Received: 15 December 2021 | Accepted: 22 July 2022

DOI: 10.1097/HC9.0000000000000019

ORIGINAL ARTICLE

OPEN

Prevalence of at-risk NASH and its association with metabolic syndrome in US adults with NAFLD, 2017–2018

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Funding information
The study is funded by AHRQ R01HS026937.

Abstract

Patients with metabolic syndrome (MetS) have a higher risk for NASH and significant fibrosis. Presence of NASH and advanced fibrosis are associated with adverse outcomes in patients with NAFLD. Using a noninvasive method, we determined the prevalence of at-risk NASH and its association with MetS components in a large population-based analysis. We used the 2017–2018 National Health and Nutrition Examination Survey and included adults ≥18 years with NAFLD (controlled attenuation parameter ≥274 dB/m). Pregnancy, subjects with other causes of liver disease or missing data were excluded. FibroScan-AST (FAST) score was calculated using aspartate aminotransferase, liver stiffness measurement, and controlled attenuation parameter. Patients with a FAST score >0.35 were considered to have at-risk NASH, defined as NASH with NAFLD activity score ≥4 and fibrosis stage ≥2 on liver biopsy. The sample included 687 patients. The overall prevalence of at-risk NASH was 11.6% (95% CI: 8.8–15.1) and was higher in males than females (15.8% vs. 6.5%; $p < 0.001$). Subjects with comorbidities (diabetes mellitus, obesity, MetS, and insulin resistance) had between 1.3 and 1.7 times higher prevalence than the general population. Among MetS components, elevated glucose/diabetes, large waist circumference, and low HDL were independent risk factors for at risk-NASH. The number of MetS components was also important—one additional component increased the odds of at-risk NASH by 2 times. The FAST score had the highest correlation with alanine aminotransferase ($r = 0.70$; $p < 0.001$). We estimated ~9 million people in the US have at-risk NASH and may benefit from active surveillance and therapy.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CAP, controlled attenuation parameter; FAST, FibroScan-AST; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; MetS, metabolic syndrome; NAS, NAFLD activity score; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; T2DM, type 2 diabetes mellitus; VCTE, vibration controlled transient elastography.

INTRODUCTION

NAFLD encompasses a spectrum from simple fat accumulation to liver fibrosis.[1] It can also progress to more advanced diseases such as advanced fibrosis, cirrhosis, or liver cancer.[2] The prevalence of NAFLD is estimated to be 25% globally and 32% in the US.[3,4] Underlying comorbidities, specifically components of metabolic syndrome (MetS), are risk factors for NASH/progression of NAFLD. Some patient subgroups, for example, those with type 2 diabetes mellitus (T2DM) or obesity, had a higher prevalence of NASH than the general population with NAFLD.[3,5] In particular, the presence of MetS was associated with more than 3 times the odds of having NASH or significant fibrosis (stage 3 or higher).[6] Within patients with NAFLD, ~25%–35% have the progressive form of NASH.[7] The rising prevalence of NASH has resulted in an increase of 170% in liver transplant registrants with NASH between 2004 and 2013.[8] It has surpassed viral hepatitis in becoming one of the leading causes of liver transplantation.[9]

Both NASH and advanced fibrosis are associated with worse liver-related outcomes. The estimated annual incidence rate of HCC in patients with NASH was nearly 12 times higher than in the general NAFLD patient population.[3] Patients with NASH also have increased liver-specific and all-cause mortality compared with those with simple steatosis.[3] The risk of all-cause mortality increased in NAFLD patients with each additional MetS condition compared with those with no condition.[10] With the increasing prevalence of MetS and NAFLD, it is important to identify patients at high-risk of NASH and advanced fibrosis to provide the best opportunity for early intervention.[11,12]

Although liver biopsy remains the gold standard for diagnosis of NASH and fibrosis, it is not suitable for population-based risk stratification. Noninvasive methods, therefore, have been increasingly used to identify at-risk patients.[13] The fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS) are among the most commonly used tools for the noninvasive diagnosis of advanced fibrosis.[14] A meta-analysis reported a FIB-4 cutoff between 1.51 and 2.24 for advanced fibrosis diagnosis, with a sensitivity of 77.0% (range: 70.6%–89.5%) and specificity of 79.2% (range: 67.1%–93.6%).[15] For the NFS score with a threshold of −1.455, the meta-analysis reported a sensitivity of 72.9% (range: 22.7%–96.0%) and a specificity of 73.8% (range: 42.9%–100%).[15] Although these noninvasive methods are helpful in detecting simple steatosis and advanced fibrosis, they lack the ability to detect the presence or severity of NASH, or progression in NAFLD such as changes within fibrosis stages.[16,17] In recent years, there is increasing interest in liver vibration-controlled transient elastography (VCTE), an ultrasound-based modality for assessing liver fibrosis, with an AUROC of 0.87 (95% CI: 0.83–0.90) for detecting advanced fibrosis and AUROC of 0.93 (95% CI: 0.90–0.94) for detecting liver cirrhosis.[15,18] FibroScan can measure liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) in a single scan.[19] The advantages of VCTE include being noninvasive, ability to measure a larger region of the liver, its reproducibility, and a short duration of the test.[18] VCTE is a potential noninvasive tool for population-based epidemiological studies for liver fibrosis.[20]

To improve the ability to noninvasively detect patients with at-risk NASH, defined as progressive NASH [NAFLD activity score (NAS) ≥ 4 and fibrosis stage 2 or higher], a FibroScan-AST (FAST) score based on LSM, CAP, and aspartate aminotransferase (AST) has been used.[21] Multiple studies have shown the FAST score to have an excellent test performance with an AUROC ranging from 0.74 to 0.95.[21–23] With no current approved treatments for NAFLD/NASH, it is important to identify patients who are at risk of progression to cirrhosis or HCC and to conduct longitudinal follow-up studies to allow for prioritization of resource allocation in managing these patients and evaluating therapeutic response. While a biopsy is generally believed to be required for the diagnosis of NASH, noninvasive indices that include an elevated alanine aminotransferase (ALT) are increasingly recognized as a surrogate for underlying NASH.[24]

The National Health and Nutrition Examination Survey (NHANES), for the first time in 2017–2018, includes VCTE data, providing an opportunity to use composite noninvasive tests for determining the epidemiology of NAFLD at the population level.[25] A recent publication using 2017–2018 NHANES showed that among US adults, the prevalence of fatty liver was 47.8% (95% CI: 45.3%–50.3%) and the prevalence of fibrosis ($F \geq F2$) for those with fatty liver was 13.8% (95% CI: 10.4%–15.9%).[26] Other studies using the same data estimated the prevalence of NAFLD and fibrosis within different subgroups.[27,28] However, no studies to date have examined at-risk NASH or the contribution of different MetS components to disease severity. Our primary aim was to estimate the prevalence of at-risk NASH and examine the hierarchical effect of different MetS components on at-risk NASH in US adults using the FAST score and 2017–2018 NHANES. We also assessed the correlation among FAST score, ALT, FIB-4, and NFS.

