Poor Awareness of Liver Disease Among Adults With NAFLD in the United States

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Population-based studies that estimate awareness of nonalcoholic fatty liver disease (NAFLD) in the United States are scant. We aimed to understand public awareness of NAFLD and its temporal trends. Our study included 11,700 adults (18+ years old) from five National Health and Nutrition Examination Surveys (2007-2016). NAFLD was determined by the improved Fatty Liver Index for the multiethnic U.S. population (US-FLI) in the absence of secondary causes of liver disease. Overall prevalence of NAFLD, hepatitis C virus, and hepatitis B virus were 36.6%, 1.02% and 0.35%, respectively. From 2007-2008 to 2015-2016, awareness of liver disease among adults with NAFLD improved from 4.4% to 6.3% (trend P = 0.026) but 4 to 10 times lower than awareness about viral hepatitis. In 2015-2016, among adults with NAFLD, awareness of liver disease was lower among young adults (aged 18-29 years) compared with those aged ≥ 30 years (0% vs. 6.9%) and lower among non-Hispanic Blacks compared with other races (0.7% vs. 6.6%) (all P < 0.001). In multivariable analysis, young adults (adjusted odds ratio [aOR] = 0.29; confidence interval [CI] 0.10-0.87) and non-Hispanic Blacks (aOR = 0.43; CI 0.20-0.96) were negatively associated with awareness of liver disease among adults with NAFLD, whereas diabetes (aOR = 2.22; CI 1.37-3.58), advanced fibrosis (aOR = 2.34; CI 1.17-4.68), and a higher number of health care visits (aOR = 1.33; CI 1.15-1.50) were positively associated with awareness of liver disease. Nearly 96% of adults with NAFLD in the United States were unaware they had liver disease, especially among young adults and non-Hispanic Blacks. Findings indicate efforts are needed to improve awareness of NAFLD. (*Hepatology Communications* 2021;5:1833-1847).

The global prevalence of nonalcoholic fatty liver disease (NAFLD) is 24%, accounting for nearly 1.8 billion individuals.[1] NAFLD is the leading cause of chronic liver disease in the United States and in most developed and developing countries. In the United States, NAFLD accounts for 75% of all chronic liver diseases.[2] NAFLD is the fastest increasing indication for liver transplantation (LT), in which, among LT etiologies, NAFLD recently outpaced hepatitis C virus (HCV) to emerge as the second-leading LT indication—only after alcohol-associated liver disease.[3] The prevalence and burden of NAFLD is expected to continue to rise in parallel to the global epidemic of obesity and type 2 diabetes mellitus (T2DM) unless public health efforts are available to reverse the present trajectory.[4,5]

NAFLD can go undiagnosed for some time, as symptoms may only arise when the disease has progressed to advanced liver disease. Progression of NAFLD can lead to nonalcoholic steatohepatitis (NASH), with or without fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[6] Although at this

current time there are no medication-based treatments specifically for NAFLD, a Mediterranean-based diet and moderate exercise, which results in a weight loss of 5%-10%, has been shown to cause reversal of hepatic steatosis and regression of fibrosis (if present).[7] In addition, because the metabolic risks for NAFLD are similar to the metabolic risks for cardiovascular disease (CVD), CVD is the number-one cause of mortality among those with NAFLD.[8]

In this context, treating the comorbidities associated with NAFLD such as T2DM and dyslipidemia remains part of the treatment of NAFLD and for the reduction of the risk for CVD.[9] Finally, there are several medications that are showing promise in reversing fibrosis among those with NASH fibrosis.[10-13] Therefore, as we learn more about NAFLD and treatments become available, being aware of NAFLD will become increasingly important. However, several studies have shown that awareness of having a liver disease is very low among patients with NAFLD (≤5%).[14-17] All investigators of these studies concluded that broad public efforts are needed to increase awareness of NAFLD, its associated risk factors, and its potential adverse outcomes as a means of preventing the development of NAFLD—especially as treatments are limited.[14-17]

On the other hand, as treatments do become available, research has shown that awareness of having a liver disease is imperative to increasing uptake of treatment, as noted with the fight against hepatitis c virus (HCV). Empirical evidence demonstrated that low awareness was a major barrier among adults with HCV for care and treatment. As such, large-scale public health education campaigns as well as guidelines from the Centers for Disease Control and Prevention (CDC) were developed to improve HCV awareness and to help denote when screening should be done.[18,19]

Therefore, it is important to continue to understand the level of awareness of NAFLD so that targeted interventions identifying those with NAFLD can be developed alongside the treatment evolution for NAFLD. Using repeated-measures cross-sectional data from the National Health and Nutrition Examination Survey (NHANES), we determined the level of NAFLD awareness overtime from 2007 to 2016. We also compared the prevalence of liver disease awareness among adults with viral hepatitis (VH) in the United States, another major cause of chronic liver disease.[20,21]

Patients and Methods

STUDY DESIGN AND SAMPLING STRATEGY

For this retrospective study, we combined and analyzed five cycles of data (e.g., 2007-2008, 2009-2010, 2011-2012, 2013-2014, and 2015-2016) from NHANES. NHANES is a population-based program of studies conducted by the National Center for Health Statistics (NCHS). To monitor the health and nutritional status of civilian, noninstitutionalized individuals in the United States, NCHS collects sociodemographic, dietary, laboratory values, and medical data through interviews and physical examinations. The sampling frame for the current study consisted of 29,553 adults (≥ 18 years old) across the five cycles (2007-2008 to 2015-2016) of NHANES data (Fig. 1).

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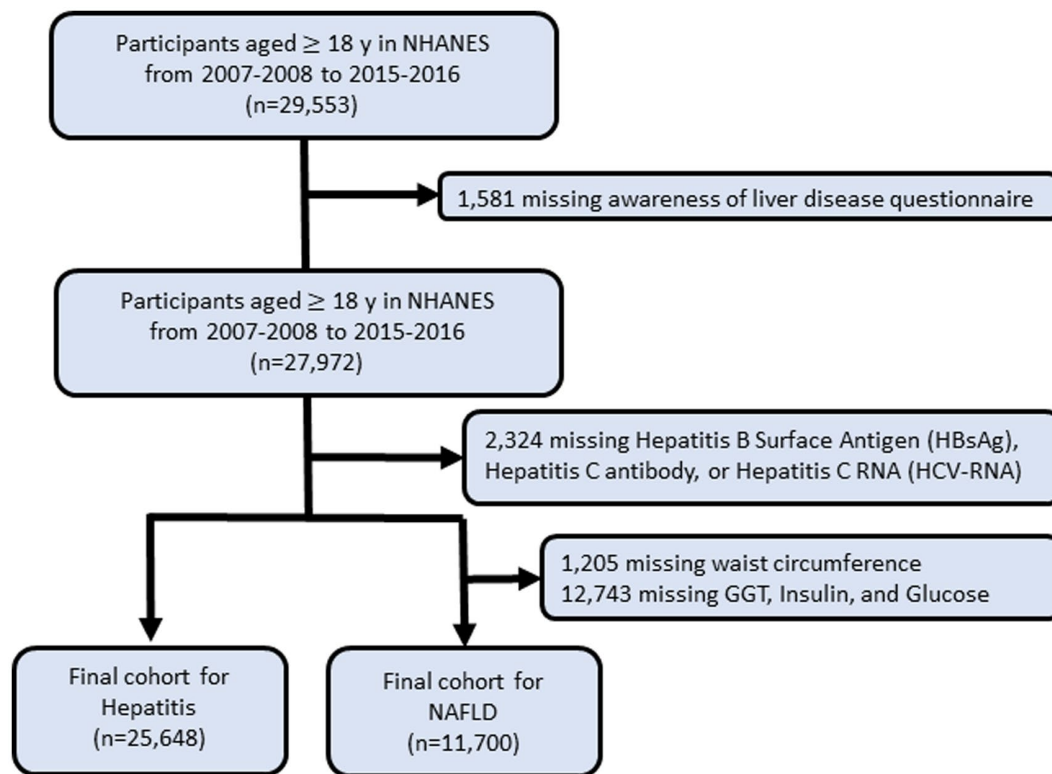Tel.: +1-703-776-2540

FIG. 1. Flow diagram for patient study inclusion.

