Annals of Gastroenterology (2023) **36,** 1-8

Prevalence and risk factors of nonalcoholic fatty liver disease, high-risk nonalcoholic steatohepatitis, and fibrosis among lean United States adults: NHANES 2017-2020

Markos Kalligeros[a]*, Stephanos Vassilopoulos[a]*, Athanasios Vassilopoulos[a], Fadi Shehadeh[a,b], Ingrid Lazaridou[a], Eleftherios Mylonakis[c], Kittichai Promrat[d], Jack R. Wands[e]

Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI, USA; National Technical University of Athens, Greece; Houston Methodist Hospital, Houston, TX, USA; Providence VA Medical Center, Providence, RI, USA

Abstract

Background Nonalcoholic fatty liver disease (NAFLD) is a growing public health concern worldwide. Early detection and management of modifiable risk factors are critical to mitigating its impact. This study aimed to investigate the prevalence and risk factors of NAFLD, nonalcoholic steatohepatitis (NASH), and fibrosis among lean adults in the United States (US), using the latest National Health and Nutrition Examination Survey (NHANES) dataset from 2017-2020.

Methods Using controlled attenuation parameter scores of ≥285 dB/m, we assessed the age-adjusted prevalence of lean NAFLD. To determine the age-adjusted prevalence of high-risk NASH and significant fibrosis, we used the FibroScan-aspartate aminotransferase (FAST) score (cutoffs 0.35 and 0.67) and vibration-controlled transient elastography (liver stiffness measurement ≥8 kPa). Multivariate logistic regression was used to identify potential risk factors.

Results We found the age-adjusted prevalence of lean NAFLD to be 6.30%. Among lean US adults, the age-adjusted prevalence of high-risk NASH and significant fibrosis was 1.29% and 4.35%, respectively. Older age and metabolic comorbidities, such as hypertension, diabetes, and dyslipidemia were associated with NAFLD and its complications.

Conclusion These findings suggest that the prevalence of NAFLD is of concern among lean individuals, particularly those aged 40 and older with metabolic comorbidities, while a targeted approach to screening and risk stratification for hepatic fibrosis upon lean NAFLD diagnosis is warranted.

Keywords Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, fibrosis, NHANES

Ann Gastroenterol 2023; 36 (XX): 1-8

Introduction

Nonalcoholic fatty liver disease (NAFLD) can manifest as simple hepatic steatosis, but it may progress to nonalcoholic steatohepatitis (NASH), severe fibrosis, and even cirrhosis [1]. It has been estimated that NAFLD affects 25% of the global adult population [2]. The development of NAFLD has been linked to a number of risk factors, of which the most commonly observed are diabetes, obesity, hyperlipidemia, and hypertension [2]. However, NAFLD can also manifest in individuals with lean body habitus [3,4] and "lean NAFLD" is defined as the presence of hepatic fat accumulation in patients with a body mass index (BMI) <25 kg/m^2 or <23 kg/m^2 in individuals of Asian descent [5].

Conflict of Interest: None

*Authors contributed equally

Correspondence to: Markos Kalligeros, Department of Medicine, The Warren Alpert Medical School of Brown University, Rhode Island Hospital, RI 02903 Providence, USA,
e-mail: markos_kalligeros@brown.edu

Received 17 July 2023; accepted 24 October 2023;
published online 3 November 2023

DOI: https://doi.org/10.20524/aog.2023.0840

Lean NAFLD has recently garnered significant attention for several reasons, including its uncertain metabolic profile, the influence of conventional metabolic risk factors, and its natural history and long-term outcomes [6]. In addition, NASH and fibrosis prevalence in this population are not well established. In the present study, we used data from the latest National Health and Nutrition Examination Survey (NHANES) dataset from the 2017-2020 period to estimate the prevalence of lean NAFLD, NASH, and fibrosis among United States (US) adults. Additionally, potential risk factors that may contribute to the development of these conditions were also investigated.

Materials and Methods

Data source

We derived our data from the NHANES archive, a program that aims to evaluate the health and nutritional status of individuals in the US [7]. The survey has adopted a unique approach that combines interviews and physical examinations to gather data. NHANES is an important project of the National Center for Health Statistics, which operates under the Centers for Disease Control and Prevention and is responsible for producing essential health statistics for the nation. Our study is based on an analysis of data from the survey cycles spanning from 2017 to March 2020.

Study population

Participants were considered eligible for inclusion in this study if the following criteria were met: 1) adult patients (age ≥18 years old); 2) having a complete transient elastography (TE) exam, i.e., fasting time of at least 3 h, 10 or more complete stiffness (E) measures, and a liver stiffness interquartile range (IQR) to median E ratio <30%; and 3) having body mass index (BMI) data. We excluded patients who met any of the following conditions: 1) BMI <18.5 kg/m^2 or >25 kg/m^2 (>23 kg/m^2 for patients of Asian descent); 2) heavy alcohol use, defined as >2 drinks per day for men and >1 per day for women; 3) positive hepatitis C (HCV) RNA; 4) positive hepatitis B surface antigen (HBsAg); or 5) exposure to steatogenic drugs, such as tamoxifen, valproic acid, amiodarone, methotrexate, and glucocorticoids.