METHODS

Study

Design and population

A cross-sectional analysis of 2017–2018 NHANES was performed. NHANES combines interviews and

physical examinations to assess the health and nutritional status of a representative sample of non-institutionalized adults and children in the US.[25] All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. All survey participants provided informed consents before their data were collected for NHANES. Because NHANES data is publically available and de-identified, our study was exempt from Institutional Review Board approval. Our study population included participants aged ≥18 years old with NAFLD. We defined NAFLD as having a CAP score of ≥274 dB/m.[29] We excluded pregnant women, patients with incomplete VCTE measurements, missing or excessive alcohol consumption (defined as >2 drinks/day for males and >1 drink/day for females, hepatitis B or C, ALT or AST >500 IU/L), or missing values for AST and MetS components.

Regarding comorbidities, we defined T2DM as either having ever been diagnosed with T2DM, HbA1C ≥6.5%, fasting glucose >125 mg/dL, or taking medication. MetS was defined as consisting of at least 3 of the 5 criteria: waist circumference over 40 inches in men or 35 inches in women, blood pressure >140/90 mm Hg or taking medication, fasting triglyceride ≥150 mg/dL or taking medication, fasting HDL cholesterol <40 mg/dL in men or 50 mg/dL in women, and fasting glucose >100 mg/dL or with T2DM.[30] We defined obesity as a body mass index (BMI) of ≥30 kg/m^2 (≥25 kg/m^2 for Asians) and insulin resistance as a HOMA-IR score of ≥3. The noninvasive tests were calculated as[31,32:]

$$\text{FIB-4} = \frac{\text{age} \times \text{AST}\left[\frac{\text{U}}{\text{L}}\right]}{\left(\text{platelet count}\left[\frac{10(9)}{\text{L}}\right]\right) \times \left(\text{ALT}\left[\frac{\text{U}}{\text{L}}\right]\right) \times (1/2)}.$$

$$\text{NFS} = -1.675 + 0.037 \times \text{age(years)} + 0.094 \times \text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) + 1.13 \times \frac{\text{IFG}}{\text{Diabetes (yes = 1, no = 0)}} + 0.99 \times \frac{\text{AST}}{\text{ALT}} - 0.013 \times \text{platelet}\left(\frac{109}{\text{L}}\right) - 0.66 \times \text{albumin}\left(\frac{\text{g}}{\text{dL}}\right).$$

Outcome measures

NHANES used FibroScan model 502 V2 Touch equipped with medium and extra-large probes to non-invasively detect liver disease. We utilized the FAST score to identify patients with at-risk NASH, defined as having NASH with a NAS of ≥4 and fibrosis stage ≥F2 following the original paper of the FAST score. The FAST score was calculated using the equation[21]:

$$\text{FAST} = \frac{\exp(-1.65 + 1.07 \times \log(\text{LSM}) + 2.66 \times 10^{-8} \times (\text{CAP})^3 - 63.3 \times (\text{AST})^{-1})}{1 + \exp(-1.65 + 1.07 \times \log(\text{LSM}) + 2.66 \times 10^{-8} \times (\text{CAP})^3 - 63.3 \times (\text{AST})^{-1})}.$$

Patients with a FAST score of >0.35 were considered to have at-risk NASH and ≤0.35 were considered low-risk NASH.[21]

Statistical analysis

Descriptive statistics were used to compare patient characteristics between those with at-risk versus low-risk NASH. We estimated the prevalence of at-risk NASH for the overall study population and stratified by sex, age groups, race/ethnicity, comorbidities, and medications. For T2DM patients, we calculated the prevalence by patients using metformin only, insulin only, and other diabetes medications only. In patients with hypertension, we assessed those using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In patients with hypertriglyceridemia, prevalence was estimated for those using statins versus nonstatin medications. To assess the association between at-risk NASH and MetS, we used univariate logistic models to examine MetS criteria individually. We then examined the association of MetS components in 2 multivariable logistics regression models: model 1 included each individual MetS criteria as predictors, and model 2 included each individual MetS criteria and patient demographics (age, sex, and race/ethnicity). To examine whether the impact of MetS differed by the number of criteria met, we used the number of MetS criteria as a predictor in addition to demographic factors in model 3. Finally, we assessed the association between advanced fibrosis (F≥F3, defined as LSM≥9.7 kPA) and MetS using a similar modeling approach.[29] ORs and 95% CIs were calculated. Finally, we assessed the correlation between FAST score, FIB-4, NFS, and ALT. Appropriate survey weights were applied for all analyses which were performed using Stata version 17.[33]

RESULTS

We identified 687 subjects with NAFLD, representing 31.4 million US adults (Figure 1). A total of 4719 NHANES participants in the 2017–2018 cycle had missing values for excessive alcohol consumption. Because patients with a larger body weight might be more likely to have partial or incomplete transient

elastography results and hence excluded from analysis, we compared participants' mean body weight across the 4 categories of elastography exam status (complete, partial, ineligible, and not done). We found significant differences in weight amongst the groups ($p < 0.05$). On average, the partial group weighted 7.3 kg (95% CI: 2.7–11.8) more than the completed group. However, after imputing excessive alcohol consumption, we were able to include an addition of 1480 people (16% of NHANES participants) in the analytical sample. The imputed sample included patients with incomplete elastography exams. Because the estimates using imputed data were not significantly different from those using original data, we reported results based on the latter.

