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ORIGINAL ARTICLE

Race/ethnicity-based temporal changes in prevalence of NAFLD-related advanced fibrosis in the United States, 2005–2016

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Abstract

Background and aim Advanced fibrosis associated with nonalcoholic fatty liver disease (NAFLD) has been reported to have a higher risk of hepatic and non-hepatic mortality. We aim to study the recent trends in the prevalence of NAFLD-related advanced fibrosis in a large population sample.

Methods Cross-sectional data from 28,739 participants in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2016 were utilized. NAFLD was defined using the hepatic steatosis index (HSI) and the US fatty liver index (USFLI) in the absence of other causes of chronic liver disease. The presence and absence of advanced fibrosis in NAFLD was determined by the NAFLD fibrosis score, FIB-4 score, and aspartate aminotransferase-to-platelet ratio index.

Results The prevalence of NAFLD-related advanced fibrosis increased from 2.6% [95% confidence interval (CI) 2.1–3.1] in 2005–2008 and 4.4% (95% CI 3.7–5.1) in 2009–2012, to 5.0% (95% CI 4.2–5.9) in 2013–2016 using HSI as the NAFLD prediction model; and from 3.3% (95% CI 2.5–4.5) in 2005–2008 and 6.4% (95% CI 3.7–5.1) in 2009–2012, to 6.8% (95% 5.3–8.7) in 2013–2016 using USFLI ($p < 0.01$). A similar trend was observed in entire NHANES cohort regardless of NAFLD status. While the prevalence of advanced fibrosis increased steadily in non-Hispanic whites through the duration of the study, it leveled off during 2013–2016 in non-Hispanic blacks.

Conclusions Prevalence of advanced fibrosis associated with NAFLD increased steadily from 2005 to 2016. More importantly, race/ethnicity-based temporal differences were noted in the prevalence of NAFLD-related advanced fibrosis during the study.

Keywords Hepatic steatosis · National Health and Nutrition Examination Survey · Nonalcoholic steatohepatitis

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
NFS	NAFLD fibrosis score
APRI	Aspartate aminotransferase-to-platelet ratio index
NHANES	National Health and Nutrition Examination Survey
BMI	Body mass index
HSI	Hepatic steatosis index
USFLI	US fatty liver index
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval

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Introduction

In the past 20 years, the prevalence of obesity in the US has more than doubled [1, 2]. In tandem and mimicking the trends in obesity, nonalcoholic fatty liver disease (NAFLD) is now recognized as the most prevalent chronic liver disease in the US and in many parts of the world [2, 3]. The increasing prevalence of NAFLD, in particular the subset with advanced fibrosis, is concerning because these patients are at a higher risk of mortality from liver-related and non-liver-related complications when compared to the general population [4, 5]. In 2014, the overall burden of liver-related mortality in the US adults was ranked as the 12th leading cause of death, and 4th among adults aged 45–64 years [6].

A recent study based on the US National Center for Health Statistics mortality records showed that age-standardized mortality rates increased for NAFLD with an annual rate of 6.1% from 2007 through 2013 to 11.3% from 2013 through 2016 [7]. It is expected that an increasing proportion of the population will develop advanced liver disease as they age in future. However, estimates of the burden of advanced fibrosis in the general population are limited due to the lack of large population-based data with available liver biopsies. Currently, several noninvasive scoring systems have been employed to diagnose advanced fibrosis in patients with NAFLD. Among these, the NAFLD fibrosis score (NFS), aspartate aminotransferase-to-platelet ratio index (APRI), and FIB-4 score have been validated as scoring systems designed to identify or exclude advanced fibrosis in subjects with an established diagnosis of NAFLD [8, 9]. Therefore, the aim of our study was to investigate the recent trends in NAFLD and NAFLD-related advanced fibrosis using non-invasive panels in a large national database.

Materials and methods

Study design and data sources

This study represents a cross-sectional analysis of the recent six 2-year cycles of the continuous National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2016 (the National Center for Health Statistics, the Center for Disease Control and Prevention). We combined NHANES dataset into three 4-year consecutive survey periods to estimate the trends in the prevalence of NAFLD and advanced fibrosis for yielding more stable estimates. NHANES data employ a stratified, multistage, and clustered probability sampling design to reach a representative sample of the non-institutionalized civilian population in the US.