[a]Department of Medicine, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI, USA (Markos Kalligeros, Stephanos Vassilopoulos, Athanasios Vassilopoulos, Fadi Shehadeh, Ingrid Lazaridou); [b]Department of Electrical and Computer Engineering, National Technical University of Athens, Greece (Fadi Shehadeh); [c]Department of Medicine, Houston Methodist Hospital, Houston, TX, USA (Eleftherios Mylonakis); [d]Division of Gastroenterology and Hepatology, Providence VA Medical Center, Providence, RI, USA (Kittichai Promrat); [e]Liver Research Center, The Warren Alpert Medical School of Brown University, Providence, RI, USA (Jack R. Wands)

Definitions

Starting in the 2017-2018 period, NHANES employed vibration-controlled TE to estimate liver fibrosis, which involved measuring liver stiffness and quantifying liver fat using the controlled attenuation parameter (CAP) with the aid of the FibroScan® model 502 V2 Touch machine, equipped with a medium (M) or extra-large (XL) probe. Healthcare technicians were trained and certified by both NHANES staff and the equipment manufacturer, Echosens™ North America, and followed the guidelines provided by the manufacturer while carrying out the examinations. To maintain standardized data quality, the FibroScan® machine conducted and displayed several quality control (QC) measures during the test, including the median of all valid measurements, the IQR, and the ratio of the IQR to the median stiffness. The machine recalculated these QC indexes after each new measurement. The health technicians (HTs) were trained to obtain 10 valid measurements with an IQR/M ratio below 30%. NHANES HTs performed the elastography examination inside the NHANES Mobile Examination Center. The procedures for this examination are explained in detail in the Liver Ultrasound TE Procedures Manual [8].

We defined hypertension as a systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or taking prescription for hypertension, or participants being told by their doctor that they had high blood pressure. We classified prediabetes as having no prior history of diabetes diagnosis and meeting at least one of the following criteria: fasting plasma glucose levels of 100-125 mg/dL or glycosylated hemoglobin (HbA1c) in the range 5.7-6.4%. Diabetes was diagnosed if one or more of the following criteria were met: fasting plasma glucose ≥126 mg/dL or HbA1c level ≥6.5%, or current use of glucose-lowering medications/insulin, or when participants were told by their doctor that they had diabetes. Regarding dyslipidemia, our definition required one of the following: triglycerides ≥150 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein <40 mg/dL or total cholesterol ≥200 mg/dL, or when participants were told by their doctor that they needed lipid-lowering prescription.

To diagnose NAFLD in the present study, a median CAP score of ≥285 dB/m was considered, providing an optimized sensitivity of 80% and specificity of 77% for differentiating steatosis grade 0 from grades 1-3 [9]. Since other studies suggested different CAP cutoffs for NAFLD, we conducted additional sensitivity analyses with a CAP cutoff of 263 dB/m [10]. To detect High-risk NASH, we used the FibroScan-aspartate aminotransferase (FAST) score estimates and 2 cutoffs: 0.35 for 90% sensitivity and 0.67 for 90% specificity, as described in the study by Newsome *et al* [11]. Finally, we defined significant fibrosis and advanced fibrosis using liver stiffness measurements (LSM) of ≥8.0 kPa and ≥13.1 kPa, respectively. It is pertinent to note that the tests utilized in this study were noninvasive and do not represent the gold standard for diagnosing the aforementioned conditions; the gold standard remains liver biopsy. Consequently, the diagnoses of NAFLD, high-risk NASH, and fibrosis (significant

or advanced) are not definitive, but are indicative, based on values exceeding our abovementioned cutoff thresholds.

Outcomes of interest

Our primary outcome of interest was to estimate the age-adjusted prevalence of NAFLD, NASH and fibrosis among lean US adults using the cutoffs described above. As a secondary outcome we aimed to identify predictors of NAFLD, NASH and fibrosis among lean US adults.

Statistical analysis

To ensure accuracy, we implemented NHANES-recommended sample weights in our analyses, which accounted for the intricate, multistage, probability-sampling design of the survey. To calculate age-adjusted prevalence estimates of NAFLD, NASH and fibrosis, we applied the direct method to the 2000 U.S. Census standard population, using the age groups 18-39 years, 40-59 years and ≥60 years. We conducted multivariate logistic regression analyses to examine the association between selected demographic factors (age, sex, race) and metabolic risk factors (hypertension, diabetes, dyslipidemia) with NAFLD, NASH and fibrosis. We used the Student's *t*-test to analyze continuous variables and the chi-square test to compare the distribution of categorical variables. All analyses were performed using Stata 17 (StataCorp, TX). We considered P<0.05 as statistically significant. Additional details are provided in the Supplementary methods.

Results

Of the 15,560 participants who took part in the NHANES project during the 2017-2020 cycle, 9698 had completed a TE exam. We excluded 1381 participants who were <18 years old, and 924 participants who had positive HBsAg, HCV RNA, excessive alcohol use, or exposure to steatogenic medications. Finally, 5765 participants with BMI <18.5 or >25 kg/m^2 were also excluded. The remaining 1628 participants were classified as lean (BMI<25 kg/m^2 for non-Asians and <23 kg/m^2 for Asians) and were eligible for our analysis (Fig. 1).

Prevalence and characteristics of NAFLD among lean US adults

Compared to lean adults without NAFLD, participants with lean NAFLD were more likely to be 40 years and older, males, Non-Hispanic (NH) White or NH Asian. Detailed baseline characteristics are presented in Table 1. Using a cutoff value of 285 dB/m, we found that the age-adjusted prevalence of NAFLD among lean US adults was 6.30% (95% confidence interval [CI] 3.84-10.16%) (Fig. 2). We found a lower prevalence among young