Overall, the mean age was 51.4 years (95% CI: 49.4–53.4), the mean BMI was 33.4 kg/m^2 (95% CI: 32.6–34.2), and 54.5% were male (Table 1). Patients with at-risk NASH were more likely to be male and had a higher BMI than low-risk patients. Among US adults with NAFLD, 26.4% (95% CI: 21.9–31.4) had T2DM, 65.7% (95% CI: 61.0–70.11) were obese, 64.1% (95% CI: 56.3–71.3) had insulin resistance, and 64.9% (95% CI: 58.0–71.2) had MetS (Table 2). Compared with patients with low-risk, those with at-risk NASH had significantly higher prevalence of comorbidities including MetS (93.3% vs. 60.3%) and its individual components except for hypertension and hypertriglyceridemia. In addition, patients with at-risk NASH had higher AST, ALT, GGT, and ferritin levels than the low-risk group ($p < 0.001$) (Table 3).

The overall prevalence of at-risk NASH in patients with NAFLD was 11.6% (95% CI: 8.8–15.1). The prevalence did not differ by age group ($p = 0.22$) or race/ethnicity ($p = 0.28$) but was significantly higher in males than females, 15.8% versus 6.5% ($p = 0.002$). Patients with comorbidities had a higher prevalence of at-risk NASH than the general NAFLD population. Specifically, patients with coexisting NAFLD and T2DM had the highest prevalence of at-risk NASH, followed by NAFLD patients with insulin resistance and MetS (20.8% vs. 16.9% vs. 15.5%, respectively) (Table 4). Among MetS components, patients having low HDL had the highest prevalence, 19.7% (95% CI: 13.4–28.0) (Figure 2). In addition, the higher the number of MetS criteria the patients had, the higher the prevalence of at-risk NASH. Patients who had all 5 components of MetS had the highest prevalence, which was 2 times higher than those with 3 components. Among those taking medications, NAFLD participants with T2DM who took metformin had a prevalence of 10.5% (95% CI: 4.9–21.2). (Table 4). Participants with hypertriglyceridemia and taking statins had a prevalence of 10.5% (95% CI: 6.9–15.6). Finally,

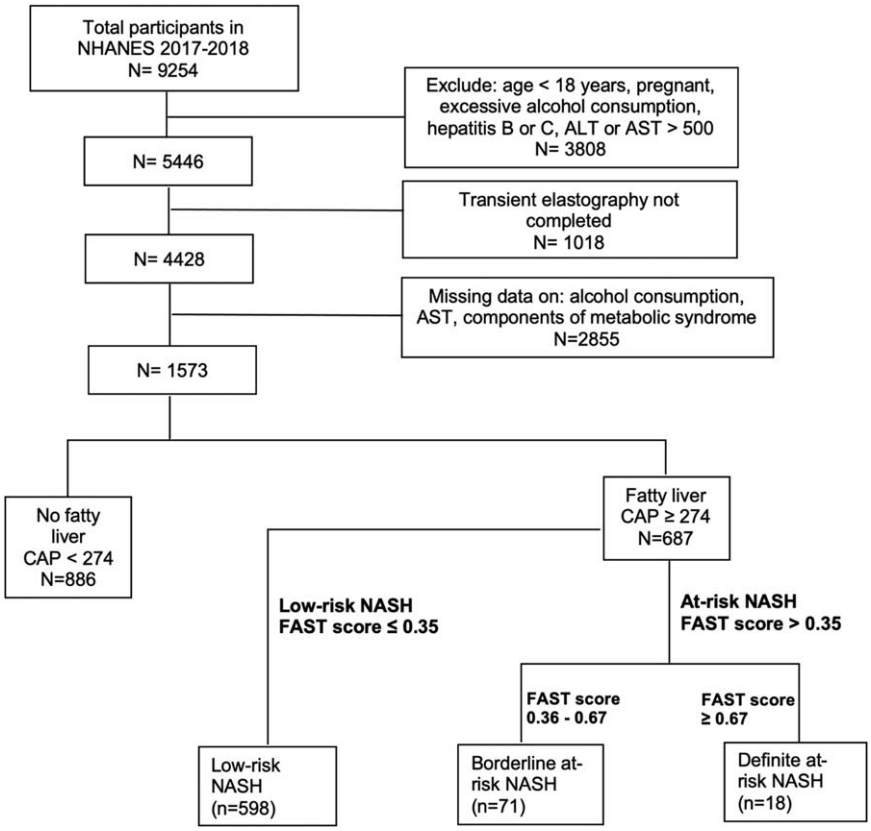


FIGURE 1 Flow chart of participants in the study. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FAST, FibroScan-AST; NHANES, National Health and Nutrition Examination Survey.

TABLE 1 Baseline characteristics in US adults (≥18 y) with NAFLD

	All patients, N = 687	Low risk NASH (FAST score ≤0.35), N = 598	At-risk NASH (FAST score >0.35), N = 89	*p*
Age (y)—mean (95% CI)	51.4 (49.4–53.4)	51.8 (49.4–54.2)	48.5 (45.2–51.8)	0.14
Male—% (95% CI)	54.5 (47.3–61.6)	25.7 (18.4–34.6)	74.3 (65.4–81.6)	<0.001
BMI (kg/m^2)—mean (95% CI)	33.4 (32.6–34.2)	32.7 (31.9–33.5)	38.7 (35.9–41.6)	<0.001
Race/ethnicity—% (95% CI)				
Non-Hispanic White	64.5 (59.4–69.2)	65.4 (60.3–70.2)	57.1 (45.2–68.2)	0.15
Non-Hispanic Black	8 (5.6–11.3)	8 (5.8–10.8)	8.1 (3.5–18)	
Hispanic	18.9 (13.2–26.2)	17.8 (12.1–25.3)	27.1 (16.4–41.2)	
Other	8.7 (5.9–12.6)	8.8 (5.7–13.3)	7.7 (4.5–12.8)	
Education—% (95% CI)				
<High school	9.6 (7.4–12.3)	9.3 (7–12.3)	11.7 (5.5–23.2)	0.19
High school or GED	30.4 (26.3–34.8)	30.9 (26.2–35.9)	26.7 (15.2–42.6)	
Associate degree or some college	31.4 (24.8–38.9)	29.8 (22.6–38.2)	43.5 (26.9–61.8)	
≥College	28.6 (20.5–38.4)	30 (21–40.9)	18 (12.3–25.6)	
Income-to-poverty ratio—% (95% CI)				
<1	12.8 (9.3–17.3)	13 (9.1–18.3)	11.1 (5.4–21.4)	0.29
1–2	20.2 (16.1–25)	20.6 (16.2–26)	16.6 (9.9–26.6)	
2–4	28.1 (21.8–35.4)	26.2 (20.1–33.4)	42.8 (22.5–66)	
≥4	38.9 (30.3–48.3)	40.1 (30.9–50)	29.5 (11.4–57.5)	
Insurance type—% (95% CI)				
None	10.4 (7.3–14.5)	9.5 (6.4–13.8)	17 (7.4–34.5)	0.11
Private	41.3 (34.8–48.1)	40.2 (32.3–48.7)	49.4 (36.1–62.7)	
Government	48.4 (41.7–55)	50.3 (42.7–57.9)	33.6 (25.3–43)	
Smoking status—% (95% CI)				
Never	56.4 (51.6–61)	56.7 (51.6–61.6)	54.1 (38.5–69)	0.46
Former	29.7 (24.1–35.9)	28.8 (22.8–35.7)	36.1 (21.4–54)	
Current	13.9 (10.6–18.1)	14.5 (10.7–19.3)	9.8 (4.9–18.4)	