Of adult (≥ 20 years in age) participants in the NHANES 2005–2016 survey ($n = 34,187$), 96.3% ($n = 32,927$) underwent laboratory examination at a mobile examination center. Of these, we excluded 3164 subjects with significant alcohol consumption (> 21 drinks/week in males and > 14 drinks/week in females), viral hepatitis (positive serum hepatitis B surface antigen and positive serum hepatitis C antibody), and pregnant females. In addition, we also excluded 1024 subjects for whom data on serum aminotransferase, body mass index (BMI), platelet, and albumin were not available. Thus, the final study sample consisted of 28,739 adults with complete data (Fig. 1). The original survey was approved by the Center for Disease Control and Prevention's Institutional Review Board, and all participants reviewed and signed a comprehensive informed consent. This analysis per se was deemed exempt by the Institutional Review Board at our institution, as the dataset used in the analysis was completely de-identified.

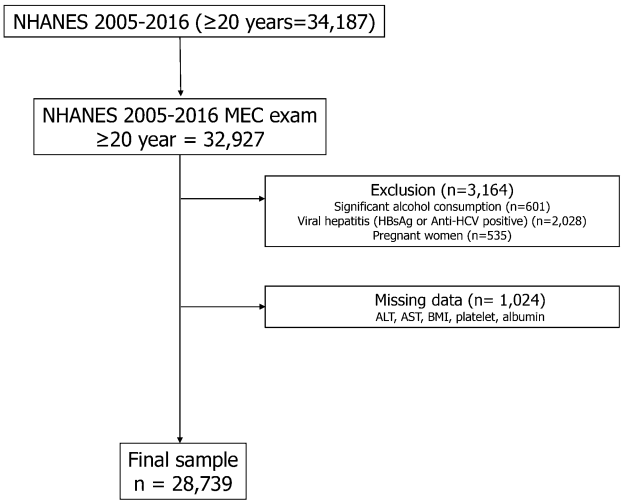

Fig. 1 Flow diagram of the study participants

Clinical and laboratory evaluations

Each subject underwent a detailed interview which covered a wide array of demographic, lifestyle and dietary information as well as an anthropometric assessment and a comprehensive laboratory evaluation. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican-American, other Hispanic), or other. Education was dichotomized to high school graduation versus no high school graduation. Marital status was categorized as being married or cohabitating with a partner versus other. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and/or current use of antihypertensive medication. Diabetes mellitus was diagnosed in subjects with a fasting plasma glucose concentration ≥ 126 mg/dl and/or treatment with a hypoglycemic agent or insulin. Current smokers were defined as those who reported ongoing smoking among subjects who had smoked at least 100 cigarettes in their lifetime. Alcohol consumption was calculated using self-reported data on the amount and frequency of alcohol use, as previously described [10]. There were no changes to the laboratory methods or laboratory site during the study periods.

Definition of NAFLD and advanced fibrosis

NAFLD was defined using the hepatic steatosis index (HSI) and the US fatty liver index (USFLI), both of which have been validated externally and used in epidemiologic studies, only in the absence of other causes of chronic liver disease

[11–14]. The HSI was calculated by using the published formula:

HSI = 8 × [alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio] + BMI (+2, if female; +2, if diabetes).

We utilized the published cut-off of 36 to define presence of NAFLD [11]. As USFLI indices require fasting blood tests, analyses using USFLI included a subgroup of 13,918 subjects who were examined after an overnight fast of a minimum of 8 h. The USFLI was calculated according to the published formula [14]:

$$\text{USFLI} = [e^{-0.8073 \times \text{non-Hispanic black} + 0.3458 \times \text{Mexican-American} + 0.0093 \times \text{age} + 0.6151 \times \log_e(\text{gamma-glutamyltransferase}) + 0.0249 \times \text{waist circumference} + 1.1792 \times \log_e(\text{insulin}) + 0.8242 \times \log_e(\text{glucose}) - 14.7812}]/[1 + e^{-0.8073 \times \text{non-Hispanic black} + 0.3458 \times \text{Mexican-American} + 0.0093 \times \text{age} + 0.6151 \times \log_e(\text{gamma-glutamyltransferase}) + 0.0249 \times \text{waist circumference} + 1.1792 \times \log_e(\text{insulin}) + 0.8242 \times \log_e(\text{glucose}) - 14.7812}] \times 100.$$

The markers used for assessment of advanced fibrosis have been previously described [4]. The NFS was calculated according to the following formula:

NFS = [− 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glycemia or diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet ($\times 10^9$/L) − 0.66 × albumin (g/dL)] [15].

