabolic abnormalities.[15] Metabolic abnormalities included elevated BP (as previously specified), triglyceride levels ≥ 150 mg/dl, high-density lipoprotein (HDL) cholesterol levels < 40 mg/dL, and triglycerides-to-HDL cholesterol ratio > 2.25 (while adult MAFLD criteria were applied for adolescents 16 years and older).

Statistical analysis

All analyses were conducted using Stata version 16 (Stata Corp, College Station, TX), accounting for the complex survey design of NHANES. We used appropriate weighting for each analysis, as suggested by the NCHS. Data are expressed as numbers and weighted proportions for categorical variables and as weighted means ± SEM for continuous variables.

Participants' characteristics were compared using linear regression for continuous variables and the design-adjusted Rao-Scott chi-square test for categorical variables. Multivariable logistic regression analysis was performed to evaluate the effect of meeting MAFLD criteria on the odds of significant liver fibrosis, estimated by an elevated liver stiffness measurement (LSM). A two-tailed value of $p < 0.05$ was considered statistically significant.

RESULTS

Features of participants with and without steatosis

Clinical and metabolic features of the 1446 study participants according to the presence or absence of steatosis are found in Table 1. Mean age was 14.9 years,

TABLE 1 Clinical features of the study population according to the presence or absence of steatosis assessed through CAP values

	CAP < 248 dB/m (n = 1057)		CAP ≥ 248 dB/m (n = 389)		
	N or mean	% or SEM	N or mean	% or SEM	*p*
Age (years)	14.9	(0.1)	15.2	(0.1)	0.034
BMI (kg/m^2)	22.1	(0.2)	29.7	(0.4)	<0.001
Waist circumference (cm)	76.9	(0.4)	96.1	(1.0)	<0.001
Triglycerides (mg/dl)	85.7	(1.8)	108.0	(3.4)	<0.001
Direct HDL cholesterol (mg/dl)	53.4	(0.5)	47.6	(0.6)	<0.001
AST (IU/L)	19.2	(0.3)	20.9	(0.5)	0.006
ALT (IU/L)	14.2	(0.3)	21.9	(1.0)	<0.001
SBP (mm Hg)	108.0	(0.4)	109.4	(0.6)	0.025
DBP (mm Hg)	63.1	(0.3)	66.5	(0.5)	<0.001
Ratio of family income to poverty	2.8	(0.1)	2.4	(0.1)	0.002
Sex (%)					0.322
Male	538	51.0%	215	55.3%	
Female	518	49.0%	174	44.7%	
Race-ethnicity (%)					0.002
Non-Hispanic White	570	54.0%	178	45.8%	
Hispanic	226	21.4%	129	33.2%	
Non-Hispanic Black	142	13.5%	42	10.7%	
Non-Hispanic Asian	54	5.1%	15	3.9%	
Other	63	6.0%	24	6.3%	
Overweight (%)	242	25.0%	84	27.1%	0.234
Obese (%)	120	9.3%	245	57.5%	<0.001
Prediabetes or diabetes (%)	188	17.8%	97	24.9%	0.013
Elevated BP (%)	20	1.9%	10	2.6%	0.546
Elevated triglycerides (%)	62	5.9%	63	16.1%	<0.001
Low HDL (%)	93	8.8%	80	20.5%	<0.001
High triglyceride/HDL ratio (%)	177	16.7%	135	34.6%	<0.001
Elevated ALT (%)	60	5.6%	89	22.9%	<0.001
ALT > 2× ULN (%)	7	0.7%	22	5.4%	<0.001
ALT > 80 U/L	0	0.0%	4	1.4%	0.005
LSM ≥ 7.4 kPa	36	3.4%	40	10.4%	0.001
LSM ≥ 8.6 kPa	19	1.8%	23	5.9%	0.020
LSM ≥ 8.0 kPa	24	2.3%	26	6.6%	0.025
Meeting MAFLD criteria (%)	0	0.0%	341	87.7%	<0.001

Note: Data are expressed as numbers and weighted proportions for categorical variables and as weighted means and SEM for continuous variables. Linear regression and Rao-Scott chi-square test were used to compare distributions of continuous and categorical variables across groups, respectively. Alanine aminotransferase (ALT) levels were considered elevated if >22 UI/L in females and >26 UI/L in males.

Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MAFLD, metabolic dysfunction–associated fatty liver disease; SBP, systolic blood pressure; ULN, upper limit of normal.

52.0% (95% confidence interval [CI] 46.6–57.4) were male, and 47.3% (95% CI 42.4–52.3) were overweight or obese. Steatosis was present in 389 participants (weighted prevalence 25.9%, 95% CI 23.3–28.9). Distribution of LSM values in the entire population is shown in Figure 2.

Participants with steatosis were significantly older, more frequently overweight or obese (84.6% vs. 34.3%, $p < 0.001$), and of Hispanic origin (33.2.2% vs. 21.4%, $p = 0.002$), with no significant differences found in sex distribution. They came from families with a lower income to poverty ratio. Patients with steatosis were also characterized by a generally worse metabolic profile, demonstrated by lower HDL cholesterol, higher triglyceride levels, higher SBP and DBP levels (although no significant difference was found in the prevalence of elevated BP), and a higher prevalence of prediabetes or diabetes. From a liver-related

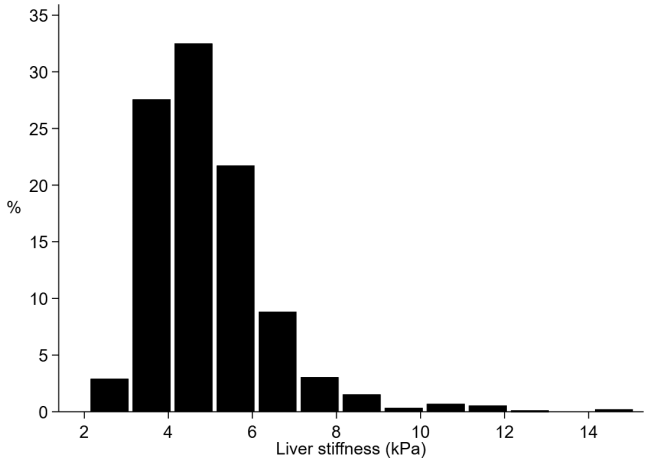

FIGURE 2 Distribution of liver stiffness measurement (LSM) values in the study population

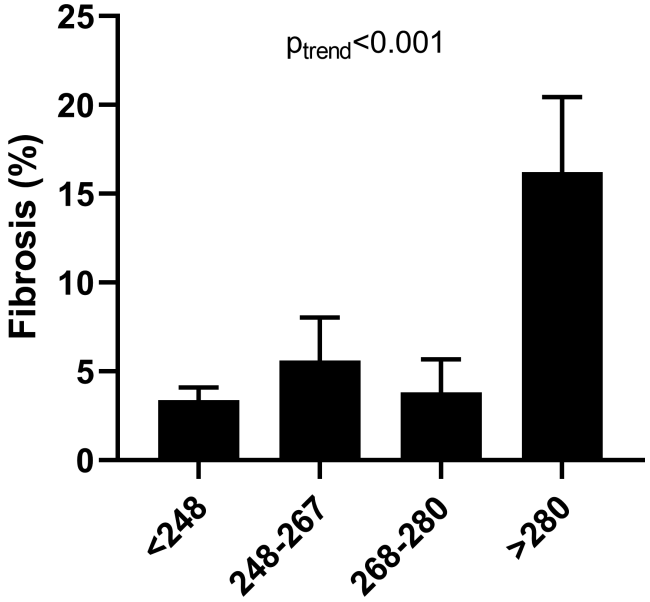

FIGURE 3 Prevalence of significant liver fibrosis (LSM ≥7.4 kPa) according to controlled attenuation parameter (CAP) values in the studied population

standpoint, both AST and ALT levels were higher in patients with MAFLD. Nonetheless, only 22.9% had elevated ALT levels according to the NASPGHAN guidelines. Participants with steatosis showed a higher prevalence of elevated LSM levels, indicative of significant fibrosis, regardless of the specific cutoff used. Prevalence of significant liver fibrosis increased significantly with increasing CAP values, as shown in Figure 3. Features of participants with LSM > 12 kPa, indicative of more advanced liver fibrosis, are provided in Table S3.