Abbreviations: BMI, body mass index; FAST, FibroScan-AST.

patients with hypertension taking ACE inhibitors or ARBs had a prevalence of 16.8% (95% CI: 10.2–26.5) and 10.3% (3.8–25.2), respectively.

The association between at-risk NASH and MetS components are shown in Table 5. In univariate analysis, being male, having elevated glucose or diabetes, large waist circumference, low HDL, or a higher number of MetS criteria were associated with higher odds of having at-risk NASH ($p < 0.05$). When all MetS components were controlled for (model 1), elevated glucose/diabetes, large waist circumference, or low HDL remained significant, with elevated glucose/diabetes having the highest adjusted odds (OR: 3.46, 95% CI: 1.15–10.37). When age, sex, and race/ethnicity were added to the model (model 2), the effect sizes of these 3 MetS components were enhanced, with large waist circumference having the highest effect (OR: 4.66; 95% CI: 1.53–14.17). In model 3, having one additional MetS component was associated with 2.27 (95% CI: 1.64–3.15) times the odds of having at-risk NASH.

Regarding advanced fibrosis (F≥F3), the associations are shown in Table 6. In univariate analysis, having a higher number of MetS criteria was associated with higher odds of having F≥F3 ($p < 0.05$). When all MetS components were controlled for (model 1), none of the variables were significant. Similarly, when age, sex, and race/ethnicity were added to the model (model 2), none of the variables were significant. In model 3, having one additional MetS component was associated with 1.45 (95% CI: 1.07–1.98) times the odds of having F≥F3 fibrosis.

Finally, the FAST score was highly correlated with ALT ($r = 0.70$, $p < 0.001$) and LSM ($r = 0.61$, $p < 0.001$) but not as much with FIB-4 ($r = 0.23$, $p < 0.001$) or NFS ($r = 0.18$, $p < 0.001$) (Figure 3). The other 2 noninvasive

TABLE 2 Comorbidities in US adults (≥18 y) with NAFLD

	All patients	Low risk NASH (FAST score ≤0.35)	At-risk NASH (FAST score >0.35)	*p*
Comorbidities—% (95% CI)	N = 687	N = 598	N = 89	
T2DM	26.4 (21.9–31.4)	23.9 (19–29.6)	45.2 (31.9–59.2)	0.01
Obesity	65.7 (61–70.1)	63 (57.9–67.8)	86.1 (74.9–92.8)	0.002
Insulin resistant	64.1 (56.3–71.3)	60.3 (52.1–68)	93.3 (83.2–97.5)	<0.001
MetS criteria				
Elevated glucose/diabetes	79.5 (75.1–83.3)	77.7 (72.7–82)	93.3 (83.9–97.4)	0.01
Large waist circumference	80.8 (75.7–85)	79 (73.8–83.3)	94.3 (84.5–98.1)	0.01
Hypertension	53.7 (45.4–61.8)	52.5 (43.3–61.5)	63.2 (49.8–74.7)	0.19
Hypertriglyceridemia	50.3 (42.8–57.8)	49.2 (40.8–57.5)	58.8 (45.4–71)	0.23
Low HDL cholesterol	35.8 (30.8–41.2)	32.5 (27.8–37.6)	60.9 (39.3–79)	0.01
MetS[a]	64.9 (58.0–71.2)	62 (54.8–68.8)	87 (66.4–95.7)	0.02
Number of MetS criteria				
0	2 (0.9–4.6)	2.3 (1–5.2)	NA	0.03
1	11.4 (7.5–16.8)	12.4 (8.5–17.9)	3.1 (0.5–16.2)	
2	21.7 (17.1–27.1)	23.2 (18.5–28.7)	9.9 (2.6–31.5)	
3	26.4 (20.5–33.2)	27 (21.7–33)	21.7 (9.9–41)	
4	26.5 (20–34.2)	24.2 (18.7–30.7)	43.8 (25.4–64.1)	
5	12.1 (8.7–16.5)	10.8 (7.3–15.8)	21.4 (10.5–39)	

[a]*Note:* Defined as having ≥3 criteria.
Abbreviations: MetS, metabolic syndrome; NA, not applicable; T2DM, type 2 diabetes mellitus.

scores, FIB-4 and NFS, were highly correlated with each other ($r = 0.72$, $p < 0.001$) but not with ALT.

