Environmental exposures are important risk factors for advanced liver fibrosis in African American adults

Authors

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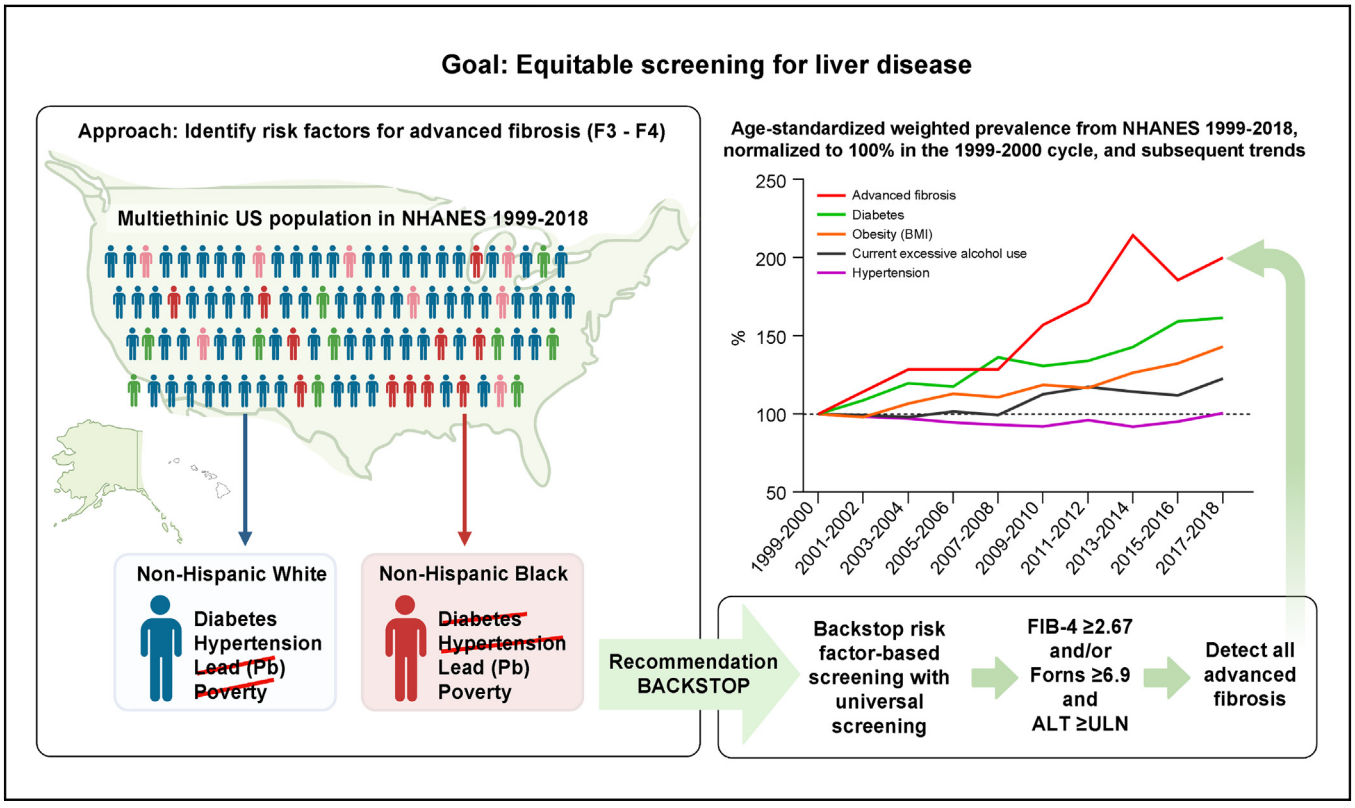
Graphical abstract



Highlights

- The prevalence of advanced liver fibrosis doubled in the past 20 years in the United States.
- Prevalence was higher in non-Hispanic Black persons than in non-Hispanic White persons.
- Risk factors in non-Hispanic Black persons included lead exposure, but not diabetes.
- Cadmium was a risk factor in all racial/ethnic groups examined.

