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Risk stratification of adolescents for the screening of non-alcoholic fatty liver disease

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Summary

Background: Non-alcoholic fatty liver conditions in adolescence are associated with premature mortality in adulthood. Effective screening could impact the population burden of this disease.

Objectives: We sought to determine which adolescents should be screened for non-alcoholic fatty liver using vibration-controlled transient elastography.

Methods: We simulated a non-alcoholic fatty liver screening program of 938 adolescents from the National Health and Nutritional Examination Survey of 2017/2018. We stratified subjects by body mass index and metabolic parameters and analyzed our data using standard diagnostic statistical measures.

Results: The weighted prevalence of non-alcoholic fatty liver and non-alcoholic fatty liver disease was 24.4%, and 3.8%, respectively. For all subjects with obesity (21.8% of the population), screening identified 61.8% of the non-alcoholic fatty liver cases. In a category of all subjects with obesity and overweight subjects with metabolic abnormalities (26.7% of the population), screening identified 71.2% of non-alcoholic fatty liver cases.

Conclusions: The two groups most likely to benefit by transient elastography screening are adolescents with obesity and overweight adolescents with one metabolic abnormality. These criteria reduce the number of individuals to be tested by approximately 80% (from an approximate 32 million adolescents to 6–7.5 million adolescents), while retaining a diagnostic accuracy of 84%–85%.

KEYWORDS
non-alcoholic fatty liver, screening, transient elastography

1 | INTRODUCTION

The most recent estimated prevalence of non-alcoholic fatty liver (NAFL-simple steatosis) and non-alcoholic fatty liver with fibrosis (NAFLD) in a nationally representative sample of American adolescents using Liver ultrasound with Vibration-Controlled Transient Elastography (VCTE), (FibroScan, Echosens, Paris, France), is 24% and 5%, respectively.[1] Previously, autopsy prevalence estimates for NAFL in US adolescents were assumed to be in the 9%–11% range[2] and NAFLD was considered rare. In addition, while it was known that both disorders are highly associated with insulin resistance, dyslipidaemia, metabolic syndrome, diabetes, liver disease, cancer, and heart disease, in adults and adolescents,[3,4] it was not appreciated until recently that NAFL and non-alcoholic steatohepatitis result in poor long-term outcomes in adolescents. A recent Swedish cohort study of 718 adolescents and young adults with biopsy-proven NAFL conditions, who were followed for a median duration of 15.8 years, showed significantly higher mortality rates for participants with non-alcoholic steatohepatitis (hazard ratio 5.88 [95% CL 3.77–9.17]) and NAFL (hazard ratio 5.26, [95% CL 3.05–9.07]).[5] These higher rates of mortality were associated with increased cause-specific mortality rates from either cancer, cardiometabolic disease, or liver disease as compared to matched controls. Finally, paediatric studies demonstrate improvement

in hepatic steatosis, fibrosis, ALT, and enhanced insulin sensitivity in adolescents who undergo a rigorous lifestyle program of weight loss, and/or exercise.[6–8]

Thus, a new picture has emerged regarding NAFL and NAFLD in adolescence. The disease is significantly more common than previous estimates, the health consequences of these disorders are potentially more severe than previously appreciated, and clinical remission with appropriate lifestyle changes is possible. Today's picture of NAFL and NAFLD in adolescence suggests a potential benefit from a broad-based screening program for adolescents to detect NAFL conditions in an early and more treatable stage.

Because there are few predictors for NAFL and NAFLD other than BMI, it has been suggested that all adolescents be screened using VCTE.[1] In our current healthcare system, however, it is clear that cost and limited medical resources make it impractical to screen 32 million US adolescents. However, if it were possible to identify a specific group of adolescent patients who were more likely to test positive using VCTE, then, a more standardized screening program might be feasible. In 2017, the American Academy of Pediatrics (AAP) issued guidelines that recommended using serum alanine transaminase (ALT), aware of its limitations, to screen for NAFL and NAFLD.[9] However, recent studies, have demonstrated the poor diagnostic sensitivity of serum ALT for identifying adolescents with NAFL or NAFLD.[10,11] Therefore, there are limited clinically useful parameters by which to determine who should be screened for NAFL and NAFLD.

In this study, we sought to identify medical criteria which could be used to identify a group of adolescents to target for screening with VCTE. Since the 2017–2018 NHANES survey collected information on adolescents that included VCTE, we explored the question of identifying a target screening population by simulating a NAFL and NAFLD screening program using a nationally representative audience of adolescents.