DISCUSSION

The average annual rate of progression in NASH globally has been estimated to be 0.09/1000 person-years (95% CI: 0.06–0.12) and the liver-specific mortality among NASH patients to be 11.77/1,000 person-years (95% CI: 7.10–19.53).[3] The highest increase in liver transplant waitlist registration since 2004–2018 was related to a diagnosis of NASH, the leading cause for liver transplant for women in the US.[8,9] Using 2017–2018 NHANES and the noninvasive FAST score, we examined the population-based prevalence of at-risk NASH in patients with NAFLD and in those with comorbidities. We found the overall prevalence was 12% and about 1 in 6 patients with at-risk NASH was identified as Hispanic. However, given the increasing recognition of heterogeneity within the group of Hispanics, more details are needed to identify which specific Hispanic subpopulations are at higher risk.[34] The proportion of Hispanic population in our final sample was 18.9%, which may appear to be overrepresented demographically. However, the prevalence was not significantly different by race/ethnicity in our study although a previous meta-analysis showed a higher risk of NASH in Hispanics than Whites.[35] In addition, we found that subjects with comorbidities, such as T2DM, obesity, insulin resistance, or MetS had a prevalence 1.3–1.7 times higher than the overall population. Our univariate logistic regression showed being male, Hispanic, elevated glucose/diabetes, large waist circumference, and low HDL increased the odds of having at-risk NASH. The prevalence of at-risk NASH also increases in parallel with increasing number of MetS components. Comparing subjects with only 1 MetS component to all 5 MetS components, the prevalence of at-risk NASH jumped from 3.2% to 20.6%. The multivariable analyses confirmed the importance of elevated glucose/diabetes, large waist circumference, low HDL in developing at-risk NASH. Furthermore, each additional MetS component doubled the odds of at-risk NASH. Our logistic regression also showed having a higher number of MetS criteria increased the odds of having F ≥ F3 fibrosis. However, the multivariable analysis did not show a significant association between F ≥ F3 fibrosis and individual MetS components.

Numerous studies have validated the efficiency of FibroScan to diagnose fibrosis and steatosis using LSM and CAP values.[29,36,37] In patients with NAFLD, the FAST score offers good discrimination with an AUROC of 0.85 (95% CI: 0.83–0.87) for pooled cohort and 0.86 (95% CI: 0.80–0.93) for US cohort.[21] Due to limited sample size, we stratified our cohort into FAST >0.35 which included patients with rule-in or gray-zone NASH score (at-risk NASH) versus ≤0.35 (low-risk NASH). Future studies with larger sample size

TABLE 3 Lab values and noninvasive tests in US adults (≥18 y) with NAFLD

	All patients, N = 687	Low risk NASH (FAST score ≤0.35), N = 598	At-risk NASH (FAST score >0.35), N = 89	*p*
Lab values—mean (95% CI)				
Total bilirubin (mg/dL)	0.49 (0.46–0.52)	0.48 (0.45–0.51)	0.52 (0.45–0.6)	0.30
AST (IU/L)	22.15 (21.16–23.14)	20.03 (19.09–20.97)	38.31 (34.11–42.51)	<0.001
ALT (IU/L)	26.25 (25.03–27.46)	22.89 (21.51–24.26)	51.89 (44.19–59.59)	<0.001
GGT (IU/L)	32.8 (28.73–36.86)	28.3 (24.57–32.02)	67.15 (47.33–86.96)	0.001
Albumin (g/dL)	4 (3.94–4.06)	4.01 (3.94–4.07)	3.96 (3.9–4.03)	0.25
Alkaline phosphatase (IU/L)	78.68 (75.42–81.95)	78.72 (75.44–82)	78.42 (71.2–85.64)	0.93
Platelet count (10^3 cells/μL)	243.92 (235.08–252.76)	246.43 (236.51–256.36)	224.77 (212.82–236.72)	0.01
Total cholesterol (mg/dL)	187.44 (176.16–198.72)	187.49 (176.1–198.88)	187.08 (172.15–202)	0.94
Triglyceride (mg/dL)	142.19 (124.75–159.63)	135.71 (118.84–152.59)	191.61 (132.71–250.52)	0.06
HDL cholesterol (mg/dL)	49.28 (47.11–51.45)	50.34 (48.01–52.67)	41.22 (38.4–44.04)	0.001
LDL cholesterol (mg/dL)	110.98 (102.4–119.56)	110.68 (101.85–119.5)	113.49 (99.65–127.33)	0.65
Fasting plasma glucose (mg/dL)	119.8 (114.84–124.75)	117.86 (112.49–123.23)	134.54 (126.1–142.99)	0.002
Insulin (uU/mL)	18.54 (16.65–20.43)	16.85 (15.12–18.58)	31.43 (23.41–39.45)	0.002
HOMA score	5.83 (5.18–6.48)	5.24 (4.58–5.9)	10.31 (7.77–12.86)	0.001
HbA1C (%)	5.94 (5.82–6.06)	5.89 (5.75–6.02)	6.36 (6.1–6.62)	0.01
Serum iron (μg/dL)	89.36 (83.52–95.2)	89.55 (83.79–95.32)	87.86 (76.22–99.5)	0.75
Ferritin (μg/L)	163.56 (143.2–183.92)	149.97 (131.57–168.36)	267.21 (201.54–332.88)	<0.001
Transferritin receptor (mg/L)	3.32 (3.1–3.54)	3.32 (3.09–3.55)	3.36 (2.91–3.81)	0.83
Noninvasive test—mean (95% CI)				
FAST score	0.16 (0.14–0.18)	0.11 (0.1–0.12)	0.55 (0.52–0.59)	<0.001
FIB-4	1.04 (0.96–1.12)	1.01 (0.92–1.09)	1.29 (1.12–1.46)	0.01
NAFLD fibrosis score	−0.35 (−0.51, −0.19)	−0.42 (−0.57, −0.27)	0.15(−0.09, 0.39)	<0.001
VCTE—mean (95% CI)				
Controlled attenuation parameter score (dB/m)	321.48 (317.12–325.84)	316.28 (312.59–319.98)	361.17 (350.07–372.27)	<0.001
Interquartile range, mean	34.44 (32.90–35.99)	35.32 (34.08–36.56)	27.78 (18.55–37.01)	0.10
Liver stiffness measurement (kPa)	6.27 (5.65–6.89)	5.42 (5.17–5.67)	12.78 (9.22–16.33)	<0.001
Interquartile range, mean	0.96 (0.79–1.12)	0.78 (0.72–0.85)	2.28 (1.27–3.29)	0.01

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAST, FibroScan-AST; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; VCTE, vibration controlled transient elastography.

may provide more granular details for the highest risk population (FAST ≥0.67). The use of noninvasive measures, such as the FAST score, to diagnose at-risk NASH presents a great opportunity to identify patients in the general population eligible for interventions to prevent progression of the disease to cirrhosis and complications related to advance liver disease. The 2017–2018 NHANES is the first national survey containing transient elastography data for the multiethnic population in the US. Using this unique dataset, our study was among the first to examine the epidemiology of at-risk NASH (NASH with NAS ≥4 and fibrosis stage ≥2) and its association with different components of MetS.