Impact and Implications

Because liver disease often produces few warning signs, simple and inexpensive screening tests that can be performed by non-specialists are needed to allow timely diagnosis and linkage to care. This study shows that non-Hispanic Black persons have a distinctive set of risk factors that need to be taken into account when designing liver disease screening programs. Exposure to exogenous toxins may be especially important risk factors for advanced liver fibrosis in non-Hispanic Black persons.

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Research article

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Environmental exposures are important risk factors for advanced liver fibrosis in African American adults

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Background & Aims: The prevalence and aetiology of liver fibrosis vary over time and impact racial/ethnic groups unevenly. This study measured time trends and identified factors associated with advanced liver fibrosis in the United States.
Methods: Standardised methods were used to analyse data on 47,422 participants (≥20 years old) in the National Health and Nutrition Examination Survey (1999–2018). Advanced liver fibrosis was defined as Fibrosis-4 ≥2.67 and/or Forns index ≥6.9 and elevated alanine aminotransferase.
Results: The estimated number of people with advanced liver fibrosis increased from 1.3 million (95% CI 0.8–1.9) to 3.5 million (95% CI 2.8–4.2), a nearly threefold increase. Prevalence was higher in non-Hispanic Black and Mexican American persons than in non-Hispanic White persons. In multivariable logistic regression analysis, cadmium was an independent risk factor in all racial/ethnic groups. Smoking and current excessive alcohol use were risk factors in most. Importantly, compared with non-Hispanic White persons, non-Hispanic Black persons had a distinctive set of risk factors that included poverty (odds ratio [OR] 2.09; 95% CI 1.44–3.03) and susceptibility to lead exposure (OR 3.25; 95% CI 1.95–5.43) but did not include diabetes (OR 0.88; 95% CI 0.61–1.27; p =0.52). Non-Hispanic Black persons were more likely to have high exposure to lead, cadmium, polychlorinated biphenyls, and poverty than non-Hispanic White persons.
Conclusions: The number of people with advanced liver fibrosis has increased, creating a need to expand the liver care workforce. The risk factors for advanced fibrosis vary by race/ethnicity. These differences provide useful information for designing screening programmes. Poverty and toxic exposures were associated with the high prevalence of advanced liver fibrosis in non-Hispanic Black persons and need to be addressed.
Impact and Implications: Because liver disease often produces few warning signs, simple and inexpensive screening tests that can be performed by non-specialists are needed to allow timely diagnosis and linkage to care. This study shows that non-Hispanic Black persons have a distinctive set of risk factors that need to be taken into account when designing liver disease screening programs. Exposure to exogenous toxins may be especially important risk factors for advanced liver fibrosis in non-Hispanic Black persons.

Introduction

Liver disease causes an estimated 2 million deaths globally each year[1] but is under-diagnosed. In a recent US study, nearly 50% of primary care patients who experienced a serious liver-related event did not have a prior diagnosis of liver disease.[2] Similarly, in the United Kingdom, 'around three-quarters of patients who will die from cirrhosis are currently unaware that they have liver disease'.[3] Increased diagnosis will require screening for liver fibrosis (LF) in primary care settings.

The Fibrosis-4 (FIB-4) index provides a validated estimate of LF risk.[4,5] An American Gastroenterology Association task force reported that 'it provides a useful, inexpensive, first-line assessment of liver fibrosis for use in primary care'.[5] The Forns index is a second well-validated non-invasive fibrosis test.[6] In the National Health and Nutrition Examination Survey (NHANES) population, FIB-4 ≥2.67 and Forns ≥6.9 have hazard ratios (HRs) for liver-related death of 42 and 117, respectively.[4] When combined with alanine aminotransferase (ALT) elevation, both FIB-4 and Forns indices had areas under the receiver operating curve of 0.83 for predicting serious liver-related events over 10 years in the community setting.[6] Several

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additional screening tests have been proposed, and it is likely that one or more will be broadly implemented soon.[6–8]

The American Association for the Study of Liver Diseases is currently developing guidelines for non-invasive LF screening.[9] According to EASL guidelines,[10] screening should be limited to individuals with known risk factors, such as type 2 diabetes. This restriction raises questions about which risk factors can be relied on to yield equitable and inclusive screening protocols.