Two cut-off points were selected to categorize subjects with NAFLD into three groups, including those with high probability (NFS > 0.676), intermediate probability (NFS 0.676 to − 1.455) and low probability for advanced fibrosis (NFS < − 1.455) [15]. FIB-4 score was calculated by the following formula:

FIB-4 = [age (years) × AST (U/L)]/[platelet [10^9/L] × (ALT [U/L])$^{1/2}$].

Similar to NFS, subjects with NAFLD were divided into three groups, including those with low (FIB-4 < 1.30), intermediate (FIB-4 1.30–2.67) and high probability for advanced fibrosis (FIB-4 > 2.67) [16]. APRI was also calculated by the published formula:

APRI = [(AST/upper limit of normal)/platelet count (10^9/L)] × 100 [17].

We used the cut-offs for low and high probability of advanced fibrosis as published, namely 0.5 and 1.5, respectively [17]. Advanced fibrosis was defined as having at least one of the high probabilities for advanced fibrosis calculated using these three noninvasive fibrosis markers.

Statistical analysis

Given the complex sample design employed by NHANES, combining overall 6 survey cycles and constructing the appropriate weights were used to reconstitute nationally representative sample for the entire US according to NHANES guideline [18]. Frequencies of categorical variables and the means ± standard errors of the continuous variables were calculated among comparison groups. To test for trends across periods, we regressed periods as an ordinal variable in the outcome of baseline characteristics, NAFLD, and advanced fibrosis among subjects with NAFLD. This test for a linear trend permits complete correction for the probability weights and survey design of the NHANES, which is not available in many other trend tests. All data analyses were implemented using STATA 15.0 (StataCorp, College Station, TX, USA) utilizing Taylor series linearization.

Results

Prevalence of NAFLD defined by hepatic steatosis index and NAFLD-related advanced fibrosis

The estimated prevalence of NAFLD defined by USFLI and HSI was 32.0% (95% CI 30.6–33.4) and 53.6% (95% CI 52.6–54.6), which corresponds to a range of 64 (95% CI 60–69) to 106 (95% CI 101–111) million persons in the US. Among these, the estimated prevalence of advanced fibrosis in subjects with NAFLD was 5.6% (95% CI 4.8–6.6, by USFLI) and 4.0% (95% CI 3.7–4.5, by HSI), which corresponds to a range of 3.6 (95% CI 3.0–4.2) to 4.3 (95% CI 3.8–4.8) million persons in the US.

The overall characteristics and trends in demographic and clinical characteristics of subjects during the study period are summarized in Table 1. The mean age and proportion of gender and race/ethnicity did not change over time. The mean BMI, waist circumference and the prevalence of diabetes increased, whereas the prevalence of hypertension did not change during the study. The proportion of subjects with poverty status and married status did not change over time. Decline in triglycerides and cholesterol levels and increase in high-density lipoprotein-cholesterol levels over the study period were noted. This may be due to increase in use of lipid-lowering medications; 20% in 2003–2004 to 28% in 2011–2012 [19]. Among subjects with NAFLD defined by HSI, the mean BMI and prevalence of diabetes increased, but ALT level decreased during the 2013–2016 period compared to 2005–2008 period.

Table 2 summarizes the prevalence of NAFLD defined by HSI and advanced fibrosis. The weighted prevalence of NAFLD using HSI as the NAFLD prediction model increased from 51.6% (95% CI 50.3–53.2) during 2005–2008, and from 53.1% (95% CI 51.3–54.8) during 2009–2012, to 55.9% (95% CI 53.8–54.6, $p = 0.002$) in 2013–2016. NAFLD subjects with advanced fibrosis increased from 2.6% (95% CI 2.1–3.1) in 2005–2008, and 4.4% (95% CI: 3.7–5.1) in 2009–2012, to 5.0% (95% CI 4.2–5.9) in 2013–2016 ($p < 0.001$). A similar trend was found when a sensitivity analysis was performed to include