After implementation of exclusionary criteria (e.g., incomplete or missing data on the following: awareness of liver disease questionnaire, hepatitis B surface antigen (HBsAg) or HCV RNA, waist circumference, gamma-glutamyltransferase (GGT) activity, insulin, and glucose), the NAFLD cohort consisted of 11,700 adults, and the VH cohort consisted of 25,648 adults (Fig. 1). In both the NAFLD and VH cohorts, excluded subjects were more likely to be younger, non-Hispanic Black, and low income (Supporting Table S1).

liver disease among adults with NAFLD. Secondary outcomes of interest for VH were identical to the primary outcomes of NAFLD. The improved US-FLI, a noninvasive semi-quantitative measure of hepatic steatosis, was calculated and used to determine which adults had NAFLD.[22] The US-FLI is a biochemical model that predicts the presence of fatty liver based on age, race/ethnicity, waist circumference, GGT activity, and fasting insulin and fasting glucose. The algorithm is as follows:

$$
\begin{aligned}
\text{USFLI} = (&e - 0.8073 * \text{non - Hispanic black} + 0.3458 * \text{Mexican American} + 0.0093 * \text{age} \\
&+ 0.6151 * \log_e(\text{GGT}) + 0.0249 * \text{waist circumference} + 1.1792 * \log_e(\text{insulin}) \\
&+ 0.8242 * \log_e(\text{glucose}) - 14.7812)/(1 + e - 0.8073 * \text{non - Hispanic black} + 0.3458 * \text{Mexican American} \\
&+ 0.0093 * \text{age} \quad + 0.6151 * \log_e(\text{GGT}) + 0.0249 * \text{waist circumference} \\
&+ 1.1792 * \log_e(\text{insulin}) + 0.8242 * \log_e(\text{glucose}) - 14.7812) * 100.
\end{aligned}
$$

OUTCOMES OF INTEREST

Primary outcomes of interest were the prevalence of and trends in awareness of liver disease among adults with NAFLD, as well as predictors of awareness of

The US-FLI has been previously validated with an area under the receiver operating characteristic curve of 0.80 (95% confidence interval [CI] 0.77-0.83) for the detection of NAFLD in subjects with US-FLI scores ≥ 30.[22] In this study, subjects were presumed

to have NAFLD if they had a US-FLI score ≥ 30 in the absence of any other possible cause of chronic liver disease and excessive alcohol consumption. Women who self-reported four or more drinks and men who self-reported five or more drinks during a single occasion were defined as having excessive alcohol consumption.[23] As a sensitivity analysis, NAFLD was also defined using a Fatty Liver Index (FLI) ≥ 60.[21] VH was defined as a positive HCV RNA for HCV or positive HBsAg for HBV.

Adults who met the diagnostic criteria for NAFLD or who had positive HCV RNA or HBsAg but endorsed "no" on the single-item NHANES question, "Has a doctor or health professional ever told you that you had any kind of liver condition?" were defined as having NAFLD or VH but being unaware that they had liver disease. Those who met the diagnostic criteria for NAFLD or who had positive HCV RNA or HBsAg and endorsed "yes" on the single-item question were defined as having NAFLD or VH and being aware that they had liver disease.

DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics included self-reported age (years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, or other race [other race was defined as those who self-reported mixed race or races other than non-Hispanic White, non-Hispanic Black, Mexican American, or other Hispanic]), income level (poverty-income ratio [PIR] < 1.3 as low, PIR 1.3-3.5 as middle, and PIR > 3.5 as high), college degree, and current medical conditions.

CLINICAL CHARACTERISTICS

The fibrosis-4 (FIB-4) index for liver fibrosis score was calculated to identify those with advanced fibrosis (FIB-4 > 2.67) among patients with NAFLD or VH.[24] The 10-year lifetime risk for developing atherosclerotic CVD (ASCVD) was calculated from the ASCVD risk score (American College of Cardiology/ American Heart Association), which includes each participant's age, race, sex, smoking status, the presence of diabetes, systolic blood pressure, antihypertensive medication, serum cholesterol, and high-density lipoprotein levels. Individuals with a 10-year ASCVD

risk score of ≥ 7.5% were defined as being high risk for CVD.[25] Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2. T2DM was defined as a fasting glucose level ≥ 126 mg/dL, self-reported medical history of diabetes, use of oral hypoglycemic agents, insulin use, or hemoglobin A1c of ≥ 6.5%.[26] Hypertension was defined as systolic blood pressure measurements ≥ 130 mm Hg or diastolic blood pressure measurements ≥ 80 mm Hg from an average of three measurements, or a history of high blood measurements.[27] Hyperlipidemia was defined by either a serum cholesterol level ≥ 200 mg/dL, low density lipoprotein level ≥ 130 mg/dL, high density lipoprotein cholesterol level ≤ 40 mg/dL for men and 50 for women, or history of hyperlipidemia.[28] Metabolic syndrome was defined by the National Cholesterol Education Program Adult Treatment Panel III definition.[28] Number of health care visits was assessed with the following single-item NHANES question: "During the past 12 months, how many times have you seen a doctor or other health care professional about your health at a doctor's office, a clinic or some other place?"

STATISTICAL ANALYSIS

To combine data from the five cycles of NHANES data, sampling weights and adjustment coefficients were used in compliance with the NHANES Analytic and Reporting Guidelines.[29] The Rao-Scott chi-square test and the Wald test were used to compare groups on categorical and continuous variables, respectively. Test for trends in prevalence and awareness across survey cycles were performed by including the midpoint of each survey period as a continuous variable in logistic regression model. Multivariable logistic regression models were used to identify predictors of awareness of liver disease among adults with NAFLD and VH. Examination sample weights, accounting for nonresponse, noncoverage, and unequal selection probabilities for certain categories of the population, were incorporated to produce national estimates for all analyses. Sampling errors were estimated by the Taylor series linearization method. In addition, the total number of U.S. adults with NAFLD in 2016 was calculated by multiplying the prevalence estimates from NHANES 2015-2016 and the corresponding population totals from the Current Population Surveys.[30] Analyses were performed with

SAS software, version 9.4 (SAS Institute, Cary, NC) using "SURVEY" procedure, which incorporates the sample design. Statistical tests were considered significant at $P < 0.05$ (two-tailed).