Comprehensive information about risk factors in the multiethnic population of the United States is lacking, but essential, particularly if screening is going to be limited to patients with specific risk factors. Given the high accuracy of FIB-4 and Forns indices when combined with elevated ALT to identify individuals at high risk for liver-related events,[6] the objectives of this study are to use the nationally representative NHANES data (1) to determine time trends, (2) to compare risk factors among racial/ethnic groups, and (3) to determine the percentage of people with advanced LF who might be missed by aetiology-based screening. The results show that the prevalence of advanced fibrosis nearly doubled over the past 20 years and was higher in non-Hispanic Black (NHB) persons than in non-Hispanic White (NHW) persons. NHB persons had a distinctive set of risk factors that included lead and poverty but did not include diabetes or hypertension, which were risk factors in NHW persons. These differences need to be considered in risk factor-based screening guidelines. High cadmium exposure was a risk factor in all racial/ethnic groups, highlighting the potential role of environmental toxins in LF.

Materials and methods

Study population and data sources

NHANES uses standardised procedures to collect data under a protocol approved by the National Center for Health Statistics Research Ethnic Review Board. Analysis of de-identified NHANES data is exempt from institutional review board review.[11] Ten cycles of NHANES (1999–2018) were used in the main analyses (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). Sub-studies used liver ultrasound data from NHANES III (1988–1994) and measurements of organic chemicals (polychlorinated biphenyls [PCBs]) from NHANES 2003–2004. The public-use linked mortality file was obtained through 2019.[12]

Indicators of fibrosis

FIB-4 and Forns indices were calculated as before.[4] Advanced LF was indicated by FIB-4 ≥2.67 and/or Forns ≥6.9 and ALT above the upper limit of normal (ULN) (≥40 IU/L for men and ≥31 IU/L for women).

Demographic variables

Analysis used self-reported sex (male/female) and race/ethnicity (NHW, NHB, Mexican American [MA], and other race [O; non-MA Hispanic and others]). The main analysis was performed on people aged 20–85 years. Sensitivity analyses were conducted on people aged 35–64 years because FIB-4 may underestimate fibrosis in individuals younger than 35 years[13] and because changes in health insurance may alter association with poverty after age 64 years.

Definition of risk factors

Kidney insufficiency (KI) was a urinary albumin-to-creatinine ratio ≥30 mg/g and/or an estimated glomerular filtration rate <60 ml/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine-based formula (race agnostic).[14] Diabetes was self-reported, and/or haemoglobin A_{1c} ≥6.5%, and/or fasting plasma glucose ≥126 mg/dl.[15] Hypertension was systolic blood pressure ≥130 mmHg, and/or diastolic blood pressure ≥ 80 mmHg, and/or use of antihypertensive medication.[16] BMI was categorised as normal weight (<25 kg/m^2), overweight (25 ≤BMI <30 kg/m^2), and obese (≥30 kg/m^2). Waist circumference (WC) was categorised as normal (<94 cm for men and <80 cm for women), moderate (94 ≤WC <102 cm for men and 80 ≤WC <88 cm for women), and high (≥102 cm for men and ≥88 cm for women).[17] Metabolic syndrome was defined as ≥3 of the following: WC ≥102 cm for men and ≥88 cm for women; triglyceride ≥150 mg/dl; HDL cholesterol <40 mg/dl for men and <50 mg/dl for women; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking hypertension medications; and fasting plasma glucose ≥100 mg/dl.[18] Past/current smokers answered 'Yes' to the question 'Have you smoked at least 100 cigarettes in your lifetime?' Never smokers answered 'No'.[19] The responses to questions about alcohol consumption were used to create four mutually exclusive groups, lifetime abstainers (<12 drinks in lifetime), former drinkers (≥12 drinks in their lifetime but none in the past year), non-excessive current drinkers (on average, ≤14 drinks/week for men and ≤7 drinks/week for women, and never ≥5 in a single day during the past year for either), and excessive current drinkers (on average, >14 drinks/week for men and >7 drinks/week for women, or >5 drinks in a single day at least once during the past year for either).[20] Blood levels of lead and cadmium were analysed as continuous and binary variables (quartile 1 [Q1]–Q3 *vs.* Q4). Lipid-adjusted plasma levels of PCBs were classified by quartiles (Q1–Q3 *vs.* Q4) (see Fig. S6 for details).[21] Poverty was defined as a family poverty–income ratio below 1.0.[22]