Table 1 Baseline characteristics of US population between 2005 and 2016

	Total population	2005–2008	2009–2012	2013–2016	*p* value
N	28,739	8967	9961	9811	
Age (year)	47.5 ± 0.25	47.2 ± 0.43	47.2 ± 0.49	48.0 ± 0.37	0.164
Male sex (%)	48.1 ± 0.27	48.2 ± 0.47	48.0 ± 0.48	48.0 ± 0.44	0.715
Ethnicity (%)					0.339
Non-Hispanic white	68.4 ± 1.43	71.5 ± 2.25	68.3 ± 2.58	65.5 ± 2.57	0.085
Non-Hispanic black	10.5 ± 0.72	10.5 ± 1.28	10.5 ± 1.14	10.6 ± 1.30	0.920
Hispanics	13.9 ± 0.99	12.4 ± 1.23	14.1 ± 1.92	15.2 ± 1.84	0.202
Others	7.18 ± 0.41	5.7 ± 0.61	7.15 ± 0.77	8.60 ± 0.70	0.002
BMI (kg/m^2)	28.8 ± 0.08	28.3 ± 0.14	28.7 ± 0.13	29.3 ± 0.15	< 0.001
Waist circumference (cm)	97.0 ± 0.25	94.2 ± 0.43	96.5 ± 0.53	99.9 ± 0.36	< 0.001
Smoking status (%)					< 0.001
No smoker	56.0 ± 0.58	53.0 ± 1.03	56.8 ± 1.11	57.9 ± 0.91	
Current	19.4 ± 0.45	22.1 ± 0.88	18.5 ± 0.71	17.9 ± 0.72	
Ex-smoker	24.6 ± 0.43	24.9 ± 0.61	24.7 ± 0.89	24.3 ± 0.73	
Diabetes (%)	10.6 ± 0.27	9.8 ± 0.53	10.0 ± 0.40	11.9 ± 0.49	0.005
Hypertension (%)	30.9 ± 0.49	30.4 ± 0.67	30.4 ± 1.07	31.8 ± 0.78	0.181
High education (%)	83.2 ± 0.65	81.4 ± 1.07	82.6 ± 1.03	85.5 ± 1.19	0.013
Married status (%)	64.4 ± 0.63	65.6 ± 1.18	63.4 ± 1.08	64.3 ± 1.00	0.415
Poverty status (%)	13.9 ± 0.53	11.9 ± 0.71	15.3 ± 0.95	14.4 ± 1.04	0.060
Total cholesterol (mg/dL)	195.3 ± 0.42	199.5 ± 0.64	193.8 ± 0.70	192.9 ± 0.83	< 0.001
HDL-cholesterol (mg/dL)	53.3 ± 0.22	52.9 ± 0.30	52.8 ± 0.32	54.1 ± 0.46	0.025
Triglycerides (mg/dL)	131.6 ± 1.51	139.1 ± 2.08	129.7 ± 2.77	121.6 ± 3.07	< 0.001
Among subjects with NAFLD, *N*	15,905	4826	5486	5593	
Age (year)	48.2 ± 0.24	47.8 ± 0.44	48.1 ± 0.42	48.7 ± 0.40	0.106
BMI (kg/m^2)	33.3 ± 0.08	33.0 ± 0.15	33.2 ± 0.13	33.7 ± 0.13	0.002
ALT (IU/L)	29.3 ± 0.20	30.0 ± 0.35	29.0 ± 0.35	28.9 ± 0.33	0.036
AST (IU/L)	25.8 ± 0.14	26.0 ± 0.24	25.8 ± 0.24	25.6 ± 0.25	0.315
Diabetes (%)	16.6 ± 0.4	15.6 ± 0.9	15.8 ± 0.6	18.2 ± 0.7	0.017
Platelet (10^9/L)	254.1 ± 1.0	277.6 ± 1.6	245.9 ± 1.4	242.0 ± 1.5	< 0.001
Albumin (g/dL)	4.23 ± 0.005	4.20 ± 0.01	4.22 ± 0.01	4.27 ± 0.01	< 0.001

Data are presented as mean or percent ± SE

BMI body mass index, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *HDL* high-density lipoprotein, *NAFLD* nonalcoholic fatty liver disease

the entire NHANES cohort regardless of NAFLD status; 2.4% in 2005–2008, and 4.3% in 2009–2012, to 4.8% in 2013–2016 ($p < 0.001$). Additionally, we conducted another sensitivity analysis defining advanced fibrosis as at least two out of three positive tests using noninvasive hepatic fibrosis panels with high probabilities for advanced fibrosis (Supplementary Table 1). As expected, the prevalence of advanced fibrosis by this definition was lower than that by original definition. However, overall results were identical to those obtained using the original definition of advanced fibrosis.