Features of participants with steatosis according to the presence of MAFLD

Among participants with elastographic evidence of steatosis, 346 (87.7%, 95% CI 82.8–91.3) met the MAFLD criteria. The criterion most frequently met was overweight/obesity (84.6%, 95% CI 80.0–88.3). Clinical and laboratory features of participants with steatosis according to the presence or absence of MAFLD are given in Table 2.

Mean age and family income to poverty ratio were not significantly different between the two groups. As required by diagnostic criteria, participants without MAFLD were normal weight (mean BMI = 20.4 kg/m^2), without prediabetes or diabetes. Few of them met any metabolic derangement criteria, the most frequent being an elevated triglyceride/HDL ratio (4.1%). From a liver-related standpoint, participants meeting the MAFLD criteria had higher ALT levels (and a higher proportion met the NASPGHAN threshold for elevated ALT), while AST did not differ significantly. On the other hand, no significant difference was found between the two groups in the prevalence of elevated LSM levels, regardless of the specific cutoff used.

Multivariable logistic regression analysis

We performed a multivariable logistic regression model to identify independent variables associated with significant liver fibrosis (LSM ≥ 8 kPa). Results of the analysis are found in Table 3. Female sex was associated with a borderline-significant reduction in the odds of liver fibrosis, whereas non-Hispanic Black adolescents had higher odds compared with non-Hispanic Whites. In this analysis, compared to participants without steatosis, odds of having elevated LSM were similarly elevated in those with steatosis who did not meet the MAFLD criteria (odds ratio [OR] 3.74, 95% CI 1.00–13.91, p = 0.50) and those who did (OR 2.93, 95% CI 1.12–7.66, p = 0.030). Results were consistent when cutoffs of 7.4 kPa or 8.6 kPa were applied (Tables S1 and S2).

DISCUSSION

While several studies investigated epidemiological implications of introducing MAFLD criteria in adults, this study reports the prevalence of MAFLD in adolescents from the general US population, as well as investigates whether MAFLD criteria are able to identify participants with more advanced liver disease (such as significant fibrosis) in this age group.

We made a series of observations. First, prevalence of steatosis is high in US adolescents, as previously reported.[23] Second, MAFLD criteria are met by most adolescents with elastographic evidence of steatosis (~90%), with overweight or obesity being the most frequently met criterium. Third, most

TABLE 2 Clinical features of adolescents with elastographic evidence of steatosis according to whether they met the MAFLD diagnostic criteria

	MAFLD− (n = 43)		MAFLD+ (n = 346)		
	N or mean	% or SEM	*N* or mean	% or SEM	*p*
Age (years)	14.8	(0.3)	15.2	(0.1)	0.316
BMI (kg/m^2)	20.4	(0.4)	31.0	(0.4)	<0.001
Waist circumference (cm)	72.4	(0.9)	99.5	(1.0)	<0.001
Triglycerides (mg/dl)	71.7	(3.7)	112.7	(3.8)	<0.001
HDL cholesterol (mg/dl)	58.3	(1.7)	46.1	(0.6)	<0.001
AST (IU/L)	19.3	(0.9)	21.1	(0.5)	0.106
ALT (IU/L)	13.5	(1.0)	23.0	(1.1)	<0.001
SBP (mm Hg)	111.0	(1.4)	109.2	(0.7)	0.306
DBP (mm Hg)	63.0	(1.1)	67.0	(0.5)	0.033
Ratio of family income to poverty	2.8	(0.3)	2.3	(0.1)	0.250
Sex (%)					0.809
Male	23	52.7%	193	55.7%	
Female	20	47.3%	153	44.3%	
Race-ethnicity (%)					0.297
Non-Hispanic White	22	51.8%	156	45.0%	
Hispanic	8	19.6%	122	35.1%	
Non-Hispanic Black	8	17.5%	34	9.8%	
Non-Hispanic Asian	1	2.4%	14	4.1%	
Other	4	8.6%	21	6.0%	
Overweight or obesity (%)	0	0.0%	334	96.6%	<0.001
Prediabetes or diabetes (%)	0	0.0%	98	28.4%	0.001
Elevated BP (%)	0	0.0%	10	3.0%	0.296
Elevated triglycerides (%)	0	0.0%	64	18.4%	0.005
Low HDL levels (%)	1	0.7%	81	23.3%	<0.001
High triglyceride/HDL ratio (%)	2	4.1%	135	38.9%	<0.001
Elevated ALT (%)	3	5.9%	87	25.3%	0.011
LSM≥7.4 kPa	7	15.2%	34	9.7%	0.276
LSM≥8.6 kPa	4	8.4%	19	5.6%	0.333
LSM≥8.0 kPa	4	8.4%	22	6.4%	0.501