2 | METHODS

2.1 | Study population and analytic sample

NHANES is an on-going cross-sectional survey of the civilian, non-institutionalized US population. Surveys are conducted biannually using stratified, multistage cluster probability sampling resulting in a representative US sample. NHANES includes a health interview survey, medical examination, and a nutritional intake survey for each participant.[12] The design and administration of the NHANES are detailed elsewhere.[13] Publicly available datasets available from NHANES do not involve human subjects and therefore are exempt from local IRB review.

Our sample included participants in the 2017–2018 NHANES survey cycle who were between the ages of 12 and 19 ($n = 1194$). We excluded individuals ($n = 15$) who were taking medications which might lead to abnormal liver assessments (i.e., prednisone, azathioprine, methotrexate, valproic acid, minocycline, demeclocycline, doxycycline, and tetracycline). Next, we excluded individuals without a valid VCTE measurement ($n = 112$), as well as those lacking measurements of body mass index (BMI), systolic and diastolic blood pressure, and other specific labs (ALT, HDL cholesterol, triglycerides, fasting glucose) ($n = 129$). A valid VCTE exam included, fasting time of at least 3 h, 10 or more complete stiffness measures, and a liver stiffness interquartile range/median $E < 30\%$. Finally, we excluded individuals with hepatitis B and C ($n = 0$).

We examined the differences in sociodemographic characteristics, BMI and NAFL prevalence between the 129 individuals excluded due to missing laboratory measures and individuals retained in the final sample ($n = 938$) using Rao-Scott chi-square test (statistical significance: $p < 0.05$). There were no significant differences regarding gender ($p = 0.12$), race/ethnicity ($p = 0.74$), income status ($p = 0.74$), BMI category ($p = 0.92$) and NAFL prevalence ($p = 0.31$) between these excluded individuals and those in the final sample.

2.2 | Outcome measures

Measurements of NAFL and liver stiffness were obtained using the liver scanning device, VCTE. To measure NAFL, the VCTE device assesses the ultrasound attenuation related to the presence of hepatic fat and derives a 'controlled attenuation parameter' (CAP score) as a qualitative indicator of fat in the liver.[14] We classified NHANES participants as having NAFL if they had a CAP score greater than 249 dB/m when using the standard M probe and a CAP score of 263 dB/m when using the XL probe based on a review of studies that compared CAP scores to the presence and quantity of liver fat seen on histological examinations from liver biopsy in children, adolescents and adults.[1,15,16] Liver stiffness, an estimate for liver fibrosis, was detected through VCTE and quantified in units termed kilopascals. We defined a liver stiffness cut-off value of 7.4 kilopascals (kPa) or greater as significant liver fibrosis (stage ≥2) based on data from a study that compared VCTE to histological examination by liver biopsy in children.[17] NAFLD was defined as the presence of NAFL with a liver stiffness of ≥7.4 kPa. In addition, we defined more severe forms of NAFLD as liver stiffnesses of ≥8.5 and ≥10 kPa.

2.3 | Primary independent variables

The primary independent variables assessed for their prediction of NAFL were BMI and measures related to metabolic conditions such as high blood pressure and selected laboratory measurements. BMI percentiles were calculated and subjects were categorized as normal weight (<85th percentile), overweight (85th–95th percentile), or having obesity (>95th percentile) using age-based CDC growth charts for boys and girls ages 12–19.[18–20] High blood pressure was defined as a diastolic blood pressure greater than or equal to 85 mm Hg or a systolic blood pressure greater than or equal to 130 mm Hg.[21] Laboratory data included measures for alanine transaminase (ALT), high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and fasting glucose. We defined abnormal measures as: ALT levels greater than or equal to 50 U/L for males and 40 U/L for females[8]; HDL levels less than or equal to 40 mg/dl; triglyceride levels greater than or equal to 150 mg/dl; and fasting glucose levels greater than or equal to 110 mg/dl.[21] Individuals with abnormal HDL, triglycerides, fasting glucose, or blood pressure measurements were

TABLE 1 Characteristics of 2017–2018 NHANES study sample aged 12–19 years ($N = 938$) stratified by the absence and presence of non-alcoholic fatty liver (NAFL)