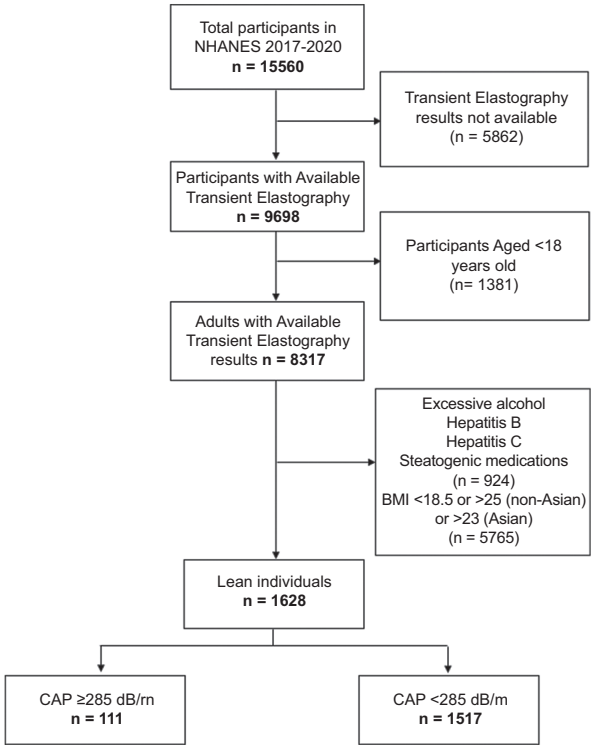


Figure 1 Study flowchart
BMI, body mass index; CAP, controlled attenuation parameter

adults aged 18-39 years, at 2.16% (95%CI 0.97-4.74%), compared to those aged 40-59 and 60 or older, at 8.46% and 10.63%, respectively. Among US adults of different ethnicities, the age-adjusted prevalence of NAFLD was 6.40 (95%CI 3.32-11.99%) among NH Whites, 7.38% (95%CI 4.64-11.53%) for Hispanics, while NH Black had the lowest prevalence at 3.87% (95%CI 1.63-8.92%) and NH Asians the highest prevalence at 7.79% (95%CI 5.44-11.04%). We also observed a higher prevalence among lean males 8.18% (95%CI 4.73-13.80%) compared to lean females 5.16% (95%CI 2.91-8.98%), and among lean individuals with diabetes at 26.90% (95%CI 11.34-51.42%). In a sensitivity analysis using a cutoff value of 263 dB/m, the overall prevalence of lean NAFLD was 11.27% (95%CI 8.17-15.35%) (the remaining data are presented in Fig. 2).

Prevalence of high-risk NASH among lean US adults

Using a FAST score cutoff value of 0.35 (with 90% sensitivity), we determined that the prevalence of high-risk NASH among lean US adults was 1.29% (95%CI 0.70-2.34%) (Supplementary Fig. 1 and Supplementary Table 1). We observed a higher prevalence among males (2.49%, 95%CI 1.18-5.20%), individuals over 60 years old (2.26%, 95%CI 0.65-7.55%), and those with diabetes (4.03%, 95%CI 1.25-12.23%) or hypertension (2.53%, 95%CI 1.12-5.59%). Furthermore, when we used a cutoff value of 0.67 (with 90% specificity), we found that the prevalence of high-risk NASH was 0.05% (95%CI 0.01-0.24%).

Table 1 Characteristics of study participants

Characteristics	Total	CAP <285 dB/m	CAP ≥285 dB/m	P-value
	N=1628	N=1517	N=111	
Age categories				<0.001
18-39	764 (46.9%)	746 (49.2%)	18 (16.2%)	
40-59	374 (23.0%)	340 (22.4%)	34 (30.6%)	
60+	490 (30.1%)	431 (28.4%)	59 (53.2%)	
Sex				0.26
Female	847 (52.0%)	795 (52.4%)	52 (46.8%)	
Male	781 (48.0%)	722 (47.6%)	59 (53.2%)	
Race/Ethnicity				0.046
Non-Hispanic White	615 (37.8%)	566 (37.3%)	49 (44.1%)	
Hispanic	296 (18.2%)	274 (18.1%)	22 (19.8%)	
Non-Hispanic Black	386 (23.7%)	373 (24.6%)	13 (11.7%)	
Non-Hispanic Asian	240 (14.7%)	220 (14.5%)	20 (18.0%)	
Other	91 (5.6%)	84 (5.5%)	7 (6.3%)	
Diabetes status				<0.001
No diabetes	1,046 (64.3%)	1,004 (66.2%)	42 (37.8%)	
Prediabetes	138 (8.5%)	108 (7.1%)	30 (27.0%)	
Diabetes	444 (27.3%)	405 (26.7%)	39 (35.1%)	
Blood pressure				<0.001
No hypertension	1,075 (71.0%)	1,028 (73.0%)	47 (44.8%)	
Hypertension	439 (29.0%)	381 (27.0%)	58 (55.2%)	
Dyslipidemia status				<0.001
Normal lipids	842 (54.7%)	809 (56.5%)	33 (31.1%)	
Dyslipidemia	696 (45.3%)	623 (43.5%)	73 (68.9%)	
Metabolic syndrome status				<0.001
No metabolic syndrome	623 (85.7%)	590 (87.9%)	33 (58.9%)	
Metabolic syndrome	104 (14.3%)	81 (12.1%)	23 (41.1%)	

CAP, controlled attenuation parameter

Prevalence of fibrosis among lean US adults

Using an LSM cutoff of 8.0 kPa we estimated the prevalence of significant fibrosis among lean US adults to be 4.35% (95%CI 2.73-6.89%) (Supplementary Fig. 2 and Supplementary Table 2). We found higher fibrosis prevalence among older adults (7.35%, 95%CI 3.80-13.79%), NH Whites (5.29%, 95%CI 3.13-8.81%) and males (7.74%, 95%CI 4.14-14.02%). The overall prevalence estimate of advanced fibrosis (LSM ≥13.1 kPa) was 0.35% (95%CI 0.13-0.94%).