Definitions of disease aetiologies

Disease aetiology was examined in participants who had data for calculating the US Fatty Liver Index (USFLI), which was previously validated for the US population.[23] Viral hepatitis (VH) was past/current infection with HBV, positive HBV core antibody, or HBsAg; or HCV, RNA, or antibody. Alcohol-associated liver disease (ALD) was meeting previous criteria: consuming on average >14 drinks/week (women) or 21 drinks/week (men) in the past 12 months, and having elevated liver enzymes, AST, or ALT (>25 U/L in women and 35 U/L in men)[24] and/or categorised as current excessive drinker[20] in this study. Non-alcoholic fatty liver disease (NAFLD) was USFLI ≥30.[23] No exposure identified (NEI) was not meeting criteria for VH, ALD, or NAFLD. In sensitivity analyses, NAFLD was defined by abdominal ultrasound (mild/moderate/severe fatty liver) from NHANES III.

Statistical analysis

All analyses were conducted according to NHANES guidelines,[11] using established methods to combine cycles. Data were adjusted for the complex NHANES design with strata, primary sampling units, and probability weights incorporated into statistical models using the survey estimation commands in SAS OnDemand for Academics (SAS Institute Inc., Cary, NC, USA). These procedures generate estimates for the housed, civilian, noninstitutionalised population in the United States. Age standardisation estimates were calculated using the direct method, standardised to the 2000 US census population with four age categories for the 20- to 85-year age group and three age