Characteristics	No NAFL ($n = 679$)	NAFL ($n = 259$)	*p*-value
Age, years, mean (SE)	15.5 (0.16)	15.6 (0.15)	0.70
Gender			
Male	50.1% (42.7%–57.5%)	56.2% (47.7%–64.7%)	0.21
Female	49.9% (42.5%–57.3%)	43.8% (35.3%–52.3%)	
Race/ethnicity			
Hispanic	21.3% (13.8%–28.7%)	35.5% (22.9%–48.2%)	0.19
White, non-Hispanic	54.8% (48.0%–61.7%)	39.1% (25.8%–52.3%)	
Black, non-Hispanic	12.0% (8.4%–15.6%)	13.3% (6.3%–20.2%)	
Other race	11.9% (8.5%–15.3%)	12.1% (7.1%–17.2%)	
Household income status			
<$20 000	14.7% (7.5%–22.0%)	19.8% (14.0%–25.6%)	<0.001
$20 000 to $99 999	56.9% (49.2%–64.6%)	58.4% (51.7%–65.0%)	
$100 000 or greater	28.4% (21.9%–34.9%)	21.8% (15.4%–28.3%)	
Diabetes			
Absent	99.4% (98.8%–100.0%)	99.0% (97.6%–100.0%)	0.37
Present	0.6% (0.0%–1.2%)	1.0% (0.0%–2.4%)	
Body mass index category			
Normal weight subjects	74.0% (70.3%–77.8%)	18.6% (13.4%–23.9%)	<0.001
Overweight subjects	17.0% (13.7%–20.3%)	19.6% (13.9%–25.3%)	
Subjects with obesity	9.0% (6.4%–11.5%)	61.8% (54.0%–69.5%)	
At least one metabolic abnormality			
Absent	84.2% (78.9%–89.4%)	57.2% (48.2%–66.2%)	<0.001
Present	15.8% (10.6%–21.1%)	42.8% (33.8% –51.8%)	
Alanine transaminase			
Normal	99.0% (98.2%–99.8%)	92.5% (88.9%–96.0%)	<0.001
Abnormal	1.0% (0.2%–1.8%)	7.5% (4.0%–11.1%)	
High density lipoprotein cholesterol			
Normal	89.6% (85.7%–93.4%)	69.0% (61.3%–76.7%)	<0.001
Abnormal	10.4% (6.6%–14.3%)	31.0% (23.3%–38.7%)	
Triglyceride			
Normal	92.9% (89.0%–96.8%)	77.0% (70.3%–83.7%)	<0.001
Abnormal	7.1% (3.2%–11.0%)	23.0% (16.3%–29.7%)	
Fasting glucose			
Normal	99.8% (99.6%–100.0%)	99.8% (99.4%–100.0%)	0.86
Abnormal	0.2% (0.0%–0.4%)	0.2% (0.0%–0.6%)	
Blood pressure			
Normal	99.5% (99.0%–100.0%)	95.4% (92.3%–98.5%)	<0.001
Abnormal	0.5% (0.0%–1.0%)	4.6% (1.5%–7.7%)	

categorized as having at least one metabolic abnormality (vs. no metabolic abnormality).

2.4 | Covariates

Health interview data included self-reported information regarding age (continuous), gender (male/female), household income (<$20 000/$20 000–$100 000/$100 000+), race (Hispanic/White, non-Hispanic/Black, non-Hispanic/Other Race), and diabetes status (present/absent).

2.5 | Statistical analysis

Survey weighted descriptive statistics were generated by NAFL status (present/absent) for subject characteristics and primary independent