Risk factors associated with NAFLD, high-risk NASH and significant fibrosis among lean US adults

Utilizing a multivariate regression model, we aimed to identify predictors of NAFLD, NASH and fibrosis among lean individuals (Fig. 3). Using a diagnostic cutoff of 263 dB/m, we found that, compared to lean adults without NAFLD, those with NAFLD were more likely to be older, aged 40-59 years (adjusted odds ratio [aOR] 2.64, 95%CI 1.22-5.70), or over 60 (aOR 2.49, 95%CI 1.00-6.25), of NH Asian ethnicity (aOR 2.01, 95%CI 1.12-3.62), with hypertension (aOR 1.72, 95%CI 1.12-2.64), or dyslipidemia (aOR 2.33, 95%CI 1.61-3.36). However, using a higher cutoff of 285 dB/m, only hypertension (aOR 3.59, 95%CI 2.02-6.38), and diabetes (aOR 2.71, 95%CI 1.20-6.11), remained as predictors of NAFLD presence among lean adults. Furthermore, hypertension (aOR 2.88, 95%CI 1.10-7.57) was the only predictor of high-risk NASH (cutoff 0.35) among lean adults. Additionally, we found that lean adults with significant fibrosis (LSM ≥8.0 kPa) were more likely to be aged ≥60 years (aOR 4.41, 95%CI 1.20-16.16), and less likely to be of Asian descent (aOR 0.09, 95%CI 0.01-0.83). We were unable to perform logistic regression for high-risk NASH (cutoff of 0.67) and advanced fibrosis (measured by ≥13.1 kPa) because of the low prevalence of these conditions. A visual summary of our main findings is provided in Fig. 4.

Discussion

Lean NAFLD is a growing concern worldwide, as it is estimated that up to 20% of patients with NAFLD may have a lean body habitus [4]. In this report, we present the first age-adjusted prevalence estimates of NAFLD, high-risk NASH and significant fibrosis among lean US adults. Using the NHANES 2017-2020 dataset we provide the most recent estimates, derived from a larger sample size with increased precision, in a nationally representative manner [12]. Our results show

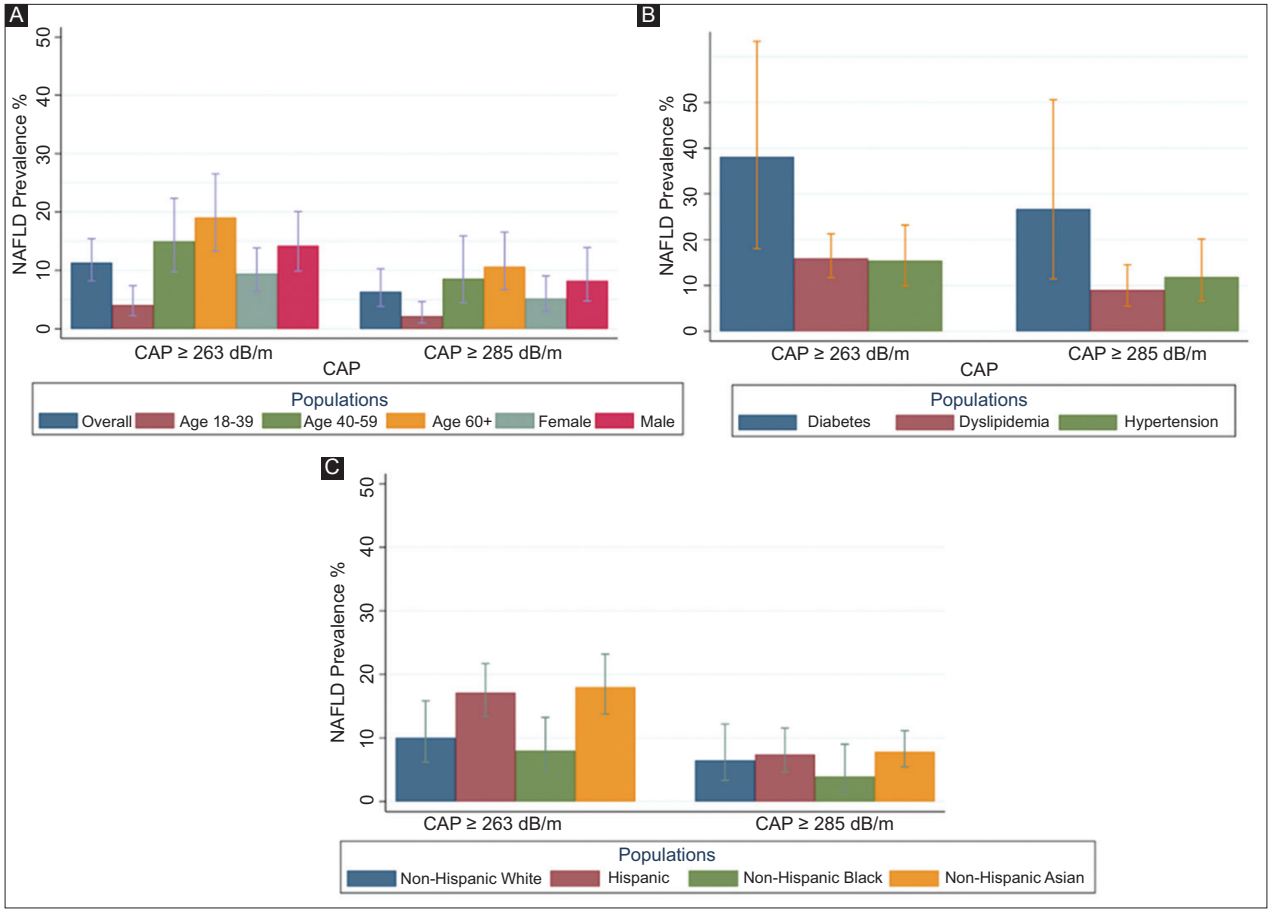


Figure 2 Age-adjusted prevalence of nonalcoholic fatty liver disease among lean United States adults stratified by: (A) overall, age and sex (B) comorbidities (C) ethnicity

CAP, controlled attenuation parameter; NAFLD, nonalcoholic fatty liver disease

that the age-adjusted prevalence of lean NAFLD among US adults is 6.30%, while using the FAST score and TE we found the prevalence of high-risk NASH and significant fibrosis to be 1.29% and 4.35%, respectively.