The prevalence of NASH among patients with NAFLD has been estimated at 60.64% (95% CI:

TABLE 4 Prevalence of probable at-risk NASH (%) by patient characteristics

	N	At-risk NASH (FAST score >0.35)	p
All patients	687	11.6 (8.8–15.1)	
Age group—% (95% CI)			
18–39	155	14.2 (8.9–21.9)	0.22
40–64	333	12.2 (8.4–17.5)	
65+	199	7.3 (4–13.1)	
Sex—% (95% CI)			
Female	312	6.5 (4.7–9.1)	0.002
Male	375	15.8 (11.7–21)	
Race/ethnicity—% (95% CI)			
Non-Hispanic White	255	10.3 (6.9–14.9)	0.28
Non-Hispanic Black	121	11.8 (6.2–21.3)	
Hispanic	199	16.6 (11.2–24)	
Other	112	10.3 (5.3–19)	
Comorbidities—% (95% CI)			
T2DM	251	19.9 (15–26)	0.01
Without T2DM	435	8.6 (5.3–13.7)	
Obesity	428	15.2 (11.3–20.2)	0.003
Without obesity	258	4.7 (2.5–8.7)	
Insulin resistant	468	16.9 (12.6–22.2)	<0.001
Without insulin resistant	218	2.2 (0.9–5)	
Metabolic syndrome	475	15.5 (12.3–19.3)	0.03
Without metabolic syndrome	212	4.3 (1.3–13.3)	
Medications—% (95% CI)			
Patients with T2DM			
Metformin	83	10.5 (4.9–21.2)	0.84
Insulin	14	6.5 (1.4–25.3)	
Not metformin or insulin	15	13.3 (2–53.9)	
Patients with hypertension			
Angiotensin receptor blockers	86	10.3 (3.8–25.2)	0.19
ACE inhibitors	137	16.8 (10.2–26.5)	
Patients with hypertriglyceridemia			
Statin	193	10.5 (6.9–15.6)	0.22
Nonstatin	18	2.9 (0.3–21.8)	

Abbreviations: ACE, angiotensin-converting enzyme; FAST, FibroScan-AST; T2DM, type 2 diabetes mellitus.

49.56–70.72) in North America and 69.75% (95% CI: 37.29–96.83) among those with coexisting NAFLD and T2DM.[3,5] Meanwhile, the proportion of patients with combined NASH and advanced fibrosis in a large US patient registry was 40% compared with 12% in our study.[38] Besides the different diagnostic methods, liver biopsy versus FAST score, the registry included patients from 8 university medical research centers who presumably had more severe disease than the general adult population that was included in our study.

MetS has been shown to be associated with NAFLD, NASH, and advanced fibrosis.[6,27,39–41] Patients with MetS had about 3 times the odds of NASH or significant fibrosis.[6] They had a higher prevalence of fibrosis and mean fibrosis score than those without MetS.[41] In addition, the increase in number of MetS components led to an increased risk of NASH and/or fibrosis. Using the Spanish HEPAmet Registry, Ampuero et al.[39] showed that the odds of having NASH increased significantly for patients with each additional component of MetS compared with those without MetS (OR: 1.66–4.88). These findings are comparable to our study, which confirmed the independent impact of elevated glucose/diabetes, large waist circumference, and low HDL, as well as the number of MetS components on the odds of at-risk NASH. The strength of our study was that we extended our understanding of at-risk NASH and MetS in the general US population rather than limiting to patients from large specialty care centers. In addition, we found a high correlation between FAST score and ALT level ($r = 0.70$, $p < 0.001$), which was similar to a study in a Japanese cohort.[42] Other studies have investigated the prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD).[43,44] Kim and colleagues found MAFLD had a higher risk of all-cause mortality but NAFLD did not after adjusting for metabolic risk factors.[43] Wong and Cheung[44] estimated the prevalence of MAFLD using NHANES 2017–2018 as 38% and our estimate for NAFLD was 41%. Future studies performing a comparative analysis using both definitions should be considered.

Studies using NHANES data before the 2017–2018 cycle mostly estimated the prevalence of NAFLD or advanced fibrosis based on other noninvasive methods, for example the Fatty Liver Index, FIB-4, NFS, or gallbladder ultrasound images.[45–47] These studies could not examine at-risk NASH. Similarly, other studies using 2017–2018 NHANES only reported the prevalence of NAFLD and/or advance fibrosis.[26,27,48] A recent study by Zhang et al.[27] estimated the prevalence of active fibrotic NASH for participants ≥ 20 years old using both 0.35 and 0.67 cutoffs for the FAST score. They reported a prevalence of 6.4% (95% CI: 5.4–7.5) with >0.35 as the cutoff, which is about half of our estimate. It's important to note that the prevalence was estimated for their whole study cohort, comprising of all eligible adults (N = 4424) instead of among patients with NAFLD as in our study. Also, alcohol consumption was calculated using dietary total nutrients data instead of the alcohol questionnaire data, which may not be as