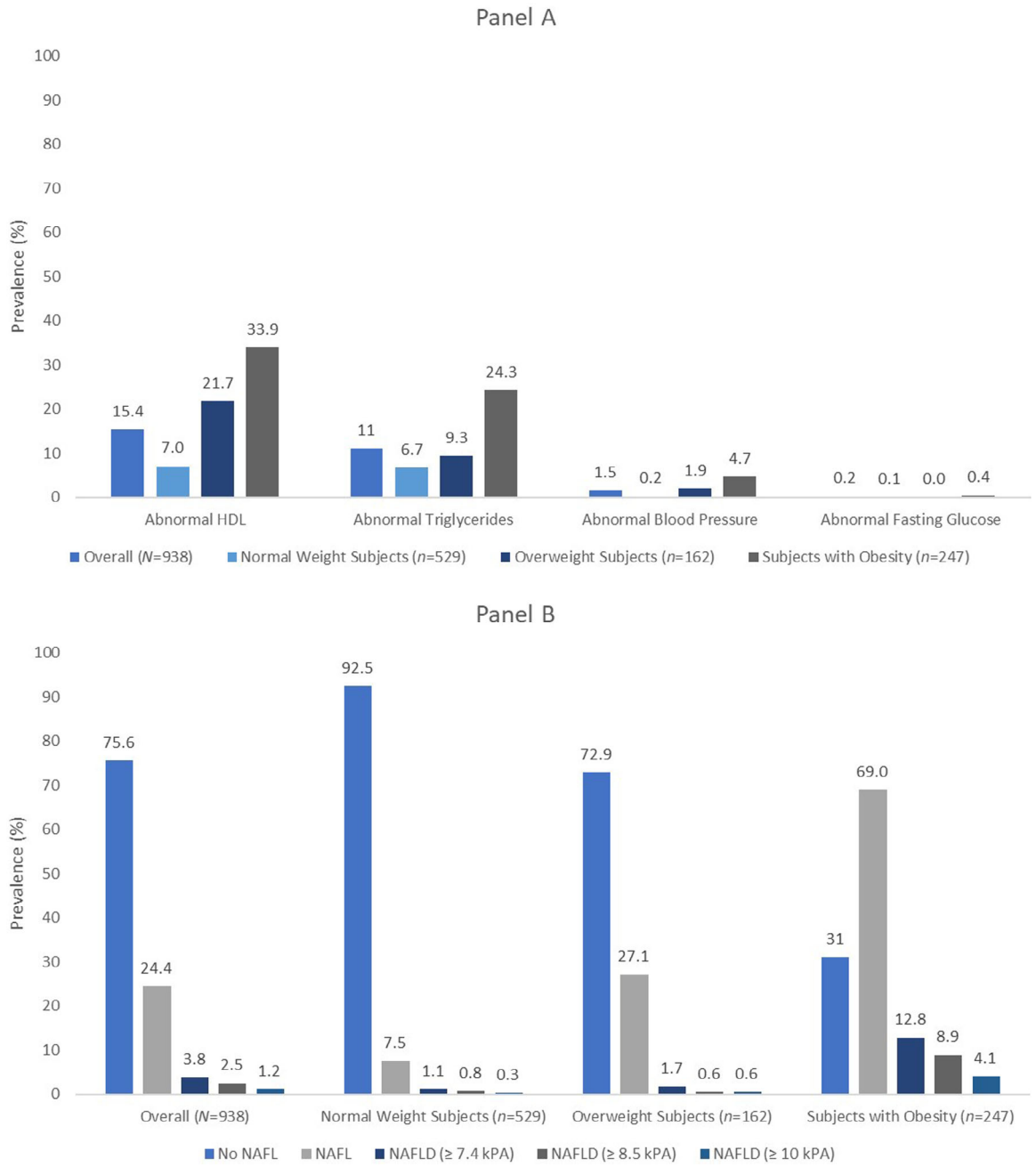

FIGURE 1 (A) Prevalence of each metabolic abnormality by weight status. (B) Prevalence of NAFL and NAFLD (mild, moderate and severe liver stiffness) overall and by weight status. NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver with fibrosis

variables using means (standard error [SE]) or percentages (95% confidence intervals [CI]) as appropriate (Table 1). Rao-Scott chi-square tests (for categorical variables) and ANOVA (for continuous variables) were used to test the difference in subject characteristics by NAFL status. The prevalence of each metabolic abnormality (MA) as well as NAFL and NAFLD (at ≥7.4, ≥8.5 and ≥10 kPa) was graphed overall and by BMI category (Figure 1). We created branching subgroups based upon BMI category and the presence of one or more metabolic abnormalities and presented the percentage of adolescents in each grouping. Next, we calculated the weighted prevalence of NAFL in each of these subgroups (Figure 2). Finally, we developed targeted-screening groups of higher risk subjects based upon BMI percentiles and metabolic status: These groups included (1) subjects with obesity (OB) and metabolic abnormality (MA); (2) subjects with OB and MA as well as overweight subjects (OW) with MA; (3) all subjects with OB; (4) all subjects with OB + OW with MA; (5) subjects with OB and MA + All OW; (6) All OB + All OW. For each of these groups, we estimated diagnostic sensitivity, specificity, positive predictive value,