The estimates presented herein contribute to our current understanding of lean NAFLD prevalence among US adults, while the use of FibroScan offers more accurate estimates compared to prior ultrasound-based reports. Using the NHANES III cohort from 1988-1994, Younossi *et al* reported the first estimates of lean NAFLD in the US and found it to be 7.4% [13]. Recently, a meta-analysis by Ye *et al*, based on 23 studies (with multiple diagnostic methods and cutoffs) found the global prevalence of lean NAFLD to be 5.1% in the general population, while lean individuals comprised almost 20% of the NAFLD population [4].

The American Gastroenterological Association (AGA) recently published a clinical practice guidance for the diagnosis and management of NAFLD [5]. Although routine general screening is not recommended, the AGA recommends screening for adults over 40 years of age with diabetes, as well as for lean individuals with metabolic diseases, such as type 2 diabetes mellitus, dyslipidemia and hypertension [5]. It is notable that our multivariate regression analysis confirmed these risk factors by identifying age >40 years, hypertension, dyslipidemia and diabetes as significant predictors of lean NAFLD. Therefore, it is important to identify and treat these modifiable risk factors to prevent and manage lean NAFLD in affected individuals.

The present study also offers the first estimated prevalence of high-risk NASH among lean US adults. Using a FAST cutoffs of 0.35 and 0.67, we found the high-risk lean NASH prevalence to be 1.29% and 0.05%, respectively. A recent report from NHANES 2017-2018 using the FAST score found high-risk NASH in the general population to be 5.8% (cutoff 0.35) and 1.2% (cutoff 0.67). Given that NASH is a histologic diagnosis, most of the available estimates of NASH in lean adults come from studies with available liver biopsies. When Fracazani *et al* assessed the presence of NASH in lean individuals with biopsy-proven NAFLD they found it to be 17% [14]. However, prior studies from lean adults with biopsy-proven NAFLD have found NASH prevalence to be as high as 50% [15]. The meta-analysis conducted by Ye *et al* [4] also revealed a notable prevalence of lobular inflammation, amounting to 25.1% in non-obese or lean individuals with NAFLD and available biopsies, confirming that, despite their apparent healthier

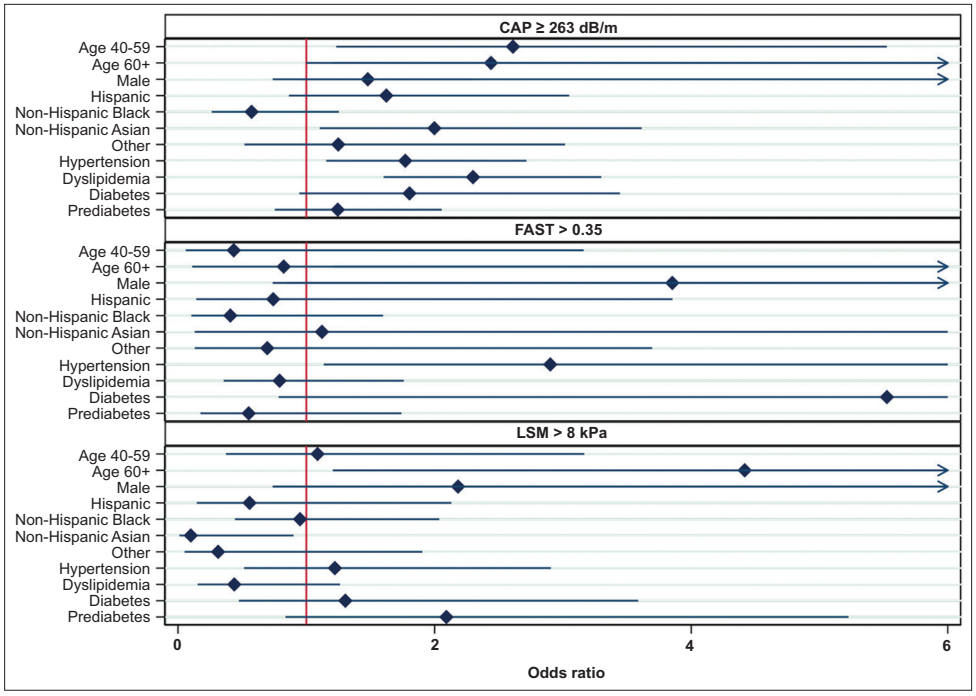


Figure 3 Multivariate logistic regression assessing the association between demographic and metabolic risk factors with nonalcoholic fatty liver disease, nonalcoholic steatohepatitis and fibrosis
CAP, controlled attenuation parameter