Results

PREVALENCE OF AND CHARACTERISTICS OF ADULTS WITH NAFLD

Among 11,700 eligible adult participants included in the NAFLD cohort (mean age 47.4 years; 48.8% male; 67.6% non-Hispanic White, 10.2% non-Hispanic Black, and 8.7% Mexican American), the overall prevalence of NAFLD was 34.2% (CI 32.8%-35.6%), and the trend was stable from 32.6% in 2007-2008 to 36.6% in 2015-2016 (trend $P = 0.286$) (Fig. 2). The demographic and characteristics of adults by the presence of NAFLD are displayed in Supporting Table S2. As consistent with typical features of NAFLD, adults with NAFLD were more likely to be older, male, Mexican American, former smokers, and more likely have to obesity, hypertension, diabetes, metabolic syndrome, a history of CVD and cancer, and high risk for CVD compared to adults without NAFLD. There were no differences among the demographic and clinical characteristics between adults with NAFLD by US-FLI and FLI (Supporting Table S2).

In 2015-2016, the prevalence of NAFLD was 36.6% (CI 33.1%-40.2%) but was noted to increase with age from 21.7% (16.5%-27.0%) among those 18-29 years old, 33.5% (26.8%-40.2%) among those 30-44 years old, 38.6% (32.5%-44.7%) among those 45-64 years old, and 47.6% (41.9%-53.4%) among those ≥ 65 years old, equating to an estimated 87.0 million adults with NAFLD in the United States (11.6, 20.5, 32.3, and 22.7 million among those 18-29, 30-44, 45-64, and ≥ 65 years old, respectively) (Supporting Table S3).

PREVALENCE OF AND CHARACTERISTICS OF ADULTS WITH VH

Among 25,648 eligible adult participants included in the VH cohort (mean age 47.1 years; 48.4% male;

67.0% non-Hispanic White, 10.9% non-Hispanic Black, and 8.7% Mexican American), the overall prevalence was 1.02% (0.85%-1.19%) for HCV and 0.35% (0.27%-0.43%) for HBV, and both prevalences have not changed over time (trend $P > 0.007$) (Fig. 2) The demographic and characteristics of adults by the presence of HCV and HBV are displayed in Supporting Table S4. Compared to those with HBV, those with HCV were more likely to be older, non-Hispanic White, active smoker, more likely to have obesity, hypertension, diabetes, excessive alcohol consumption, and advanced fibrosis, while less likely to be other race (including Asian). Of note, adults with HCV had higher waist circumference (98.9 cm vs. 92.4 cm) and more frequent health care visits (2.3 vs. 1.7), but no difference in BMI ($P = 0.247$) versus those with HBV.

In 2015-2016, the prevalence was 0.95% (0.72%-1.17%) for HCV and 0.30% (0.16%-0.44%) for HBV, equating to an estimated 2.6 million with HCV and 0.8 million with HBV in the United States. The prevalence of HCV was higher among males, those 45-64 years old, and non-Hispanic Black compared with their counterpart, whereas that of HBV was higher among males and other races but similar across age groups (Supporting Table S5).

AWARENESS OF LIVER DISEASE AMONG ADULTS WITH NAFLD

The overall prevalence of awareness of liver disease among adults with NAFLD was 4.4% (3.7%-5.1%) (Table 1). The overall prevalence of awareness of liver disease among adults with NAFLD was highest among females (5.3%) and lowest among males (3.7%), highest among those ≥ 65 years and older (5.6%) and lowest among those 18-29 years old (1.1%), and highest among other Hispanics (8.8%) and lowest among non-Hispanic Blacks (2.0%) (Fig. 3). Trends in awareness of liver disease among adults with NAFLD increased significantly from 4.3% (CI 2.9%-5.6%) in 2007-2008 to 6.3% (CI 4.8%-7.9%) in 2015-2016 (trend $P = 0.03$) (Fig. 2). Trends in awareness of liver disease among adults with NAFLD increased significantly among other Hispanics (trend $P = 0.02$), but trends did not increase significantly within other stratifications of sex, age, or race.