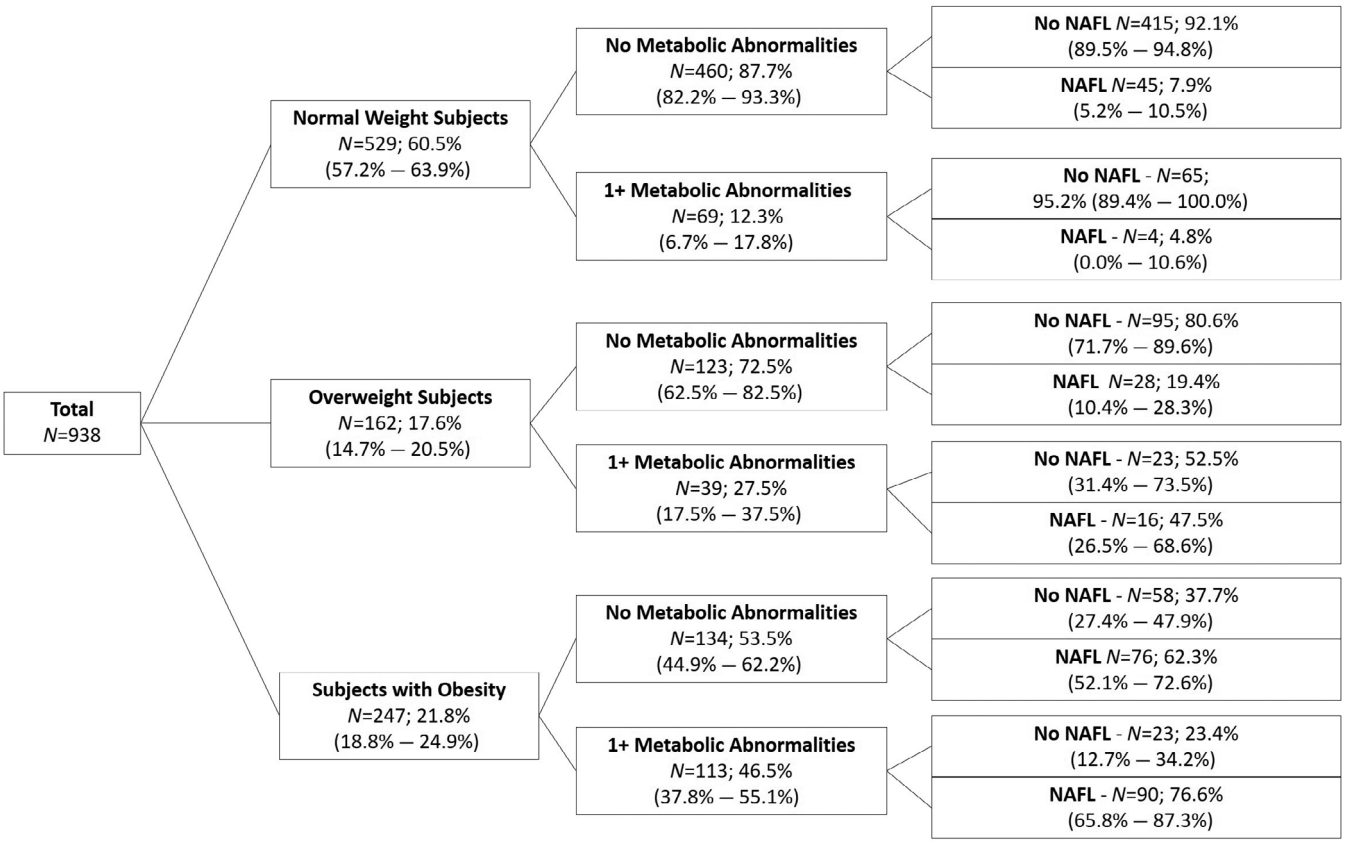

FIGURE 2 Stratification by BMI categories and presence/absence of a metabolic abnormality: Numbers (percentage) of adolescents in each grouping, and number (percentage) with NAFL vs no NAFL for each final category. BMI, body mass index; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver with fibrosis

negative predictive value, accuracy, and created receiver operating curves and their c-statistic (AUROC). All analyses accounted for the complex survey design and were performed in 2021 using SAS 9.4 (Statistical Analysis Software 9.4, Cary, NC).