Prevalence of NAFLD and advanced fibrosis according to race/ethnicity

Weighted estimates of NAFLD and advanced fibrosis according to race/ethnicity are tabulated in Table 3 and Supplementary Table 2. As expected, the prevalence of NAFLD was significantly different between Hispanics, non-Hispanic whites and non-Hispanic blacks. Regarding advanced fibrosis, the prevalence was highest in non-Hispanic whites (5.8%), followed by Hispanics (4.9%), and lowest in non-Hispanic blacks (3.1%) in the most recent period (2013–2016). Among non-Hispanic whites with NAFLD, the prevalence of advanced fibrosis rose from 2.8% in 2005–2008 and 4.6% in 2009–2012, to 5.8% in 2013–2016 ($p < 0.001$). A similar trend was found when USFLI score was utilized to determine NAFLD; 3.4% in 2005–2008 and 6.7% in 2009–2012, to 8.4% in 2013–2016. However, prevalence of advanced fibrosis remained relatively stable with a downward trend from 3.5% in 2009–2012 to 3.1% in 2013–2016 for non-Hispanic blacks. When the analyses were repeated using USFLI, results were consistently similar

Table 2 Trends in prevalence of NAFLD defined by hepatic steatosis index and advanced fibrosis by year (2005–2016) in the US

	2005–2008	2009–2012	2013–2016	*p* value
Total population, *N* (*n* = 28,739)	8967	9961	9811	
NAFLD by hepatic steatosis index (%)	51.6 (50.3–53.2)	53.1 (51.3–54.8)	55.9 (53.8–54.6)	0.002
Advanced fibrosis (%)				< 0.001
No	97.6 (97.3–97.9)	95.7 (95.1–96.2)	95.2 (94.5–95.8)	
Yes	2.4 (2.1–2.7)	4.3 (3.8–5.0)	4.8 (4.2–5.5)	
Among subjects with NAFLD, *N* (*n* = 15,905)	4826	5486	5593	
Advanced fibrosis (%)				< 0.001
No	97.5 (97.0–97.9)	95.7 (94.9–96.3)	95.0 (94.1–95.8)	
Yes	2.6 (2.1–3.1)	4.4 (3.7–5.1)	5.0 (4.2–5.9)	

p values represent tests of linear trends of proportion of NAFLD and advanced fibrosis across years

N is shown as actual number. Prevalence is shown as weighted frequency

Data are presented as percent (95% confidence intervals)

NAFLD nonalcoholic fatty liver disease

Table 3 Trends in prevalence of NAFLD defined by hepatic steatosis index and advanced fibrosis by race/ethnicity in the US

	2005–2008	2009–2012	2013–2016	*p* value
Non-Hispanic whites, *N* (*n* = 12,559)	4408	4372	3779	
NAFLD by hepatic steatosis index (%)	50.0 (47.8–52.1)	51.0 (49.0–53.1)	54.1 (51.9–56.2)	0.021
Among subjects with NAFLD, *N* (*n* = 6434)	2153	2242	2039	
Advanced fibrosis (%)				< 0.001
No	97.2 (96.5–97.8)	95.4 (94.4–96.3)	94.2 (92.9–95.2)	
Yes	2.8 (2.2–3.5)	4.6 (3.7–5.6)	5.8 (4.8–7.1)	
Non-Hispanic blacks, *N* (*n* = 5788)	1833	2025	1930	
NAFLD by hepatic steatosis index (%)	58.9 (56.5–61.2)	63.4 (60.4–66.3)	61.2 (58.2–64.0)	0.001
Among subjects with NAFLD, *N* (*n* = 3513)	1075	1253	1185	
Advanced fibrosis (%)				0.066
No	98.9 (98.3–99.2)	96.5 (95.3–97.4)	96.9 (95.8–97.7)	
Yes	1.2 (0.8–1.7)	3.5 (2.6–4.7)	3.1 (2.3–4.2)	
Hispanics, *N* (*n* = 7532)	2368	2508	2656	
NAFLD by hepatic steatosis index (%)	61.0 (58.3–63.6)	62.9 (60.3–65.5)	67.7 (65.1–70.3)	0.004
Among subjects with NAFLD, *N* (*n* = 4895)	1459	1623	1813	
Advanced fibrosis (%)				0.001
No	96.5 (95.7–97.2)	95.3 (94.3–96.2)	96.9 (95.8–97.7)	
Yes	3.5 (2.8–4.3)	4.7 (3.8–5.7)	4.9 (3.7–6.5)	

p values represent tests of linear trends of proportion of NAFLD and advanced fibrosis across years

N is shown as actual number. Prevalence is shown as weighted frequency

Data are presented as percent (95% confidence intervals)

NAFLD nonalcoholic fatty liver disease

with wide confidence intervals as previous results using HSI. The prevalence of advanced fibrosis among Hispanics with NAFLD was 3.5% in 2005–2008 and 4.7% in 2009–2012 to 4.9% in 2013–2016. We then conducted a sensitivity analysis using USFLI. The trend showing an increasing prevalence of advanced fibrosis was weakened and statistically non-significant (Supplementary Table 2). Therefore, increasing trends in advanced fibrosis may largely be attributable to increasing trends in non-Hispanic whites.