Among adults with NAFLD, compared to adults without awareness of having a liver disease, those with awareness of having a liver disease were older (56.1 vs.
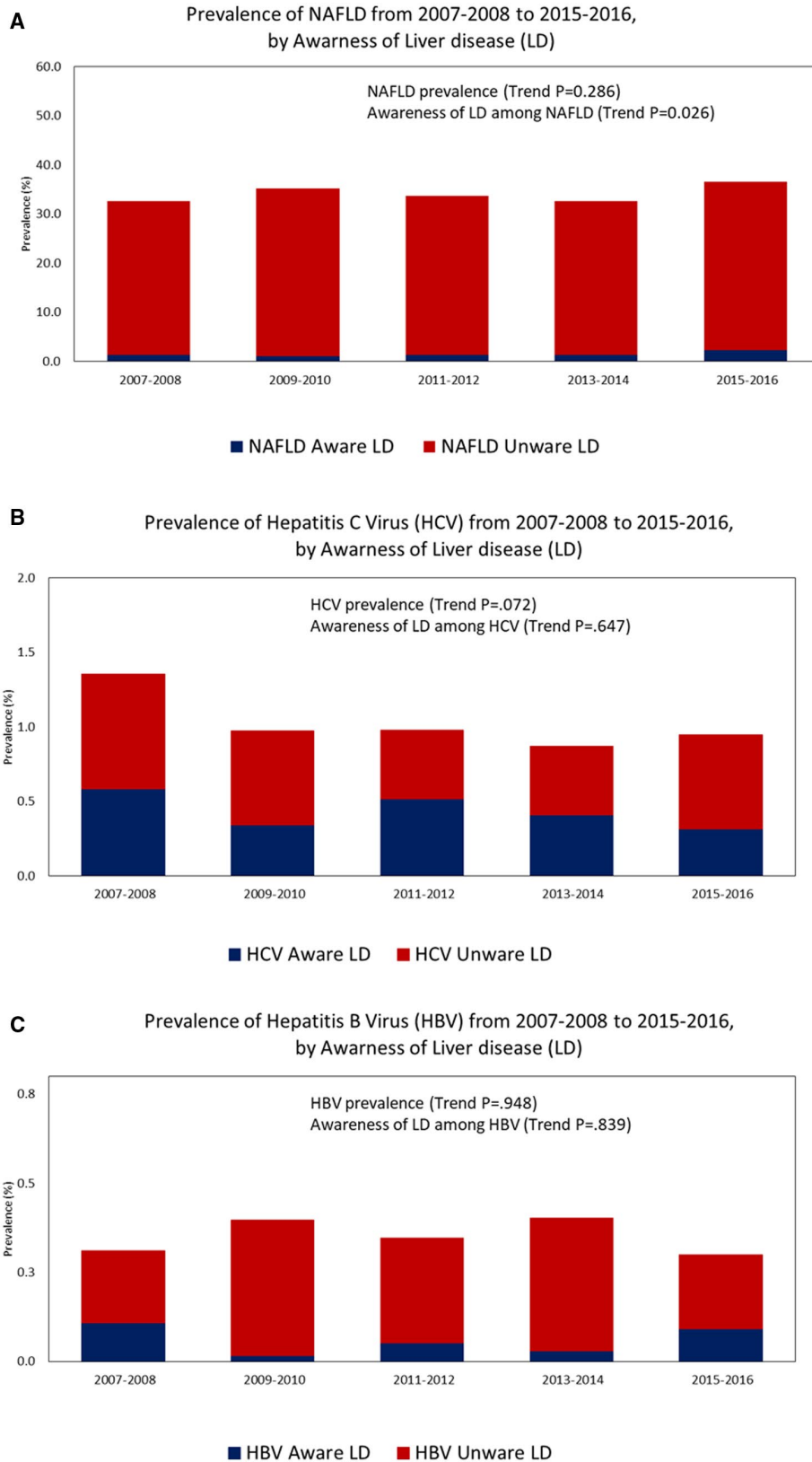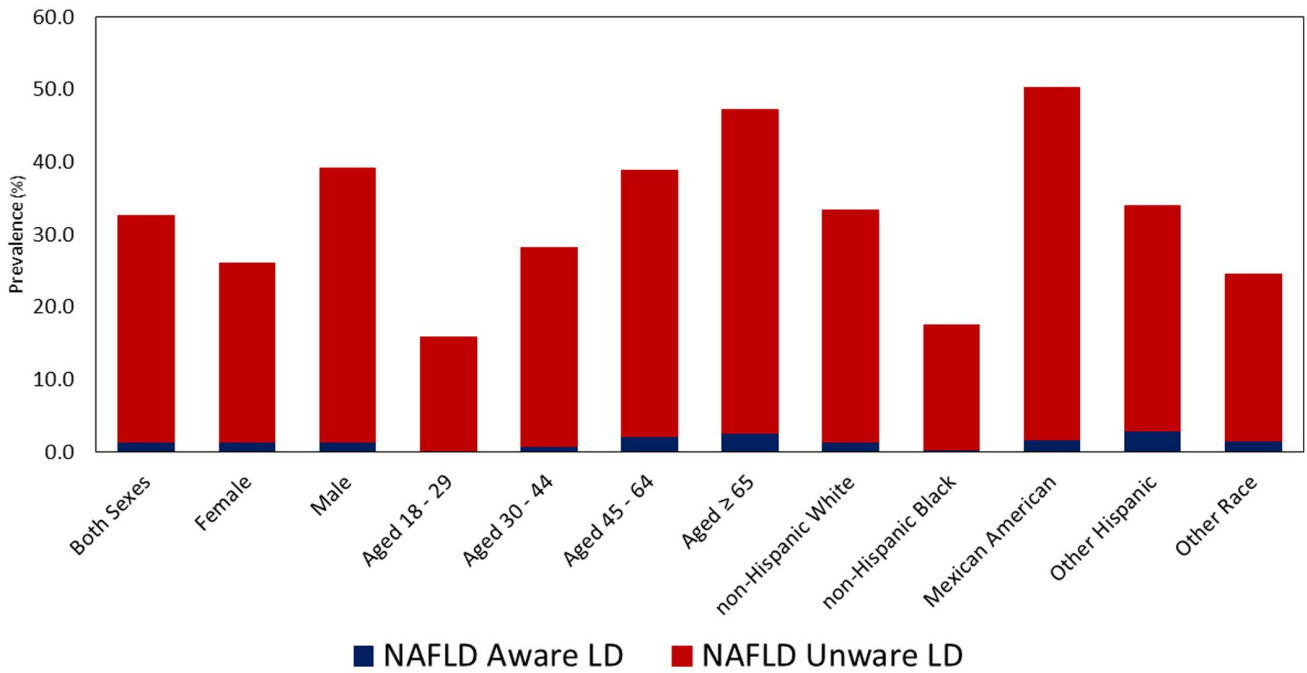
FIG. 2. (A) Awareness of NAFLD by the prevalence of NAFLD over time (2007-2016). (B) Awareness of HCV by the prevalence of HCV over time (2007-2016). (C) Awareness of HBV by the prevalence of HBV over time (2007-2016).

## TABLE 1. TRENDS IN AWARENESS AMONG ADULTS AGED 18 OR OVER WITH NAFLD AND WITH VH: NHANES 2007–2008 TO 2015–2016

	NHANES 2007-2016	NHANES 2007-2008	NHANES 2009-2010	NHANES 2011-2012	NHANES 2013-2014	NHANES 2015-2016	Trend P
Awareness among NAFLD							
Total	4.39 (3.69-5.09)	4.27 (2.92-5.63)	3.07 (1.66-4.48)	3.94 (2.43-5.45)	4.01 (2.23-5.79)	6.31 (4.76-7.86)	0.0255
Subgroup							
Sex							
Female	5.33 (3.86-6.81)	5.19 (3.09-7.29)	3.29 (1.89-4.68)	3.97 (1.62-6.32)	5.55 (2.68-8.43)	8.23 (3.2-13.25)	0.0930
Male	3.65 (2.55-4.75)	3.65 (1.68-5.61)	2.9 (0.41-5.4)	3.92 (1.62-6.22)	2.68 (0.71-4.65)	4.83 (1.86-7.8)	0.5370
Age group (years)							
18-29	1.09 (-0.03-2.21)	2.65 (-2.42-7.72)	0.5 (-0.46-1.46)	0.89 (-0.39-2.16)	1.96 (-1.59-5.52)	0 (0-0)	0.4927
30-44	2.77 (1.50-4.03)	1.18 (-0.35-2.72)	1.05 (-0.29-2.39)	3.81 (0.66-6.96)	3.8 (1.48-6.12)	3.68 (-0.63-7.99)	0.0847
45-64	5.54 (3.98-7.11)	5.45 (3.42-7.47)	4.95 (1.62-8.28)	2.94 (0.63-5.25)	5.84 (2.04-9.63)	8.28 (3.48-13.08)	0.2346
≥65	5.57 (3.97-7.17)	6.09 (2.86-9.32)	3.34 (1.15-5.54)	7.29 (3.41-11.17)	2.27 (0.23-4.31)	7.67 (3.75-11.6)	0.5194
Race							
Non-Hispanic White	4.15 (3.14-5.16)	4.49 (2.54-6.43)	3.06 (0.95-5.17)	3.17 (1.15-5.19)	3.23 (1.12-5.33)	6.48 (3.88-9.07)	0.2005
Non-Hispanic Black	1.99 (0.56-3.42)	1.71 (-1.14-4.56)	0.39 (-0.37-1.16)	4.95 (-0.47-10.36)	2.17 (-0.63-4.97)	0.69 (-0.64-2.02)	0.9191
Mexican American	3.54 (2.33-4.74)	4.61 (1.3-7.92)	3.08 (1.17-5)	1.27 (0.04-2.51)	4.2 (0.72-7.68)	4.49 (1.68-7.29)	0.7968
Other Hispanic	8.78 (5.67-11.89)	2.72 (-0.45-5.84)	3.16 (0.02-6.3)	13.41 (5.62-21.2)	13.2 (5.1-21.3)	8.73 (4.91-12.55)	0.0169
Other race	6.51 (2.59-10.43)	5.16 (-4.55-14.87)	6.29 (-1.8-14.37)	4.53 (-0.57-9.63)	5.67 (0.71-10.63)	9.13 (-1.31-19.58)	0.5633
Awareness among HCV							
Total	42.36 (37.25-47.47)	43.15 (32.13-54.17)	34.89 (23.87-45.91)	52.98 (43.41-62.54)	46.93 (32.94-60.93)	33.37 (24.09-42.65)	0.6465
Awareness among HBV							
Total	17.19 (12.60-21.77)	35.26 (28.29-42.24)	4.51 (-3.99-13.02)	15.44 (9.32-21.55)	7.56 (1.72-13.39)	30.86 (18.84-42.88)	0.8395

Note: Data are displayed as weighted percentages (95% CI) except where otherwise noted. Test for trends was performed by including the midpoint of each survey period as a continuous variable in a logistic regression model.