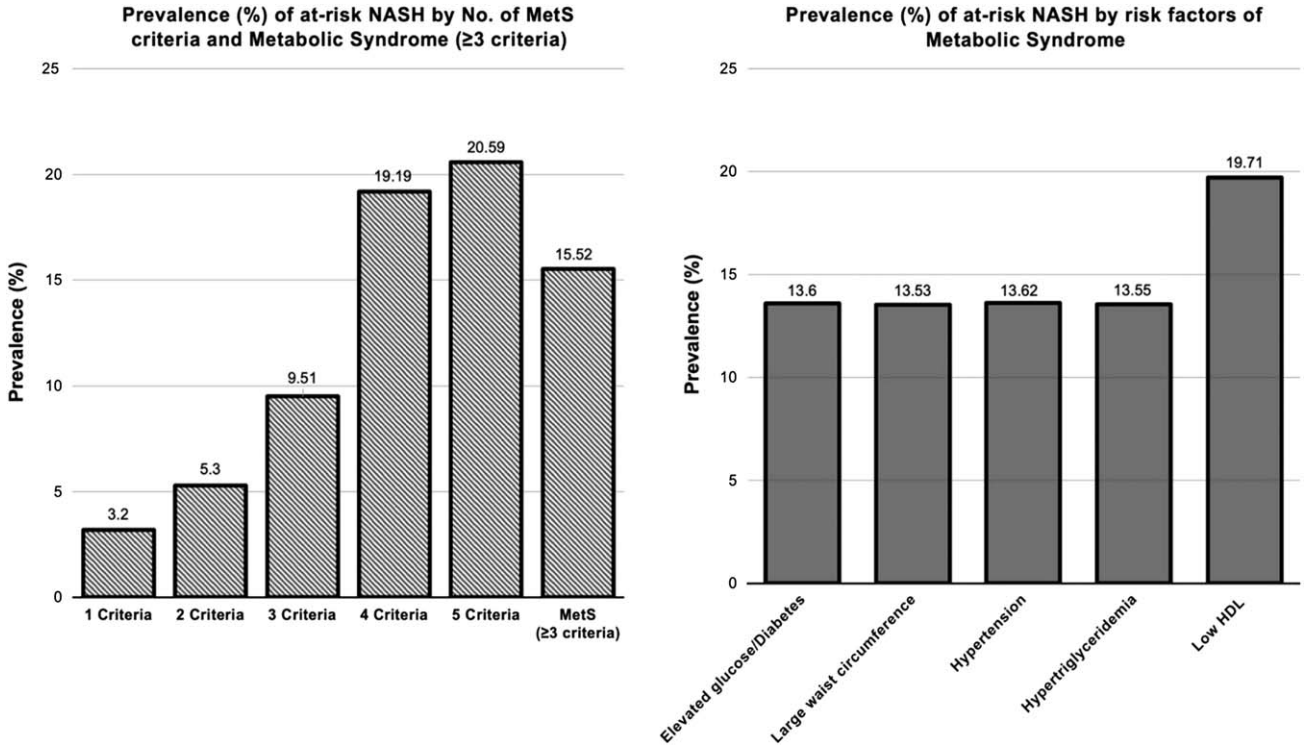


FIGURE 2 Prevalence (%) of at-risk NASH in NAFLD patients by a number of metabolic syndrome (MetS) criteria, by having MetS (≥3 criteria), and by MetS risk factors.

accurate. Furthermore, we used a CAP ≥274 dB/m to identify fatty liver, which has sensitivity of 0.90 (95% CI: 0.87–0.93) and specificity of 0.60 (0.44–0.74).[29] and excluded participants with any missing MetS components to ensure robust evaluation of the effects of MetS components. No previous study including Zhang and colleagues' evaluated the hierarchical effect of MetS components on at-risk NASH.

TABLE 5 Association between at-risk NASH and metabolic syndrome in US adults with NAFLD

Variables	Univariate	Model 1	Model 2	Model 3
Age	0.99 (0.97–1)		0.97 (0.95–0.99)	0.96 (0.94–0.98)
Sex—reference: female				
Male	2.68 (1.74–4.13)		3.35 (1.67–6.72)	2.85 (1.74–4.68)
Race/ethnicity—reference: non-Hispanic White				
Non-Hispanic Black	1.17 (0.62–2.21)		1.46 (0.7–3.06)	1.38 (0.76–2.52)
Hispanic	1.74 (0.95–3.19)		1.64 (0.73–3.69)	1.63 (0.77–3.47)
Other	1 (0.47–2.16)		0.87 (0.32–2.37)	0.83 (0.32–2.14)
Comorbidities				
MetS criteria				
Elevated glucose/diabetes	4.02 (1.36–11.91)	3.46 (1.16–10.37)	3.9 (1.37–11.11)	
Large waist circumference	4.42 (1.55–12.63)	3.23 (1.09–9.63)	4.66 (1.53–14.17)	
Hypertension	1.55 (0.78–3.08)	1.27 (0.64–2.53)	1.85 (0.74–4.62)	
Hypertriglyceridemia	0.39 (−0.28, 1.06)	1.02 (0.54–1.92)	1.21 (0.62–2.35)	
Low HDL	3.24 (1.3–8.06)	2.76 (1.15–6.63)	2.97 (1.11–8)	
Number of MetS criteria (per 1 criterion increase)	1.76 (1.3–2.38)			2.27 (1.64–3.15)

Note: Data are presented as OR (95% CI).
Model 1 included 5 MetS components as independent variables.
Model 2 included age, sex, race/ethnicity, and 5 MetS components as independent variables.
Model 3 included age, sex, race/ethnicity, and the number of MetS components as independent variables.
Abbreviation: MetS, metabolic syndrome.

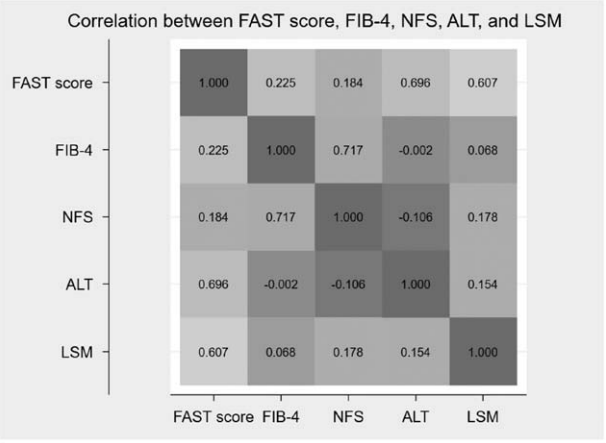
TABLE 6 Association between F ≥ F3 fibrosis (liver stiffness measurement ≥ 9.7 kPA) and metabolic syndrome in US adults with NAFLD