Prevalence of NAFLD using US fatty liver index and NAFLD-related advanced fibrosis

Overall, the trend was suggestive of increasing prevalence of advanced fibrosis in subjects with NAFLD, while there was no significant increase in the prevalence of NAFLD during the decade-long study period. Among the subjects who only fasted, prevalence of NAFLD remained relatively stable at 29.4% in 2005–2008 and 34.1% in 2009–2012, to 32.4% in 2013–2016 ($p = 0.088$). Regarding advanced fibrosis, NAFLD subjects with advanced fibrosis increased from 3.3% (95% CI 2.5–4.5) in 2005–2008 and 6.4% (95% CI 5.0–8.2) in 2009–2012 to 6.8% (95% CI 5.3–8.7) in 2013–2016 ($p = 0.001$) (Table 4). We then conducted a sensitivity analysis to include entire NHANES cohort. A similar trend was found; 2.0% in 2005–2008 and 4.3% in 2009–2012, to 4.5% in 2013–2016 ($p < 0.001$).

Discussion

In this population-based study in the US adults, the prevalence of advanced fibrosis among subjects with NAFLD increased markedly from 2005 to 2016. We estimated that the national prevalence of advanced fibrosis in the setting of NAFLD was 4.0–5.6% based on noninvasive markers, which corresponds to approximately four million persons in the US. Interestingly, we noted that race/ethnicity-based trends in the prevalence of NAFLD-related advanced fibrosis were not uniform during the span of the study. The prevalence of NAFLD-related advanced fibrosis continuously increased in non-Hispanic whites during the 12-year period and accounted for the major proportion of rise in overall prevalence of advanced fibrosis. On the contrary, the prevalence of NAFLD-related advanced fibrosis increased until 2009–2012 and then stabilized during 2013–2016 in non-Hispanic blacks.

Subjects with NAFLD-related advanced fibrosis are at a higher risk of developing end-stage liver disease and hepatocellular carcinoma. They are also at higher risk for extrahepatic complications, as advanced fibrosis is associated with systemic inflammation and metabolic dysfunction triggered by insulin resistance [4, 20]. In longitudinal studies, nonalcoholic steatohepatitis alone did not predict the risk of overall mortality in patients with NAFLD, but fibrosis stage predicted both the risk of overall and cause-specific mortality [5, 21]. Several other studies have also evaluated the role of fibrosis severity on long-term outcomes [22, 23]. Recently emerging data have suggested that the severity of fibrosis is a stronger predictor of death compared to presence of

Table 4 Trends in prevalence of NAFLD defined by US fatty liver index and advanced fibrosis by year (2005–2016) in the US

	2005–2008	2009–2012	2013–2016	*p* value
Total population, *N* (*n* = 13,918)	4362	4894	4662	
NAFLD by US fatty liver index (%)	29.4 (27.2–31.8)	34.1 (31.7–36.6)	32.4 (30.0–34.5)	0.088
Advanced fibrosis (%)				< 0.001*
No	98.0 (97.6–98.3)	95.7 (94.9–96.4)	95.5 (94.6–96.2)	
Yes	2.0 (1.7–2.5)	4.3 (3.6–5.1)	4.5 (3.8–5.4)	
Among subjects with NAFLD, *N* (*n* = 4692)	1430	1731	1531	
Advanced fibrosis (%)				0.001*
No	96.7 (95.5–97.5)	93.6 (91.8–95.0)	93.2 (91.3–94.7)	
Yes	3.3 (2.5–4.5)	6.4 (5.0–8.2)	6.8 (5.3–8.7)	

p values represent tests of linear trends of proportion of NAFLD and advanced fibrosis across years

N is shown as actual number. Prevalence is shown as weighted frequency

Data are presented as percent (95% confidence intervals)

NAFLD nonalcoholic fatty liver disease

NASH or steatosis [24]. A population-based study utilizing NHANES III evaluated the association between noninvasive fibrosis markers and mortality; the results demonstrated that subjects with a high probability of NAFLD-related advanced fibrosis had an increased risk of overall mortality compared with subjects with a low probability of advanced fibrosis (hazard ratio 1.69; 95% CI 1.09–2.63) [4].