A

Prevalence of NAFLD, by Sex, Age group, Race/ethnicity, and Awarness of Liver disease (LD): NHANES 2007-2016

B

Prevalence of NAFLD, by Sex, Age group, Race/ethnicity, and Awarness of Liver disease (LD): NHANES 2015-2016
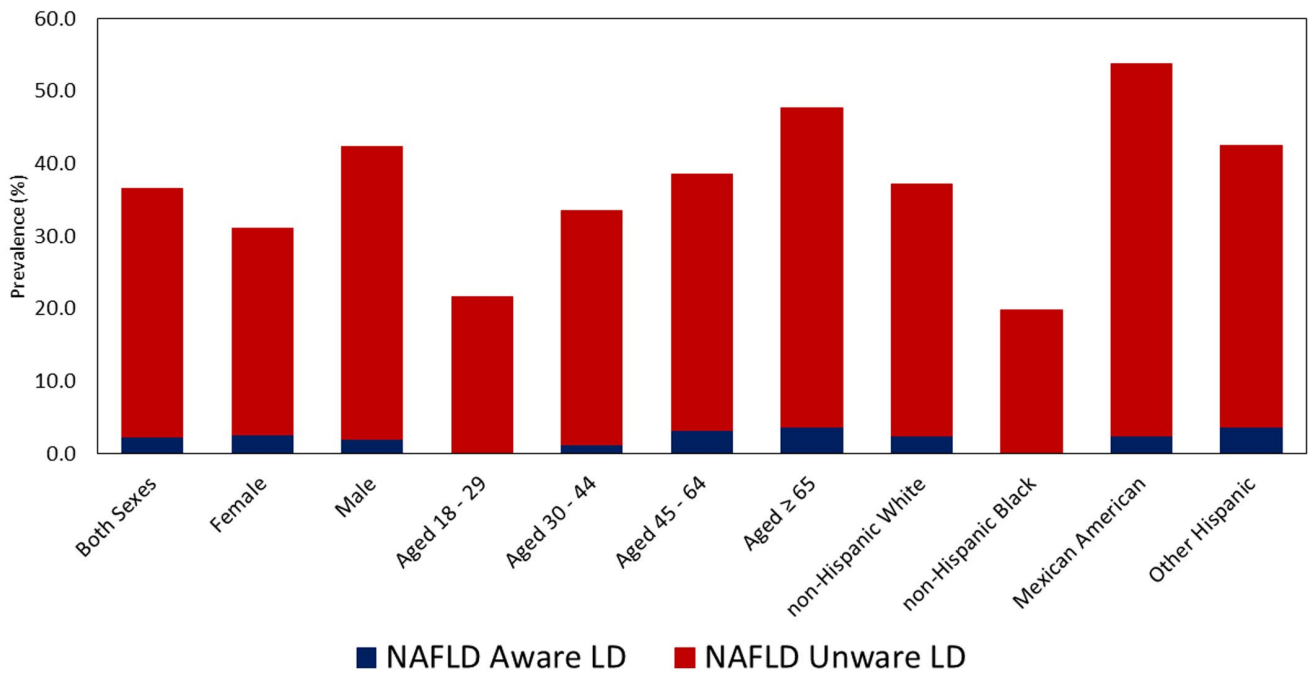
FIG. 3. (A) NAFLD awareness by age, gender, ethnicity and prevalence (2007-2016). (B) NAFLD awareness by age, gender, ethnicity and prevalence over most recent 12 months (2015-2016).

51.1 years), had a higher homeostasis model assessment (HOMA) score (9.6 vs. 7.0) and a higher number of health care visits (2.9 vs. 2.2), and were more likely to be other Hispanic (13.2% vs. 6.3%), have obesity (77.6% vs. 69.3%), hypertension (73.8% vs. 63.1%), diabetes (53.4% vs. 27.0%), history of CVD (23.4% vs. 12.6%), and advanced fibrosis (7.2% vs. 2.6%), whereas being less aware was more likely to be non-Hispanic Black (2.7% vs. 6.2%) (Table 2). There were no differences among the demographic and clinical characteristics by awareness of liver disease between adults with NAFLD by US-FLI and FLI (Supporting Table S6). In our multivariable model, young adults (adjusted odds ratio [aOR] = 0.29; CI 0.10-0.87) and non-Hispanic Black (aOR = 0.43; CI 0.20-0.96) were negatively associated with awareness

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF ADULTS WITH NAFLD, STRATIFIED BY AWARENESS OF LIVER DISEASE: NHANES 2007-2008 TO 2015-2016

| | Adults With NAFLD | | | |
| | Awareness of Liver Disease | | | |
	Yes (n = 216)	No (n = 4,005)	P	Total Adults
Age, years (mean [SEM])	56.08 (0.84)	51.14 (0.34)	<0.0001	51.35 (0.33)
18-29	2.72 (1.42)	11.31 (0.72)	0.0015	10.93 (0.71)
30-44	15.32 (3.39)	24.70 (0.96)	0.0237	24.29 (0.93)
45-64	52.44 (6.09)	41.01 (1.19)	0.0547	41.51 (1.21)
≥65	29.53 (4.30)	22.98 (0.93)	0.0879	23.27 (0.96)
Male, %	46.56 (6.09)	56.47 (1.02)	0.1143	56.03 (0.98)
Race, %				
Non-Hispanic White	64.38 (4.71)	68.23 (1.92)	0.3904	68.06 (1.90)
Non-Hispanic Black	2.73 (1.00)	6.19 (0.59)	0.0192	6.04 (0.58)
Mexican American	10.64 (1.97)	13.33 (1.42)	0.1980	13.21 (1.39)
Other Hispanic	13.24 (3.12)	6.31 (0.70)	0.0002	6.62 (0.75)
Other race	9.00 (2.84)	5.93 (0.58)	0.2080	6.07 (0.57)
Income, %				
Low	23.33 (3.14)	23.58 (1.04)	0.9389	23.57 (1.02)
Medium	39.91 (4.63)	37.40 (1.24)	0.6107	37.51 (1.17)
High	36.76 (4.72)	39.02 (1.59)	0.6678	38.92 (1.50)
Smoking status, %				
Active	13.00 (2.78)	16.65 (0.90)	0.2732	16.49 (0.85)
Former	39.98 (6.23)	30.41 (1.00)	0.0930	30.83 (1.05)
Nonsmoker	47.02 (5.53)	52.94 (1.21)	0.2728	52.68 (1.23)
College, %	27.31 (4.94)	23.39 (1.36)	0.4084	23.56 (1.34)
Obesity, %	77.63 (3.53)	69.27 (0.95)	0.0327	69.64 (0.93)
Hypertension, %	73.76 (3.71)	63.07 (1.22)	0.0106	63.54 (1.18)
Hyperlipidemia, %	84.93 (2.69)	82.84 (0.80)	0.4754	82.93 (0.77)
Diabetes, %	53.37 (5.18)	26.99 (0.94)	<0.0001	28.11 (0.91)
Metabolic syndrome, %	64.79 (4.85)	60.29 (1.16)	0.3690	60.49 (1.14)
History of CVD, %	23.38 (3.54)	12.63 (0.63)	0.0002	13.10 (0.63)
History of cancer, %	12.82 (2.87)	12.02 (0.77)	0.7726	12.05 (0.76)
High risk of CVD	49.28 (3.90)	41.99 (1.21)	0.0683	42.31 (1.18)
Advanced fibrosis (FIB-4), %	7.21 (1.61)	2.61 (0.34)	0.0001	2.82 (0.33)
Waist, cm (mean [SEM])	114.66 (1.19)	112.60 (0.35)	0.0909	112.69 (0.36)
BMI, mean (SEM)	34.79 (0.50)	33.94 (0.16)	0.0998	33.98 (0.17)
HOMA, mean (SEM)	9.58 (0.67)	7.00 (0.16)	0.0004	7.11 (0.16)
Health care visit, mean (SEM)	2.86 (0.11)	2.19 (0.03)	<0.0001	2.22 (0.03)