Note: Data are expressed as numbers and weighted proportions for categorical variables and as weighted means and SEM for continuous variables. Linear regression and Rao-Scott chi-square test were used to compare distributions of continuous and categorical variables across groups, respectively. ALT levels were considered elevated if >22 UI/L in females and >26 UI/L in males.

Abbreviation: BP, blood pressure.

adolescents with MAFLD have ALT levels within the normal range, making this a test with low sensitivity. Fourth, the prevalence of significant liver fibrosis did not differ significantly between participants with steatosis according to whether they met MAFLD diagnostic criteria.

Evidence in the literature supports the notion that metabolic dysfunction is a key determinant of disease pathogenesis and progression.[28] In particular, several cross-sectional studies identified obesity as a major risk factor for fatty liver disease, as its estimated prevalence among obese children is 36%.[29] Our data confirm these findings, as almost 90% of adolescents with steatosis were either overweight or obese. Conversely, data from prospective studies looking at histological progression and hard clinical outcomes in the pediatric population are much more limited. A recent cohort study performed on 44,248 late adolescent men (aged 18–20 years) conscribed to military service in Sweden in 1969–1979 showed that, after adjustment for confounders, being overweight increased the risk of experiencing liver-related events during a mean follow-up period of 37.8 years (hazard ratio = 1.64 for BMI 25–30 compared with BMI 18.5–22.5, 95% CI 1.16–2.32, p = 0.006).[30] Given that we report cross-sectional rather than longitudinal associations, it is possible that adolescents with MAFLD, who have worse metabolic health and

TABLE 3 Logistic regression analysis evaluating the association between liver steatosis, MAFLD, and significant liver fibrosis (LSM ≥ 8 kPa) in the studied population

	LSM ≥ 8 kPa		
	OR	95% CI	*p*
Steatosis-MAFLD			
No steatosis	1.0		
Steatosis without MAFLD	3.74	1.00–13.91	0.050
Steatosis with MAFLD	2.93	1.12–7.66	0.030
Female sex	0.51	0.26–1.00	0.052
Age (years)	1.09	0.89–1.34	0.372
Race-ethnicity			
Non-Hispanic White	1.0		
Hispanic	1.35	0.49–3.72	0.549
Non-Hispanic Black	4.05	1.39–11.74	0.012
Non-Hispanic Asian	1.43	0.36–5.62	0.595
Other	1.81	0.50–6.58	0.350

Abbreviations: CI, confidence interval; OR, odds ratio.

a very high prevalence of overweight/obesity, might not have had the time to show a higher prevalence of fibrosis, but might still be at higher risk of liver-related events in their lifetime.