3 | RESULTS

We analyzed 938 adolescent subjects (51.6% male/48.4% female) (Table 1) whose mean age was 15.5 (SE: 0.11). Subjects were 51% white, the majority (57.2%) had family incomes between $20 000 and $99 999, and 39.5% were overweight or have obesity. Rates of diabetes (0.7%) and abnormal ALT (2.6%) were low. The overall prevalence of metabolic abnormalities in the population were as follows: (1) HDL cholesterol (15.4%); (2) triglyceride (11.0%); (3) blood pressure (1.5%); and (4) fasting glucose levels (0.2%). Nearly, a quarter of the sample (22.4%) had at least one metabolic abnormality. Details by NAFL status are presented in Table 1. Household income, BMI category, the presence of at least one metabolic abnormality, as well as abnormal ALT, HDL, triglyceride, and blood pressure measurements was statistically different between those with NAFL and those without NAFL. (Table 1).

Abnormal HDL (15.4%) and triglycerides (11%) levels were the most prevalent metabolic abnormalities in sample. Abnormal HDL and triglycerides were present in 33.9% and 24.3% of subjects with obesity, respectively (Figure 1A). The prevalence of NAFL and NAFLD in the sample was 24.4%, and 3.8%, respectively. The prevalence of NAFL and NAFLD were 7.5% and 1.1% in normal-weight subjects, 27.1% and 1.7% in overweight subjects and 69% and 12.8% in subjects with obesity, respectively (Figure 2B). The prevalence of more severe levels of NAFLD is reported in Figure 2B.

When stratified by both BMI category and the presence or absence of at least one metabolic abnormality, we found that in normal-weight subjects, NAFL was present in 7.9% of subjects without MA and in 4.8% of those with one or more MA. In overweight subjects, NAFL was present in 19.4% of subjects without MA and in 47.5% of those with one or more MA. Finally, in subjects with obesity, NAFL was present in 62.3% of subjects without MA and in 76.6% of those with one or more metabolic abnormalities (Figure 2).

Examining the potential screening groups (Table 2), we found that VCTE screening for subjects with obesity and MA (10.1% of the population) identified 31.9% of the NAFL cases. In the group of subjects with obesity and MA and OW subjects with MA (15.0% of the population), screening identified 41.3% of NAFL cases. For all subjects with obesity (21.8% of the population), screening identified 61.8% of the NAFL cases. In a group of all subjects with obesity and OW subjects with MA (26.7% of the population), screening identified 71.2% of

TABLE 2 Diagnostic parameters for NAFL screening of potential screening populations based on BMI categories and presence of metabolic abnormality

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUROC (95% CI)	% Screened	US adolescent population represented
OB with MA	0.3185	0.9686	0.7658	0.8151	0.6568 (0.63–0.69)	10.1	2 807 912
OB with MA and OW with MA	0.4130	0.9350	0.6719	0.8317	0.671 (0.64–0.70)	15.0	4 149 436
All OB	0.6175	0.9104	0.6896	0.8807	0.761 (0.73–0.80)	21.8	6 044 896
All OB and OW with MA	0.7120	0.8768	0.6507	0.9043	0.775 (0.74–0.81)	26.7	7 386 421
OB with MA and All OW	0.5146	0.7987	0.4517	0.8362	0.655 (0.62–0.69)	27.8	7 689 987
All OB and all OW	0.8135	0.7404	0.5026	0.9249	0.759 (0.73–0.79)	39.5	10 926 972

Abbreviations: All, all included; AUROC, accuracy, and created receiver operating curves and their c-statistic; BMI, body mass index; CI, confidence interval; MA, at least one metabolic abnormality; NAFL, non-alcoholic fatty liver; OB, subjects with obesity; OW, overweight subjects.

NAFL cases. In a group of all OW adolescents and subjects with obesity with MA (27.8% of the population), screening identified 51.5% of NAFL cases. Finally, in a group of all overweight subjects and all subjects with obesity (39.5% of the population), VCTE screening identified 81.4% of NAFL cases. Diagnostic accuracy for the group with obesity alone was 83.8% and for the subjects with obesity plus OW + MA group was 84.6%. The diagnostic sensitivity, specificity, positive predictive value, negative predictive value and AUROC for these categories are detailed in Table 2 where the optimal AUROC was found for all subjects with obesity and OW with MA group (c-statistic 0.775, 95% CI 0.74–0.81).