Note: Data are displayed as weighted percentages (SEM) except where otherwise noted.

of liver disease among adults with NAFLD, whereas diabetes (aOR = 2.22; CI 1.37-3.58) and advanced fibrosis (aOR = 2.34; CI 1.17-4.68) and a higher number of health care visits (aOR = 1.33; CI 1.15-1.50) and were positively associated with awareness of liver disease (Table 3).

Overall, liver disease awareness remained significantly lower among ages 18-29 compared with those aged ≥ 30 years (Fig. 2). Worse awareness in young adults was driven mostly by worse measures in Mexican Americans, those with low education, active smokers, and those with hypertension (Supporting Table S7). When stratified by race/ethnicity, non-Hispanic Blacks had the lowest awareness of liver disease, followed by Mexican Americans, non-Hispanic Whites, and other Hispanics across times. Furthermore, awareness among non-Hispanic Blacks and Mexican Americans did not improve during the study period (Supporting Table S8).

AWARENESS OF LIVER DISEASE AMONG ADULTS WITH VH

The overall prevalence of awareness of liver disease among adults with HCV and with HBV was 42.4% (CI 37.3%-47.5%) and 17.2% (12.6%-21.8%), respectively. Trends in awareness of liver disease among adults with HCV and with HBV did not change significantly from 2007-2008 to 2015-2016 (trend *P* > 0.70) (Table 1 and Fig. 2).

Among adults with HCV, those with awareness of liver disease were older, other Hispanic, and more likely to have hyperlipidemia, diabetes, metabolic syndrome, and advanced fibrosis. Adults with awareness of liver disease also had higher waist circumference and more frequent health care visits (2.3 vs. 1.7) but no difference in BMI (*P* = 0.518) (Table 4). In our multivariable model, non-Hispanic Black (aOR = 0.53 [0.31-0.93]) was negatively associated with awareness of liver disease among adults with HCV, whereas

TABLE 3. ODDS RATIOS OF AWARENESS OF LIVER DISEASE AMONG ADULTS WITH NAFLD AND VH: NHANES 2007-2008 TO 2015-2016

	Adults With NAFLD		Adults With HCV		Adults With HBV	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Year	1.06 (0.99-1.14)	0.0856	1.00 (0.90-1.10)	0.9371	0.97 (0.81-1.15)	0.6775
Age, years						
45-64	Reference		Reference		Reference	
18-29	**0.29 (0.10-0.87)**	**0.0279**			**3.38 (1.08-10.59)**	**0.0373**
30-44	0.68 (0.36-1.3)	0.2392	2.06 (0.91-4.66)	0.0833	0.52 (0.23-1.19)	0.1148
≥ 65	0.73 (0.42-1.28)	0.2686	0.80 (0.25-2.54)	0.6964	0.04 (0.00-1.41)	0.0748
Male, %	0.76 (0.48-1.19)	0.2295	1.37 (0.71-2.66)	0.3428	2.16 (0.57-8.22)	0.2450
Race, %						
Non-Hispanic White	Reference		Reference		Reference	
Non-Hispanic Black	**0.43 (0.20-0.96)**	**0.0390**	**0.53 (0.31-0.93)**	**0.0266**	2.82 (0.25-32.22)	0.3886
Mexican American	1.28 (0.77-2.12)	0.3401	1.82 (0.85-3.93)	0.1226		
Other Hispanic	**2.75 (1.62-4.65)**	**0.0003**	2.18 (0.81-5.92)	0.1222		
Other race	1.94 (0.83-4.53)	0.1231	0.65 (0.13-3.16)	0.5829	**35.82 (3.50-366.35)**	**0.0041**
Obesity	1.47 (0.96-2.27)	0.0785	0.88 (0.36-2.16)	0.7796	**0.02 (0.00-0.09)**	**<0.0001**
Hypertension	1.07 (0.71-1.62)	0.7456	0.91 (0.43-1.96)	0.8127	**7.62 (2.74-21.18)**	**0.0004**
Hyperlipidemia	0.87 (0.56-1.35)	0.5184	2.05 (0.98-4.30)	0.0563	0.61 (0.25-1.50)	0.2684
Diabetes	**2.22 (1.37-3.58)**	**0.0015**	**2.62 (1.26-5.47)**	**0.0110**	6.46 (0.52-80.11)	0.1391
History of CVD	1.35 (0.75-2.46)	0.3138	0.97 (0.40-2.38)	0.9536	0.8 (0.10-6.43)	0.8220
Advanced fibrosis (FIB-4)	**2.34 (1.17-4.68)**	**0.0172**	1.31 (0.63-2.72)	0.4688	**28.19 (4.27-185.90)**	**0.0013**
Health care visit	**1.33 (1.15-1.50)**	**0.0002**	**1.71 (1.35-2.16)**	**<0.0001**	**2.21 (1.35-3.61)**	**0.0028**

Note: Significant values are indicated in bold.
Model adjusted for year, age, sex, race, obesity, hypertension, hyperlipidemia, diabetes, history of CVD, advanced fibrosis, and Health care visit.