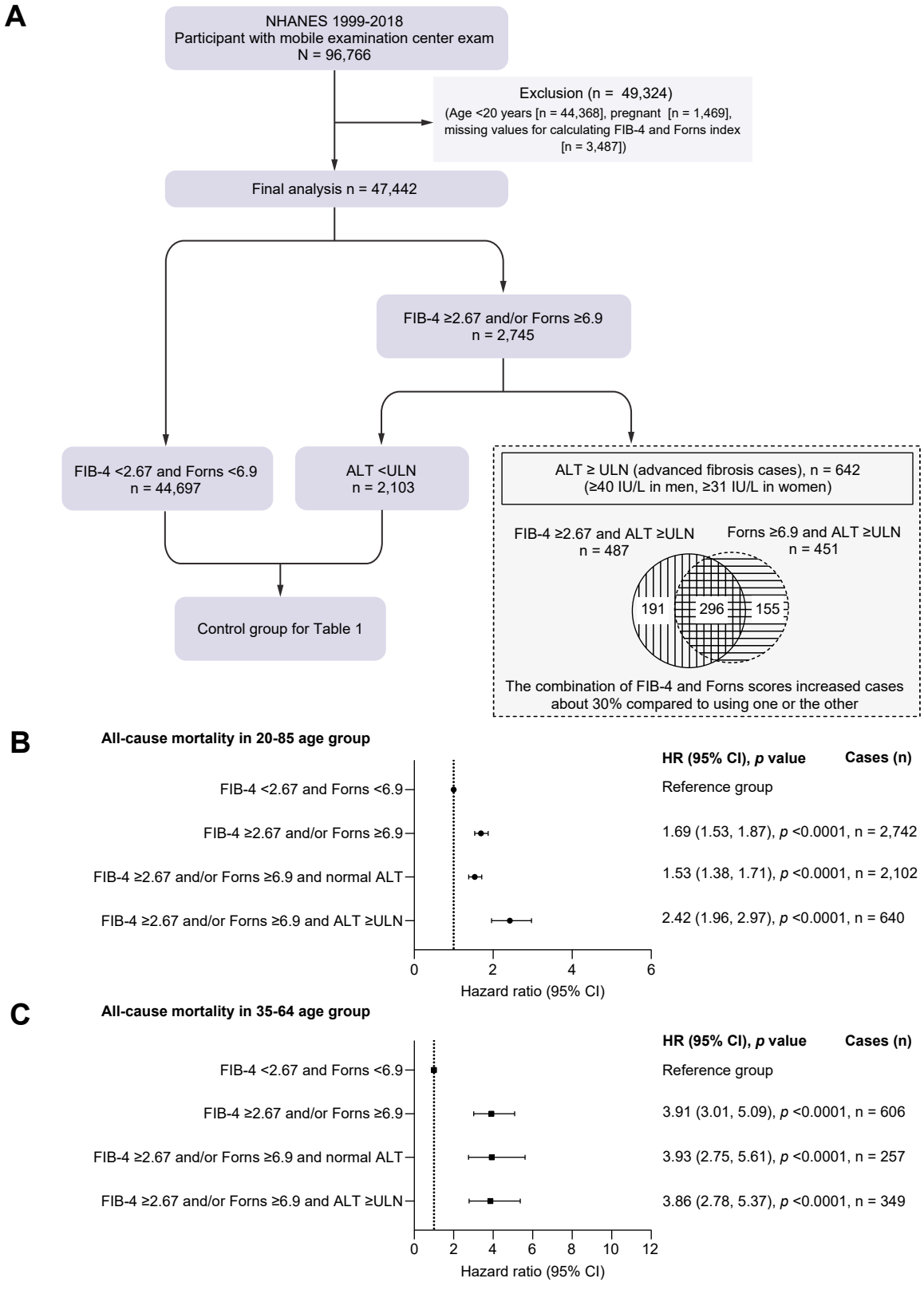

Fig. 1. Flowchart of participant selection and association between advanced fibrosis and all-cause mortality. (A) Flowchart of participant selection (47,442 adults were included in the analysis); all-cause mortality in (B) the 20- to 85-year age group and (C) the 35- to 64-year age group. Association between advanced fibrosis and all-cause mortality was analysed using survey-weighted multivariable Cox proportional models (adjusted for age, sex, race/ethnicity, BMI, alcohol and smoking status, and poverty). ALT, alanine aminotransferase; FIB-4, Fibrosis-4; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; ULN, upper limit of normal.