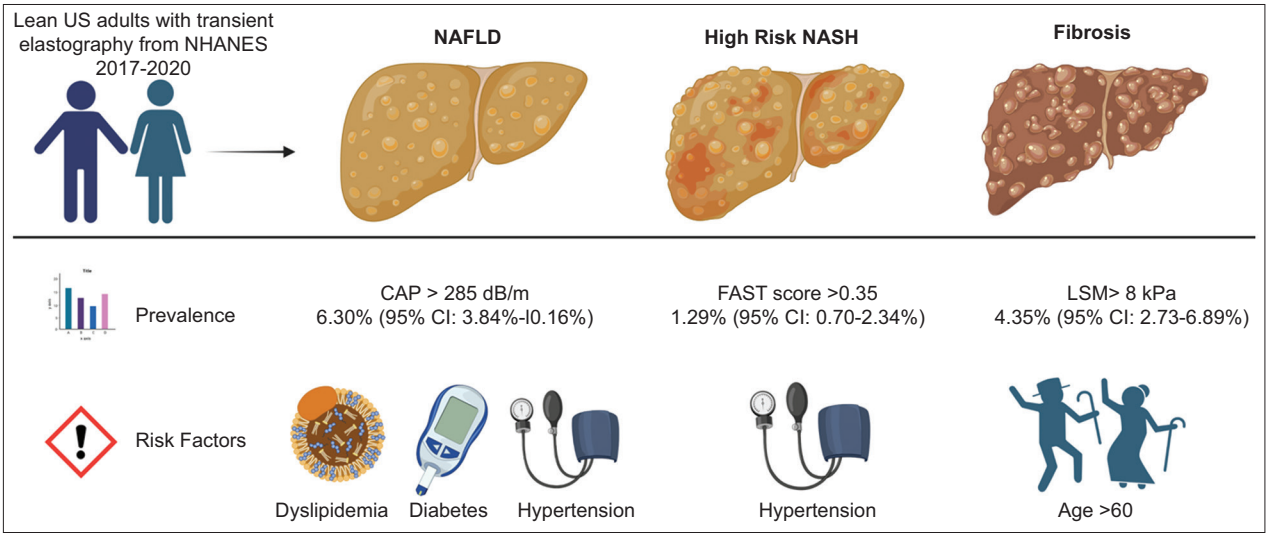


Figure 4 Visual summary of key study findings
NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; CAP, controlled attenuation parameter; FAST, FibroScan-aspartate aminotransferase; LSM, liver stiffness measurement; CI, confidence interval

phenotype, such patients may exhibit the complete range of histopathological characteristics of NASH [16].

The prevalence of significant fibrosis (defined as ≥8 kPa) among lean individuals was found to be relatively low, with only 4.35% of lean US adults being affected. This finding is not surprising, as previous studies, such as the meta-analysis conducted by Young *et al*, have demonstrated that obese individuals with NAFLD are 2.5 times more prone to have fibrosis compared to lean individuals [17]. However, the assumption that patients with lean NAFLD have a benign natural history may be incorrect. For example, a study by Hagstrom *et al*, which followed patients with NAFLD for a median of 19.9 years, found that although patients with lean NAFLD had a lower prevalence of fibrosis, they were at higher risk of developing severe liver disease compared to patients with NAFLD and a higher BMI [3]. Similarly,

during an 8-year follow up Younes *et al* found that, regardless of longitudinal progression to obesity or genetic predisposition, lean subjects with NAFLD may experience similar rates of liver disease and mortality as their non-lean counterparts [18].

Regarding fibrosis risk factors, our analysis demonstrated that, although individuals of Asian descent had the highest age adjusted prevalence of NAFLD, at 7.79%, they exhibited lower chances of significant fibrosis (aOR 0.09, 95%CI 0.01-0.83). This observation is consistent with the results reported by Weinberg *et al* in a US cohort, where Asians accounted for nearly half of the lean individuals with NAFLD, yet exhibited a markedly lower incidence of cirrhosis [19]. Additionally, we found that individuals over the age of 60 had a 4-fold greater risk of significant fibrosis. This finding highlights that, besides performing risk stratification for hepatic fibrosis at the time of lean NAFLD diagnosis, regular surveillance with noninvasive tests is also necessary to detect any progression of the disease and to identify patients with advanced fibrosis or cirrhosis [5].

Our study had several limitations that it is important to take into account when interpreting our findings. First, our prevalence estimates were derived from noninvasive tests such as CAP, TE, and FAST score, which do not match the diagnostic accuracy of a liver biopsy. For instance, factors such as underlying liver disease, BMI and diabetes can influence CAP values, while the optimal cutoff values for CAP and TE in discerning different grades of steatosis and fibrosis vary across studies [20]. Similarly, the FAST score may underperform in low-prevalence populations as well as certain demographics, such as patients with type 2 diabetes mellitus; additionally, a transient elevation in serum transaminase levels could overestimate the FAST score, consequently reducing its specificity [11,21]. Second, the study design of NHANES may introduce inherent biases, such as recall bias and underreporting of alcohol use, potentially influencing the results. Third, since NHANES is a cross-sectional survey, a causal relationship between specific risk factors and outcomes cannot be established, and other potential risk factors, such as genetic polymorphism, were not evaluated.

In conclusion, it is apparent that lean individuals are not immune to NAFLD and its complications. In particular, those over the age of 40 with metabolic comorbidities should be screened and monitored for the development of complications. Therefore, it is recommended that healthcare professionals employ a targeted approach to the diagnosis and management of NAFLD in lean individuals, to effectively mitigate the risks associated with this growing epidemic.

Acknowledgments

The visual abstract was created with BioRender.com. We would also like to thank NHANES study personnel and all study participants.

Summary Box

What is already known:

- Nonalcoholic fatty liver disease (NAFLD) is a significant and growing public health issue globally
- Early detection and management of modifiable risk factors are crucial to reducing the adverse effects of NAFLD
- The prevalence of NAFLD, nonalcoholic steatohepatitis (NASH) and fibrosis has been previously assessed in the general population, but less so among lean individuals

What the new findings are:

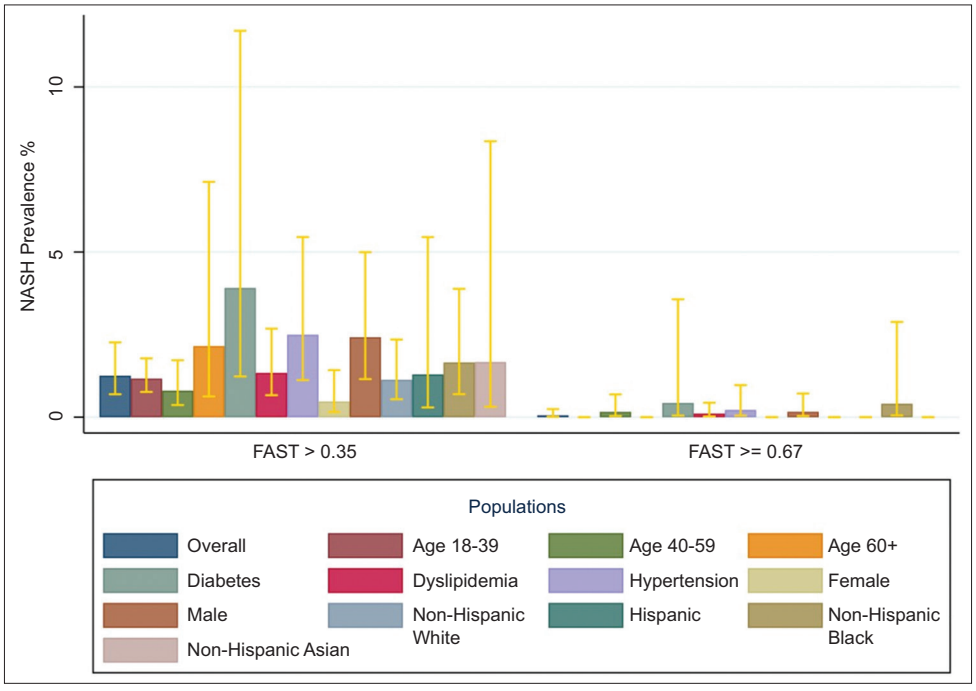
- The age-adjusted prevalence of lean NAFLD in the United States is 6.30%, with high-risk NASH and significant fibrosis prevalence at 1.29% and 4.35%, respectively, among lean adults
- Metabolic comorbidities, such as hypertension, diabetes and dyslipidemia, as well as older age, are associated with NAFLD and its complications, even among lean individuals
- A targeted approach for screening and risk stratification for hepatic fibrosis upon diagnosis of lean NAFLD is warranted, especially for individuals aged 40 and older with metabolic comorbidities

References

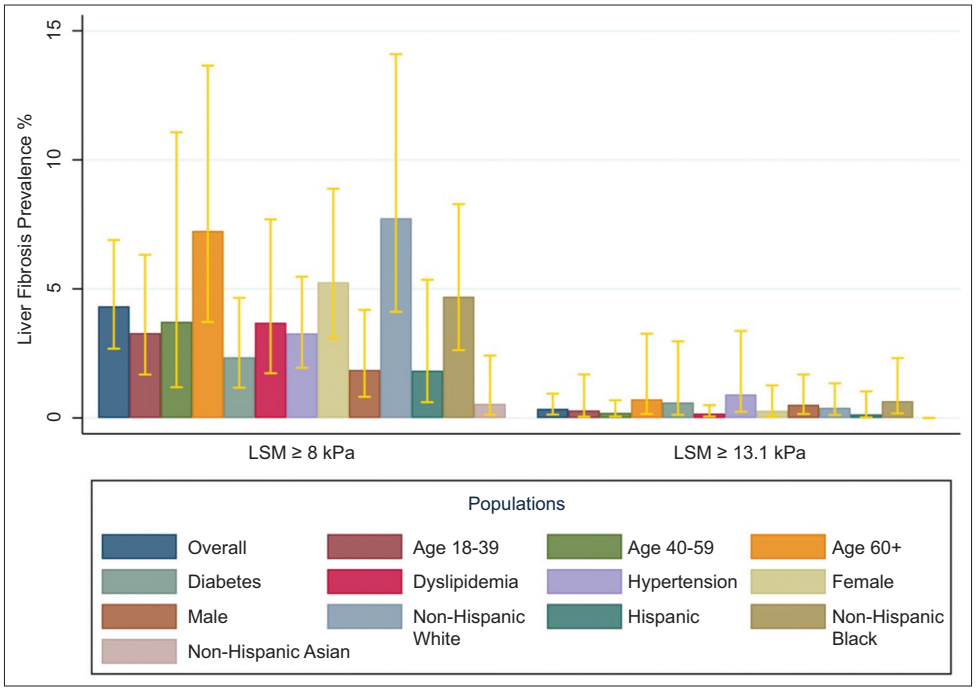
1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;**77**:1797-1835.
2. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;**64**:73-84.
3. Hagström H, Nasr P, Ekstedt M, et al. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: a long-term follow-up study. *Hepatol Commun* 2018;**2**:48-57.
4. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020;**5**:739-752.
5. Long MT, Noureddin M, Lim JK. AGA Clinical Practice Update: Diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. *Gastroenterology* 2022;**163**:764-774.
6. Ahmed OT, Gidener T, Mara KC, Larson JJ, Therneau TM, Allen AM. Natural history of nonalcoholic fatty liver disease with normal body mass index: a population-based study. *Clin Gastroenterol Hepatol* 2022;**20**:1374-1381.
7. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2017-2020. Available from: https://www.cdc.gov/nchs/

nhanes/index.htm [Accessed 26 October 2023].
8. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Surve 2017-March 2020. Available from: https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/P_LUX.htm [Accessed 26 October 2023].
9. Siddiqui MS, Vuppalanchi R, Van Natta ML, et al; NASH Clinical Research Network. Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2019;**17**:156-163.
10. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2019;**156**:1717-1730.
11. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol* 2020;**5**:362-373.
12. Stierman B, Afful J, Carroll MD, et al. National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files—Development of Files and Prevalence Estimates for Selected Health Outcomes. *Natl Health Stat Report* 2021;**158**. Available from: https://stacks.cdc.gov/view/cdc/106273 [Accessed 26 October 2023].
13. Younossi ZM, Stepanova M, Negro F, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. *Medicine (Baltimore)* 2012;**91**:319-327.
14. Fracanzani AL, Petta S, Lombardi R, et al. Liver and cardiovascular damage in patients with lean nonalcoholic fatty liver disease, and association with visceral obesity. *Clin Gastroenterol Hepatol* 2017;**15**:1604-1611.
15. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003;**37**:917-923.
16. Younes R, Bugianesi E. NASH in lean individuals. *Semin Liver Dis* 2019;**39**:86-95.
17. Young S, Tariq R, Provenza J, et al. Prevalence and profile of nonalcoholic fatty liver disease in lean adults: systematic review and meta-analysis. *Hepatol Commun* 2020;**4**:953-972.
18. Younes R, Govaere O, Petta S, et al. Caucasian lean subjects with non-alcoholic fatty liver disease share long-term prognosis of non-lean: time for reappraisal of BMI-driven approach? *Gut* 2022;**71**:382-390.
19. Weinberg EM, Trinh HN, Firpi RJ, et al. Lean Americans with nonalcoholic fatty liver disease have lower rates of cirrhosis and comorbid diseases. *Clin Gastroenterol Hepatol* 2021;**19**:996-1008.
20. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J Hepatol* 2017;**66**:1022-1030.
21. Ravaioli F, Dajti E, Mantovani A, Newsome PN, Targher G, Colecchia A. Diagnostic accuracy of FibroScan-AST (FAST) score for the non-invasive identification of patients with fibrotic non-alcoholic steatohepatitis: a systematic review and meta-analysis. *Gut* 2023;**72**:1399-1409.