TABLE 4. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF ADULTS WITH VIRAL HEPATITIS, STRATIFIED BY AWARENESS OF LIVER DISEASE: NHANES 2007-2008 TO 2015-2016

	Adults With HCV				Adults With HBV			
	Awareness of Liver Disease				Awareness of Liver Disease			
	Yes (n = 137)	No (n = 196)	P	Total Adults	Yes (n = 28)	No (n = 122)	P	Total Adults
Age, years (mean [SEM])	53.78 (0.67)	49.71 (0.90)	0.0037	51.43 (0.67)	44.21 (1.59)	47.53 (1.52)	0.3691	46.96 (1.40)
18-29	0	5.50 (2.49)		3.17 (1.48)	20.96 (6.86)	13.17 (2.42)	0.2378	14.51 (2.25)
30-44	14.55 (4.13)	22.50 (2.53)	0.1551	19.13 (2.15)	30.13 (6.51)	32.58 (4.63)	0.7372	32.15 (4.19)
45-64	78.29 (4.50)	64.33 (3.76)	0.0292	70.24 (2.81)	41.79 (6.16)	40.49 (4.27)	0.8600	40.71 (3.71)
≥65	7.16 (2.23)	7.66 (1.55)	0.8583	7.45 (1.28)	7.12 (3.54)	13.76 (4.66)	0.2824	12.62 (3.85)
Male, %	71.62 (3.95)	64.93 (4.17)	0.2180	67.76 (3.08)	73.01 (7.17)	57.38 (4.34)	0.0964	60.06 (3.66)
Race, %								
Non-Hispanic White	64.12 (4.54)	59.64 (4.43)	0.3995	61.54 (3.63)	9.28 (1.15)	25.30 (5.69)	<0.0001	22.55 (4.90)
Non-Hispanic Black	18.06 (3.24)	25.43 (3.51)	0.0530	22.31 (2.85)	13.43 (6.18)	23.04 (4.04)	0.2824	21.39 (3.29)
Mexican American	6.89 (2.13)	5.77 (1.36)	0.5276	6.24 (1.46)	3.96 (3.83)	2.89 (1.79)	0.7839	3.07 (1.62)
Other Hispanic	6.70 (2.01)	3.57 (0.88)	0.0373	4.90 (1.15)	0	2.97 (0.92)		2.46 (0.76)
Other race	4.23 (1.89)	5.58 (2.27)	0.6481	5.01 (1.52)	73.34 (6.07)	45.80 (4.57)	0.0007	50.53 (4.02)
Income, %								
Low	48.94 (5.90)	47.74 (4.61)	0.8815	48.23 (3.37)	39.58 (6.70)	36.05 (5.22)	0.6476	36.57 (4.71)
Middle	30.64 (5.61)	35.66 (5.56)	0.5483	33.60 (3.78)	39.67 (6.28)	33.77 (4.59)	0.3804	34.64 (4.24)
High	20.42 (4.29)	16.59 (4.35)	0.5671	18.17 (2.84)	20.75 (5.05)	30.18 (5.42)	0.1601	28.79 (4.83)
Smoking status, %								
Active	51.23 (4.86)	65.18 (5.44)	0.0522	59.27 (3.90)	30.01 (5.52)	16.40 (2.46)	0.0032	18.74 (2.51)
Former	29.35 (4.95)	20.56 (4.19)	0.1876	24.29 (3.11)	18.30 (2.91)	22.90 (4.68)	0.3563	22.11 (3.98)
Nonsmoker	19.41 (4.12)	14.26 (3.13)	0.3318	16.44 (2.39)	51.69 (6.32)	60.71 (4.22)	0.2231	59.16 (3.71)
College, %	6.45 (2.93)	6.94 (1.91)	0.8973	6.73 (1.54)	23.09 (8.11)	29.60 (5.38)	0.5164	28.48 (4.68)
Obesity, %	30.75 (5.56)	26.36 (4.32)	0.5719	28.24 (3.00)	1.27 (0.16)	18.13 (4.02)	<0.0001	15.32 (3.39)
Hypertension, %	67.69 (4.94)	57.02 (5.12)	0.1360	61.54 (3.64)	67.78 (7.12)	35.56 (4.03)	0.0002	41.10 (3.65)
Hyperlipidemia, %	67.10 (4.46)	48.89 (5.31)	0.0126	56.60 (3.51)	54.85 (6.37)	58.38 (4.21)	0.6683	57.77 (3.46)
Diabetes, %	27.83 (4.57)	11.20 (2.40)	0.0011	18.07 (2.24)	14.12 (6.13)	6.63 (1.76)	0.0854	7.95 (2.06)
Metabolic syndrome, %	52.47 (6.91)	25.20 (4.74)	0.0002	38.90 (4.82)	34.06 (8.07)	23.07 (5.83)	0.2389	25.13 (5.10)
Excessive alcohol consumption	22.18 (4.85)	29.07 (4.99)	0.2439	26.12 (4.00)	2.35 (0.29)	9.93 (2.53)	<0.0001	8.41 (2.01)
HBV	2.04 (1.28)	0.76 (0.54)	0.2774	1.30 (0.63)	100.00 (0.00)	100.00 (0.00)		100.00 (0.00)
HCV	100.00 (0.00)	100.00 (0.00)		100.00 (0.00)	14.50 (4.76)	1.53 (0.75)	<0.0001	3.76 (1.09)
Alcohol-associated liver disease	20.76 (4.90)	22.28 (4.28)	0.7615	21.63 (3.83)	2.41 (0.31)	3.82 (2.49)	0.4852	3.54 (2.00)
History of CVD, %	15.56 (3.81)	8.68 (1.98)	0.0621	11.59 (2.09)	8.31 (2.17)	11.42 (4.56)	0.5129	10.89 (3.78)
History of cancer, %	9.55 (3.18)	6.09 (1.79)	0.1944	7.55 (1.99)	6.22 (0.77)	6.94 (4.65)	0.8723	6.82 (3.86)
High risk of CVD	46.75 (5.48)	33.68 (4.86)	0.0923	39.09 (3.45)	44.56 (7.12)	26.05 (3.27)	0.0044	29.30 (3.28)
Advanced fibrosis (FIB-4), %	31.35 (5.12)	19.12 (3.52)	0.0409	24.37 (3.04)	20.87 (5.44)	2.73 (1.06)	<0.0001	5.82 (1.23)
BMI, mean (SEM)	29.04 (0.61)	27.10 (0.55)	0.0518	27.93 (0.41)	24.56 (0.45)	27.05 (1.11)	0.0760	26.63 (0.94)
Waist, cm (mean [SEM])	103.05 (1.63)	95.88 (1.24)	0.0046	98.82 (1.04)	88.97 (1.19)	93.10 (1.86)	0.1928	92.41 (1.61)
HOMA, mean (SEM)	6.71 (0.69)	3.45 (0.46)	0.0218	5.09 (0.47)	4.75 (0.14)	2.67 (0.45)	0.0113	3.08 (0.37)
Health care visit, mean (SEM)	2.88 (0.16)	1.92 (0.13)	0.0000	2.33 (0.12)	2.19 (0.09)	1.60 (0.17)	0.0779	1.70 (0.16)

Note: Data are displayed as weighted percentages (SEM) except where otherwise noted.

presence of diabetes (aOR = 2.62 [1.26-5.47]) and higher number of health care visits (aOR = 1.71 [1.35-2.16]) were positively associated with awareness of liver disease (Table 3).