We found that the prevalence of NAFLD slightly increased using HSI as the NAFLD prediction model ($p < 0.01$) and non-significantly increased using USFLI ($p = 0.09$). Previously, a study based on NHANES 1988–2012 reported that the prevalence of NAFLD defined by USFLI rose from 18.2 to 30.6% [14]. However, the most of this increase occurred in the early decade, from 18.2% in 1988–1991 to 28.6% in 1999–2000. In the second decade from 1999–2000 to 2011–2012, the prevalence of NAFLD increased by 7% without any significance [14]. Future prospective studies are needed to determine accurate trends in histologically and/or radiologically diagnosed NAFLD. Along with the rise in the prevalence of obesity, diabetes, and metabolic syndrome, we expect an increase in the prevalence of NAFLD-associated advanced fibrosis. Prevalence of advanced fibrosis increased rapidly with age. Therefore, based on the demographic trend in the US population of increasing age, we expected further increases in the prevalence of NAFLD-related advanced fibrosis. While the prevalence of advanced fibrosis continuously increased in the US during the 12-year period, the prevalence abruptly increased from 2005–2008 to 2009–2012 and then increased with a slower rate in 2013–2016.

The data presented in this study demonstrate current population-level impact of advanced fibrosis in patients with NAFLD. These national trends in the US are alarming and provide an insight for policy-makers and other stakeholders in steering the future healthcare policies. Our results stress the need for multidisciplinary approach to obesity-related medical complications and proactive practice guidelines for health care providers to focus on primary prevention, prompt diagnosis and institution of approved therapy or enrollment in a clinical trial for patients with NAFLD and advanced fibrosis. Further studies are needed to evaluate cost-effectiveness of screening for NAFLD and/or advanced fibrosis using noninvasive serum panels among high-risk groups with diabetes, metabolic syndrome, obesity, or dyslipidemia.

Our definition of advanced fibrosis may underestimate the true prevalence of advanced liver disease. Based on various published reports, as many as 30.9% of patients with an indeterminate assessment of hepatic fibrosis may have advanced fibrosis [8, 9, 15, 25]. Therefore, we defined NAFLD-related advanced fibrosis as having at least one of the high probabilities for advanced fibrosis calculated by utilizing these three markers. A recent study using two different periods (1999–2002 and 2009–2012) of NHANES data reported an increase in the prevalence of NASH-associated advanced fibrosis consistent with our results [26]. In contrast, our study analyzed trends utilizing the most recent and continuous 12-year NHANES data. In addition, our study was able to decipher race/ethnicity-based differences in temporal trends of NAFLD-related advanced fibrosis.

The strengths of our study include utilization of high-quality data collected by trained personnel with a systematic protocol, the wealth of metabolic variables, consecutive years, long duration and a large number of subjects from a nationally representative NHANES dataset. We used recently updated national data, which enabled us to capture current trends in NAFLD and NAFLD-related advanced fibrosis. Moreover, we believe that the subjects in our study are representatives of the US general population. Therefore, the current findings are generalizable to the US population regardless of race/ethnicity. Although this study was performed utilizing a large sample representative of the US general population, some limitations merit comment. First, we used noninvasive panels (in the absence of any other liver disease) to classify NAFLD, which may underestimate the true prevalence of NAFLD. However, the USFLI and HSI have been reported as a robust noninvasive measure for NAFLD in population-based study, and also as an independent predictor of overall and liver-related mortality [11–14, 27]. Sensitivity analyses demonstrated that our results are consistent and robust. Second, although the application of the NFS, APRI, and FIB-4 scores were validated against liver biopsies in various ethnicities [8, 9, 15], it is possible that the advanced fibrosis related to NAFLD may be underestimated in the general population. Noninvasive fibrosis panels may be more suitable to exclude advanced fibrosis, rather than diagnose patients with more advanced fibrosis. More accurate diagnostic modalities such as transient or magnetic resonance elastography for diagnosing advanced fibrosis were not available in NHANES dataset. Third, NAFLD was defined by utilizing HSI and USFLI after exclusion of significant alcohol consumption and viral hepatitis by serologies. We were unable to exclude drug-related steatosis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, and other less common metabolic and/or genetic liver diseases due to limitations of NHANES database. Additionally, self-reported alcohol consumption may likely be under-reported and may introduce bias in results. Because we are unable to obtain nutritional data and physical activity data in all subjects in NHANES, we are unable to evaluate the impact of nutrition and physical activity on trends in NAFLD-related advanced fibrosis. Finally, differential sampling error may affect comparisons over time because each period represents data from a different cross-sectional sample, while the NHANES has examined a nationally representative sample of about 5000 persons each year. Therefore, despite consistency with no

changes in the laboratory methods or laboratory site during the study periods, the cross-sectional design of the study is a limitation.