Variables	Univariate	Model 1	Model 2	Model 3
Age	1.01 (0.99–1.02)		0.99 (0.98–1.02)	1.00 (0.98–1.02)
Sex—reference: female				
Male	1.75 (0.69–4.47)		1.86 (0.76–4.53)	1.71 (0.66–4.38)
Race/ethnicity—reference: non-Hispanic White				
Non-Hispanic Black	0.65 (0.24–1.76)		0.71 (0.25–2.00)	0.72 (0.26–2.03)
Hispanic	1.31 (0.65–2.61)		1.49 (0.66–3.35)	1.42 (0.65–3.09)
Other	0.63 (0.18–2.25)		0.66 (0.17–2.61)	0.60 (0.16–2.28)
Comorbidities				
MetS criteria				
Elevated glucose/diabetes	2.03 (0.46–8.90)	1.71 (0.34–8.62)	1.49 (0.26–8.47)	
Large waist circumference	2.59 (0.50–13.52)	2.17 (0.42–11.24)	2.57 (0.53–12.60)	
Hypertension	1.74 (0.74–4.08)	1.53 (0.67–3.49)	1.52 (0.59–3.94)	
Hypertriglyceridemia	1.27 (0.45–3.57)	0.98 (0.29–3.37)	0.97 (0.29–3.22)	
Low HDL	1.68 (0.72–3.95)	1.51 (0.59–3.90)	1.56 (0.59–4.11)	
Number of MetS criteria (per 1 criterion increase)	1.41 (1.07–1.89)			1.45 (1.07–1.98)

Note: Data are presented as OR (95% CI).
Model 1 included 5 MetS components as independent variables.
Model 2 included age, sex, race/ethnicity, and 5 MetS components as independent variables.
Model 3 included age, sex, race/ethnicity, and the number of MetS components as independent variables.
Abbreviation: MetS, metabolic syndrome.

Limitations to this survey data include recall bias from participants, especially regarding alcohol usage. More robust methods of alcohol use may add strength to the NHANES data, but a diagnosis of NAFLD in clinical practice and in most clinical studies to date depends on patient-reported alcohol consumption. NHANES does not provide liver biopsy data to reliably diagnose steatosis, NASH, or fibrosis staging. However, even though VCTE is not the current gold standard for NAFLD diagnosis, its reliability has been shown in a number of publications.[49] In addition, we used a validated CAP cutoff ≥ 274 dB/m with a sensitivity of 90% and cutoffs for FAST score which were shown by others to correlate well with liver biopsy findings of NASH.[19,21] Noureddin et al.[50] proposed adopting sequential testing after FAST score with enhanced liver fibrosis or magnetic resonance elastography. Combining different options reduces dependency on a single score and should reduce liver biopsy.[50] Finally, we excluded a large number of patients due to missing data on MetS components. However, we compared the mean CAP, LSM, and FAST scores between the excluded population and our final sample, and found no statistically significant difference between the groups.

Our study, using a large population-based dataset and a composite noninvasive score, allows for the generalizability of the results to the US adult population. We examined the hierarchical effect of MetS components on at-risk NASH at the population level rather than on selected patients who visited large specialty medical centers. Our findings highlight the high prevalence of at-risk NASH in those with NAFLD, especially among participants with different comorbidities. In addition, we showed that patients with NAFLD who also had MetS or its individual components including elevated glucose/



Variables		Correlation Coefficient	p-value
FAST score	vs FIB-4	0.225	< 0.001
	vs NFS	0.184	< 0.001
	vs ALT	0.696	< 0.001
	vs LSM	0.607	< 0.001
FIB-4	vs NFS	0.717	< 0.001
	vs ALT	-0.002	< 0.001
	vs LSM	0.068	< 0.001
NFS	vs ALT	-0.106	0.02
	vs LSM	0.178	< 0.001
ALT	vs LSM	0.154	< 0.001

FIGURE 3 Heatmap showing correlation between FAST score, LSM FIB-5, NFS, and ALT level in US adults with NAFLD. Abbreviations: ALT, alanine aminotransferase; FAST, FibroScan-AST; FIB-4, fibrosis-4; LSM, liver stiffness measurement; NFS, NAFLD fibrosis score.

diabetes, large waist circumference, and low HDL, and those with a high number of MetS components had higher odds of at-risk NASH. Our analyses would allow for risk stratification of patients with NAFLD in clinical practice. Furthermore, our study suggested clinical focus on addressing these components of the MetS in primary care and specialty management of patients with NAFLD. Because each additional component of the MetS doubles the odds of at-risk NASH, having any of the components under control would benefit the patients, suggesting patients and physicians could choose to work on the components that are easier to manage first. This is especially critical given that there is increasing recognition of NAFLD, more patients are being managed by non-hepatologists and nonendocrinologists, and there are currently no approved pharmacologic treatments. Based on our analyses, we estimated that ~9 million people would benefit from active screening or possible treatments for NASH. Interventions to address the progression of NASH within these populations would be beneficial and lessen the burden on the health care system.

AUTHOR CONTRIBUTIONS

J.P. conducted data analysis and drafted the manuscript. N.A. and P.L. contributed to analytical methodology, interpretation the data, reviewed and edited the manuscript. M.R. interpreted the data, reviewed and edited the manuscript, and obtained funding. P.P. and C.S. interpreted the data, reviewed and edited the manuscript. S.D. conceptualized the study, interpreted the data, reviewed and edited the manuscript. All authors approved the final draft submitted.

CONFLICT OF INTEREST

Dr. S.D. is funded by grants NIH RO1 GM119174; RO1 DK113196; P50 AA024333; RO1 AA021890; 3U01AA026976; UO1 AA 026976; R56HL141744; UO1 DK061732; 5U01 DK062470-17S2; R21 AR 071046 which are independent of the submitted work. Dr. N.A. is a speaker for Echosens (makers of FibroScan) and received research funding from Gilead, Intercept, Allergan, Cirius, Madrigal, and Genfit which was not related to this study. All other authors reported no conflict of interest.

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How to cite this article: Payne JY, Alkhouri N, Le P, Rothberg M, Polanco P, Sakkal C, et al. Prevalence of at-risk NASH and its association with metaboMAQ:Editorial Office/AASLD: Please indicate if a visual abstract will be forthcoming for this article.lic syndrome in US adults with NAFLD, 2017–2018. Hepatol Commun. 2023;7:e0019. https://doi.org/10.1097/HC9.0000000000000019