Among adults with HBV, those with awareness of liver disease were more likely to be other race, active smoker, and more likely to have hypertension, HCV, higher risk of CVD, and advanced fibrosis, while less likely to be non-Hispanic White and less likely to have obesity and excessive alcohol consumption (Table 4). In our multivariable model, obesity (aOR = 0.02 [0.00-0.09]) was negatively associated with awareness of liver disease among adults with HBV, while young adults (aOR [1.08-10.59]), other race (aOR = 35.8 [3.50-366.35]), hypertension (aOR = 7.62 [2.74-21.18]), advanced fibrosis (aOR = 28.2 [4.27-185.9]), and a higher number of health care visits (aOR = 2.21 [1.35-3.61]) were positively associated with awareness of liver disease (Table 3).

Discussion

Using repeated-measures cross-sectional NHANES data, we estimated the prevalence of awareness of liver disease among adults with NAFLD in the general population in the United States, and secondarily estimated awareness among adults with VH. Several findings emerged from our analysis. The prevalence of NAFLD was alarmingly high, and the prevalence of NAFLD dwarfed the prevalence of HCV and HBV (34.2% vs. 1.0% and 0.4%). The prevalence of NAFLD, HCV, and HBV remained relatively steady over the 9-year study period. Although the prevalence of NAFLD was considerably higher than VH, nearly 96% of adults with NAFLD in the United States were unaware they had liver disease compared with over 42% who were aware among the HCV group and 17% among the HBV group. Among the NAFLD cohort, the lowest awareness of liver disease was found for males, young adults, and/or non-Hispanic Blacks, whereas those with the lowest awareness among the VH group were more likely to be older than 65 years old.

Prevalence estimates of NAFLD awareness found in this study are consistent with a handful of studies in the United States that previously estimated liver disease awareness.[14-17,31,32] Those respective studies estimated 95%-98% of adults with NAFLD in

the United States were unaware of their liver disease. Previous estimates in combination with our estimates are indicative of an urgent need for a wide-ranging public health response to improve population-wide awareness of NAFLD. In fact, when we look at the level of awareness among the VH group, those in the "baby boomer" group, a target of HCV screening by the CDC, had the highest level of awareness.[18,19] As the new guidelines from the CDC in which screening of all adults, women during every pregnancy, and more frequent testing for those with high risk are enacted,[33] assessment of liver disease awareness remains important.[34] On the other hand, low awareness of NAFLD in the United States is not only due to a low knowledge of NAFLD in the general population but also poor knowledge of NAFLD among non-liver specialists and inconsistencies in screening recommendations.[14-17,31,32,35,36] A few studies have demonstrated that many in the general population are unaware of or have not heard of NAFLD, including those at risk for NAFLD,[14-17,31,32] and 98% of participants in one of those respective studies reported that their physicians had not ever mentioned or discussed NAFLD.[15] Other studies reported that many non-liver specialists have poor understanding of NAFLD, uncertainty about proper diagnosis and management of NAFLD, and routinely underestimate its prevalence.[35,36]

Adding to these factors, the American Association for the Study of Liver Diseases (AASLD) does not advise routine screening for NAFLD in high-risk groups attending primary care, diabetes, or obesity clinics.[6] The recommendation cites concerns around uncertainties surrounding diagnostic tests and treatment options, along with the lack of knowledge related to long-term benefits and cost-effectiveness of screening. Conversely, the American Diabetes Association (ADA) recently recommended screening for NASH and advanced fibrosis in patients with diabetes with elevated liver enzymes,[37] and in Europe the European Association for the Study of the Liver (EASL) recommends screening among patients with obesity or a metabolic syndrome as part of routine work-up.[38]

Although universal screening for NAFLD cannot be made, we would suggest that those who appear to have risk factors associated with NAFLD should be risk-stratified using noninvasive algorithms and noninvasive assessment of hepatic fibrosis.[39-40] These suggestions

do fall in line with the ADA and EASL guidelines as well as following the recent findings from Le et al., who found that 23% of those with NAFLD had advanced fibrosis, yet only 5% of persons with NAFLD were even aware they had a liver disease.[14] These suggestions are also based on the other findings in our study, in which those with advanced fibrosis and or diabetes along with more visits to the doctors were associated with increased awareness, which may demonstrate that it is only when advanced disease is present does one become aware of having a liver disease.

Our finding that non-Hispanic Blacks and those aged 18-29 were the least likely to be aware they had a liver disease may be due to several reasons. First, despite non-Hispanic Blacks having multiple risk factors for NAFLD, they are the least likely to develop progressive NAFLD for currently unknown reasons.[41-49] Nevertheless, long-term studies are needed to better understand the role of ethnicity and other potential genetic factors in the development and progression of NAFLD.

Based on study findings, other areas of future research include the need to model and forecast annual incident cases of NAFLD and NAFLD-associated cirrhosis, HCC, and death in the coming decades if low awareness remains constant or unchanged. There is a need to approximate the number of avoidable cases of NAFLD-associated morbidity and mortality if a large-scale policy-based intervention implemented in the United States increased awareness, identification of undiagnosed cases and facilitated linkage to care. Comparisons between the prevalence of awareness of liver disease among adults with NAFLD in the United States and Europe are warranted, given the divergent AASLD and EASL screening recommendations mentioned earlier.[50,51]

The strengths of this study include a large population-based sample that was representative of the U.S. population, which spanned a large time frame unlike earlier studies.[14-17,31,32] In addition, we also performed several subgroup analyses that provided evidence that strengthened our study conclusions. However, this study has several limitations. Awareness was based on self-report, and self-report data are vulnerable to recall bias. Awareness by age and race/ethnicity for some of the NHANES survey cycles could not be reliably estimated because of a relatively small sample size in a number of stratifications. Although radiologic-based or histologic-based

diagnostic methods for NAFLD are more ideal, US-FLI was used to identify adults with NAFLD because ultrasound data were not available in the 2007-2008 to 2015-2016 NHANES cycles. GGT activity, fasting insulin and fasting glucose, and the components of US-FLI were only measured at a single point in time, which may have led to underestimations or overestimations of NAFLD prevalence. However, to potentially overcome this limitation, we compared NHANES 1984-1988 (adult 20-74 years old), which provided an estimated prevalence of NAFLD as 19.4% (CI 17.7%-21.3%), to the NAFLD prevalence using the US-FLI for the same NHANES data cycle, which provided a similar estimated prevalence of NAFLD of 23.6% (21.7%-25.5%). We also determined the prevalence of NAFLD using the FLI and found similar results as well. It is also important to note that in both the NAFLD and VH cohorts, excluded subjects were more likely to be younger, non-Hispanic Black, and low income, so the prevalence is most likely to be underestimated in these groups.

In conclusion, nearly 96% of adults with NAFLD in the United States were unaware they had liver disease despite NAFLD being the most prevalent chronic liver disease in the United States. Although many more with VH were aware of their liver disease, there remains a significant gap in those with VH and being aware of having this disease. Altogether, these findings suggest that there is an urgent need to take public health action to increase awareness of NAFLD while continuing efforts on increasing awareness of VH and linking these patients to treatment as appropriate. Although treatment options for NAFLD are limited, the significant amount of medication-based treatment research that is ongoing warrants efforts now to increase awareness of NAFLD to avoid finding NAFLD in its advanced disease stages. Therefore, we suggest that awareness efforts for NAFLD are warranted now, and efforts should be directed not only to increase awareness in the general population but also among primary care physicians and within health care systems. Targeted efforts are also needed to bolster awareness among non-Hispanic Blacks and young adults.

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Supporting Information

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