In summary, NAFLD-related advanced fibrosis is on the rise at an accelerated pace in the US adults. Our study showed that the prevalence of advanced fibrosis in NAFLD increased steadily over the span of 12-year study; now estimated to be four million US adults. We recommend that a focused approach with a high level of clinical suspicion is needed to promptly diagnose patients with NAFLD and high probability of advanced fibrosis.

Authors' contributions DK was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. WK, ACA, GC, SPT, RJW, SAG, SAH and ZMY were involved in interpretation of data and critical revision of the manuscript for important intellectual content. AA was involved in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

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Compliance with ethical standards

Conflict of interest Donghee Kim, Won Kim, Adeyinka C. Adejumo, George Cholankeril, Sean P. Tighe, Robert J. Wong, Stevan A. Gonzalez, Stephen A. Harrison, Zobair M. Younossi and Aijaz Ahmed declare that they have no conflict of interest.

References

1. Klein S. The national obesity crisis: a call for action. Gastroenterology 2004;126:6
2. Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. Clin Liver Dis 2008;12:733–746
3. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis 2007;11:1–16
4. Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 2013;57:1357–1365
5. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65:1557–1565
6. Heron M. Deaths: leading causes for 2014. Natl Vital Stat Rep 2016;65:1–96
7. Kim D, Li AA, Gadiparthi C, Khan MA, Cholankeril G, Glenn JS, et al. Changing trends in etiology-based annual mortality from chronic liver disease, from 2007 through 2016. Gastroenterology 2018;155:1154–1163
8. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59:1265–1269
9. Wong VW, Wong GL, Chim AM, Tse AM, Tsang SW, Hui AY, et al. Validation of the NAFLD fibrosis score in a Chinese population with low prevalence of advanced fibrosis. Am J Gastroenterol 2008;103:1682–1688
10. Ruhl CE, Everhart JE. Joint effects of body weight and alcohol on elevated serum alanine aminotransferase in the United States population. Clin Gastroenterol Hepatol 2005;3:1260–1268
11. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503–508
12. Meffert PJ, Baumeister SE, Lerch MM, Mayerle J, Kratzer W, Volzke H. Development, external validation, and comparative assessment of a new diagnostic score for hepatic steatosis. Am J Gastroenterol 2014;109:1404–1414
13. Hajifathalian K, Torabi Sagvand B, McCullough AJ. Effect of alcohol consumption on survival in non-alcoholic fatty liver disease: a national prospective cohort study. Hepatology. 2018. https://doi.org/10.1002/hep.30226
14. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther 2015;41:65–76
15. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–854
16. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104–1112
17. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–526
18. National Health and Nutrition Examination Survey: analytic guidelines, 1999–2010, Vital and health statistics. Series 10, Data from the National Health Survey; no. 161, DHHS publication, no. 2013-1361. https://stacks.cdc.gov/view/cdc/21305
19. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003–2012. NCHS Data Brief 2014;177:1–8
20. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138–1153
21. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547–1554
22. Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013;145:782–789
23. Hagstrom H, Nasr P, Ekstedt M, Hammar U, Stal P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265–1273
24. Vilar-Gomez E, Calzadilla-Bertot L, Wong VWS, Castellanos M, Aller-de-la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology 2018;155:443–457
25. Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff S, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol 2012;56:234–240
26. Kabbany MN, Conjeevaram Selvakumar PK, Watt K, Lopez R, Akras Z, Zein N, et al. Prevalence of nonalcoholic steatohepatitis-associated cirrhosis in the United States: an analysis of national

health and nutrition examination survey data. Am J Gastroenterol 2017;112:581–587
27. Unalp-Arida A, Ruhl CE. Liver fat scores predict liver disease mortality in the United States population. Aliment Pharmacol Therap 2018;48:1003–1016

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