On the other hand, recent data also appear to suggest that a BMI-centered approach may not be completely justified. In a study including 1339 Caucasian patients with biopsy-proven NAFLD followed for 7.8 years, lean individuals had a similar risk of experiencing a liver-related event compared with their overweight and obese counterparts.[31]

Although the main rationale for the recent definition of MAFLD was to recognize the fundamental association between liver steatosis and metabolic health and providing positive rather than negative criteria, its usefulness in clinical practice would be even more relevant if it helped identify patients at higher risk of progression. Elucidating the most effective modality to screen for liver steatosis in children is a complex task. As already described in the literature and confirmed in the current analysis, relying on ALT levels is problematic, as most individuals with MAFLD and even significant fibrosis have normal levels.[32] In the absence of well-performing noninvasive and widely available tools to identify steatohepatitis, current strategies are aimed at excluding the presence of significant liver fibrosis, based on abundant evidence coming from studies performed in the adult population showing that fibrosis stage is the main predictor of liver-related events.[33,34]

While most blood-based noninvasive scores do not appear to perform well in children and adolescents,[35] VCTE is a promising technique in this target population. In our study, 6%–10% of adolescents with steatosis had liver stiffness values indicative of significant fibrosis (depending on the specific cutoff used). These results are disconcerting, as in a similar population study by Abeysekera et al. conducted in the United Kingdom on 3600 young adults (mean age = 24 years), the authors[36] reported a prevalence significant fibrosis (LSM ≥ 7.9 KPa) of 2.7%. Although several differences exist between the aforementioned study and the current one, our estimates suggest that prevalence is significantly higher in the United States, raising considerable concerns for the number of liver-related events in the upcoming decades.

While MAFLD criteria did not appear to identify the subgroup of participants with significant fibrosis in our study, evidence from longitudinal studies will be crucial to assess their ability to predict liver-related events, the most significant hard clinical outcome.

Several limitations of our study should be mentioned. First, while VCTE has been widely validated in its ability to identify F3-F4 fibrosis in adult patients, few studies evaluated its performance in adolescents specifically and caution should be used when interpreting results in this setting. Second, data were not available on rarer causes of liver disease (including single gene defects, celiac disease, hereditary fructose intolerance, or Wilson disease), preventing us from identifying type 1 fatty liver disease as well as on alcohol intake, a factor that may have contributed to some extent to the development of fibrosis, as studies have shown that alcohol consumption (and especially binge drinking) is not uncommon among adolescents. Although these data could have helped us shed some light on concomitant causes of significant liver fibrosis both in participants with and without MAFLD, it is highly likely that the number of subjects suffering from metabolic or genetic disorders would have been extremely limited, and exclusion of these conditions is not essential given the positive diagnostic criteria for MAFLD.[37] Third, the relatively low number of patients with significant fibrosis made it difficult to assess the effect of multiple variables, because of relatively low statistical power leading to large confidence intervals. It is therefore possible that a larger sample size might have enabled us to detect a difference in the prevalence of significant fibrosis between patients with and without MAFLD. Finally, even if the agreement between NHANES and FibroScan technicians was good, previous studies suggested that more prolonged training in performing VCTE might result in more accurate results.[38]

In conclusion, this study shows that MAFLD criteria are met by most US adolescents with elastographic evidence of steatosis (~90%), with overweight or obesity being the most important contributor. Nonetheless, the prevalence of significant liver fibrosis did not differ significantly between participants with steatosis according to whether they met MAFLD diagnostic criteria. Further longitudinal studies are needed to evaluate whether metabolic dysfunction is associated with faster progression toward inflammation and fibrosis in the pediatric population.

CONFLICT OF INTEREST

Nothing to report

AUTHOR CONTRIBUTIONS

Study design and manuscript draft: Stefano Ciardullo and Gianluca Perseghin. *Manuscript editing and review:* Stefano Ciardullo, Gianluca Perseghin, Marco Carbone, and Pietro Invernizzi. *Data research and analysis:* Stefano Ciardullo. *Study guarantor:* Gianluca Perseghin. All authors approved the final version of the manuscript to be published.

ORCID

Stefano Ciardullo https://orcid.org/0000-0003-2422-3041
Gianluca Perseghin https://orcid.org/0000-0002-3024-0457

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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