Supplementary material



Supplementary Figure 1 Age-adjusted high-risk NASH prevalence among lean US adults reported by 2 diagnostic cut offs (FAST >0.35 and FAST >0.67) and stratified by demographic and metabolic risk factors
NASH, nonalcoholic steatohepatitis; FAST, FibroScan-aspartate aminotransferase



Supplementary Figure 2 Age-adjusted fibrosis prevalence among lean US adults reported by 2 diagnostic cutoffs for liver stiffness measurement (LSM, ≥8.0 kPa and ≥13.1 kPa) and stratified by demographic and metabolic risk factors

Supplementary Table 1 Baseline patient characteristics using a FAST score cutoff of 0.35

Characteristics	Total	FAST <0.35	FAST ≥0.35	P-value
	N=1493	N=1470	N=23	
Age categories				0.95
18-39	695 (46.6%)	685 (46.6%)	10 (43.5%)	
40-59	353 (23.6%)	347 (23.6%)	6 (26.1%)	
60+	445 (29.8%)	438 (29.8%)	7 (30.4%)	
Sex				0.002
Female	793 (53.1%)	788 (53.6%)	5 (21.7%)	
Male	700 (46.9%)	682 (46.4%)	18 (78.3%)	
Race/Ethnicity				0.90
Non-Hispanic White	575 (38.5%)	566 (38.5%)	9 (39.1%)	
Hispanic	283 (19.0%)	280 (19.0%)	3 (13.0%)	
Non-Hispanic Black	330 (22.1%)	324 (22.0%)	6 (26.1%)	
Non-Hispanic Asian	223 (14.9%)	220 (15.0%)	3 (13.0%)	
Other	82 (5.5%)	80 (5.4%)	2 (8.7%)	
Diabetes status				0.009
No diabetes	935 (62.6%)	922 (62.7%)	13 (56.5%)	
Prediabetes	129 (8.6%)	123 (8.4%)	6 (26.1%)	
Diabetes	429 (28.7%)	425 (28.9%)	4 (17.4%)	
Blood pressure				0.003
No hypertension	998 (71.6%)	989 (72.0%)	9 (42.9%)	
Hypertension	396 (28.4%)	384 (28.0%)	12 (57.1%)	
Dyslipidemia status				0.11
Normal lipids	828 (55.5%)	819 (55.8%)	9 (39.1%)	
Dyslipidemia	664 (44.5%)	650 (44.2%)	14 (60.9%)	
Metabolic syndrome status				0.007
No metabolic syndrome	617 (85.6%)	610 (86.0%)	7 (58.3%)	
Metabolic syndrome	104 (14.4%)	99 (14.0%)	5 (41.7%)	

FAST, FibroScan-aspartate aminotransferase

Supplementary Table 2 Baseline patient characteristics using TE with LSM cutoff of 8.0 kPa

Characteristics	Total	LSM <8.0 kPa	LSM ≥8.0 kPa	P-value
	N=1628	N=1566	N=62	
Age categories				<0.001
18-39	764 (46.9%)	749(47.8%)	15 (24.2%)	
40-59	374 (23.0%)	362(23.1%)	12 (19.4%)	
60+	490 (30.1%)	455(29.1%)	35 (56.5%)	
Sex				<0.001
Female	847 (52.0%)	830(53.0%)	17 (27.4%)	
Male	781 (48.0%)	736(47.0%)	45 (72.6%)	
Race/Ethnicity				0.005
Non-Hispanic White	615 (37.8%)	582(37.2%)	33 (53.2%)	
Hispanic	296 (18.2%)	291(18.6%)	5 (8.1%)	
Non-Hispanic Black	386 (23.7%)	367(23.4%)	19 (30.6%)	
Non-Hispanic Asian	240 (14.7%)	238(15.2%)	2 (3.2%)	
Other	91 (5.6%)	88 (5.6%)	3 (4.8%)	
Diabetes status				0.014
No diabetes	1,046 (64.3%)	1,016 (64.9%)	30 (48.4%)	
Prediabetes	138 (8.5%)	128(8.2%)	10 (16.1%)	
Diabetes	444 (27.3%)	422(26.9%)	22 (35.5%)	
Blood pressure				<0.001
No hypertension	1,075 (71.0%)	1,052 (72.2%)	23 (40.4%)	
Hypertension	439 (29.0%)	405 (27.8%)	34 (59.6%)	
Dyslipidemia status				0.069
Normal lipids	842 (54.7%)	817(55.2%)	25 (43.1%)	
Dyslipidemia	696 (45.3%)	663(44.8%)	33 (56.9%)	
Metabolic syndrome status				0.002
No Metabolic syndrome	623 (85.7%)	604 (86.5%)	19 (65.5%)	
Metabolic syndrome	104 (14.3%)	94 (13.5%)	10 (34.5%)	

TE, transient elastography; LSM, liver stiffness measurement