4 | DISCUSSION

The prevalence of NAFL/NAFLD and the associated conditions of poor metabolic and cardiovascular health have been increasing in adolescents for decades.[22] Recent data suggest that adolescents with NAFL and NAFLD experience higher rates of premature mortality,[5] and as such, screening this population requires serious consideration. While screening for health prevention is indicated when the prevalence of a condition is common, and the effectiveness of early detection is well-established, screening all adolescents for NAFL and NAFLD must also consider the practicality, expense and any potential harms that might occur. Such considerations suggest the development of a more targeted population approach to screening.

We found in a nationally representative population of adolescents that the optimal detection of NAFL, on a health policy level, occurs by screening adolescents with obesity plus overweight adolescents with at least one metabolic abnormality. Our data build on and extend the results from other studies which have identified BMI as an important predictor of NAFL.[23,24] In addition, this VCTE screening strategy identifies adolescents with NAFL and liver stiffness suggestive for stage 2, or greater, liver fibrosis.

Despite our findings that it is possible to identify subgroups of adolescents at higher risk for having NAFL conditions, and the compelling arguments that the early identification of these disorders can improve outcomes, there remain some valid arguments against a policy to recommend screening for NAFL and NAFLD. First, gold-standard evidence of screening effectiveness from randomized controlled trials is not currently available as is information regarding the potential psychological harms to adolescents that might arise from screening, as well as the expense and burden of downstream medical and diagnostic care. In addition, and importantly, adolescents identified with NAFL conditions through screening may not have the ability or resources to find successful weight loss and exercise programs to potentially reverse the disorder. A diagnosis of serious consequence without the ability to do anything about it could worsen outcomes rather than improve them. Finally, once diagnosed with NAFL and/or NAFLD, patients will likely need ongoing monitoring via various imaging tests, and if these tests suggest worsening disease, more invasive procedures such as liver biopsy might be required. Such procedures might be costly to the health-care system and involve some risk to the patient.

However, several factors support the commencement of screening now rather than waiting for the gold standard evidence. (1) RCTs require substantial time to complete. (2) NAFL conditions potentially have severe outcomes. (3) Lifestyle interventions can reverse or reduce liver injury. (4) VCTE screening is safe, inexpensive and imposes little immediate burden to the patient or health-care system. (5) Finally, and possibly most importantly, if adolescents are left unaware of having NAFL or NAFLD, they might not receive a medical evaluation for decades after transitioning into adulthood, and this could result in a prolonged, undetected phase of compensated cirrhosis in these patients.[25]

The strengths of this study include detailed NHANES data which can be used to simulate a nationally representative screening program for adolescents where reliable estimates of diagnostic accuracy and efficiency can be obtained. NHANES data are also collected using extensive quality control measures and by technicians trained and certified in all aspects of data collection. Sampling for NHANES data relies upon a probability cluster sampling method and a sampling frame that is representative of the US non-institutionalized civilian population. Finally, VCTE has advantages over traditional ultrasound including improved sensitivity to detect fat[26] and it can estimate stages of liver fibrosis.[17] Other technologies are available which could in theory be used to conduct screening, including magnetic resonance

technology;[27,28] however, these tests are expensive with limited access to the general population and are therefore an inadequate screening tool for adolescents.

There are also several limitations to these cross-sectional data including our inability to confirm a subject's outcome measured by liver histology. We have not validated our findings in an external cohort. There is no absolute agreed upon cut-off measure for both the CAP score and kPa score, and the accuracy of both scores for detecting NAFL and NAFLD using VCTE might vary depending upon the study population.[16,28–30] Our data are also limited by the unavailability of self-reported alcohol consumption in this NHANES cycle. While self-reported alcohol consumption in teenagers has limited reliability, the frequency of alcohol dependence in this age group based upon national surveillance surveys, suggests that less than 2% of adolescents have an alcohol use disorder.[31] Autoimmune markers to detect autoimmune hepatitis and data regarding a history of congenital heart disease (which can result in passive hepatic congestion and liver stiffness) were also not available for evaluation limiting our ability to exclude subjects with these disorders.

While the ideal group for targeted VCTE screening requires further investigation, including RCTs, our study shows that the target group most likely to benefit from VCTE screening are adolescents with obesity and overweight adolescents with at least one metabolic abnormality. Stratification of adolescents using these criteria reduces the number of individuals to be tested from an approximate 32 million adolescents to 6–7.5 million adolescents, while also retaining an acceptable level of disease identification and diagnostic accuracy.

CONFLICT OF INTEREST

The authors of this paper have no conflicts of interest to disclosure.

AUTHOR CONTRIBUTIONS

GA and EH conceived the research question. DW analysed the data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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