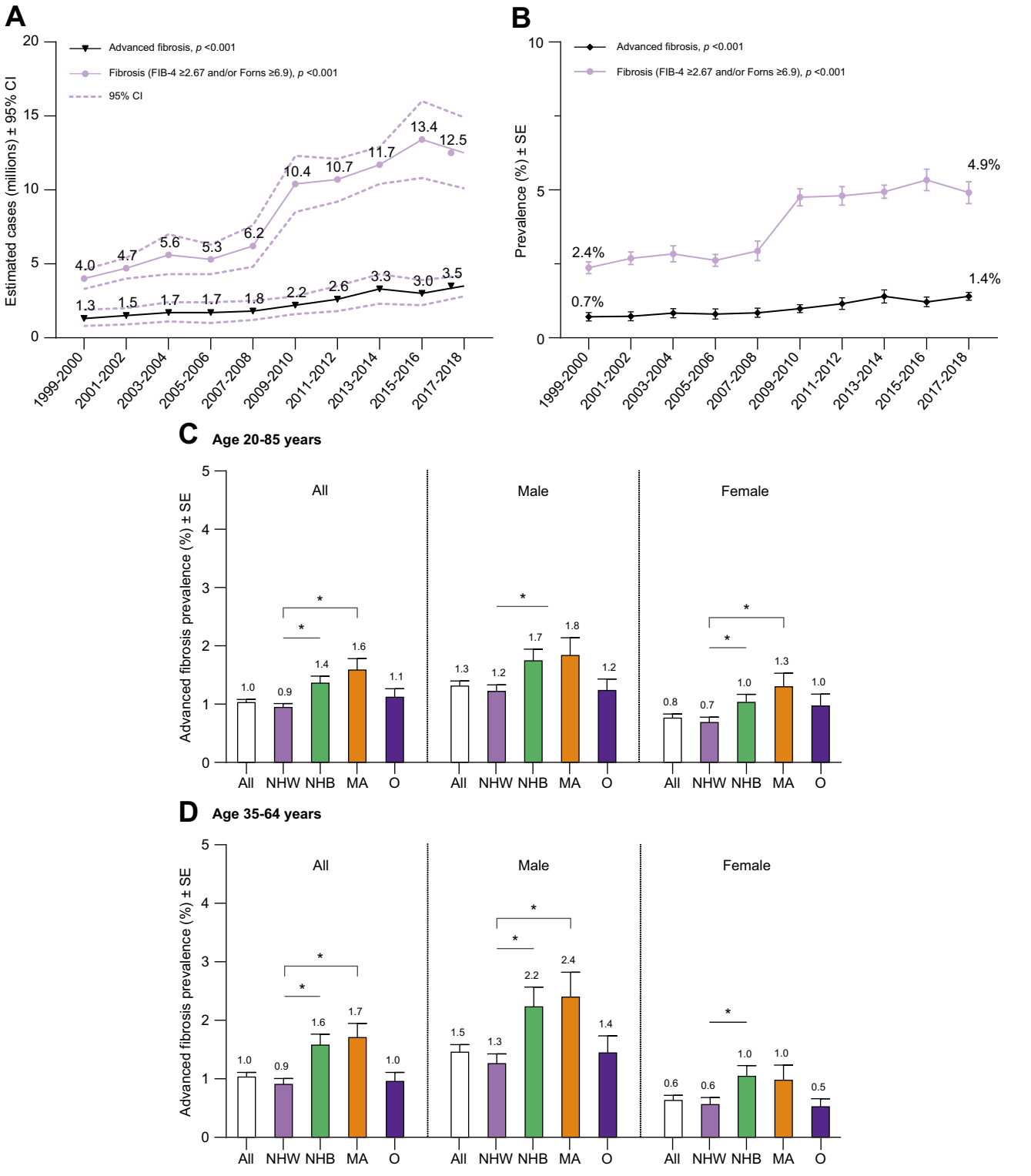

Fig. 2. Time trends and prevalence of advanced liver fibrosis. (A) The change in the number (millions) of US adults with advanced liver fibrosis (black) and fibrosis defined by FIB-4 ≥2.67 and/or Forns ≥6.9 (purple) overtime with 95% CIs (dashed). (B) Age-standardised weighted prevalence of advanced fibrosis (black) and fibrosis (purple) over time. Age-standardised weighted prevalence of advanced fibrosis in (C) people 20–85 years old and (D) people 35–64 years old (total, males, and females), stratified by race/ethnicity. Differences between groups were tested by univariate *t* statistics, **p* <0.05. FIB-4, Fibrosis-4; MA, Mexican American; NHB, non-Hispanic Black; NHW, non-Hispanic White; O, other race.

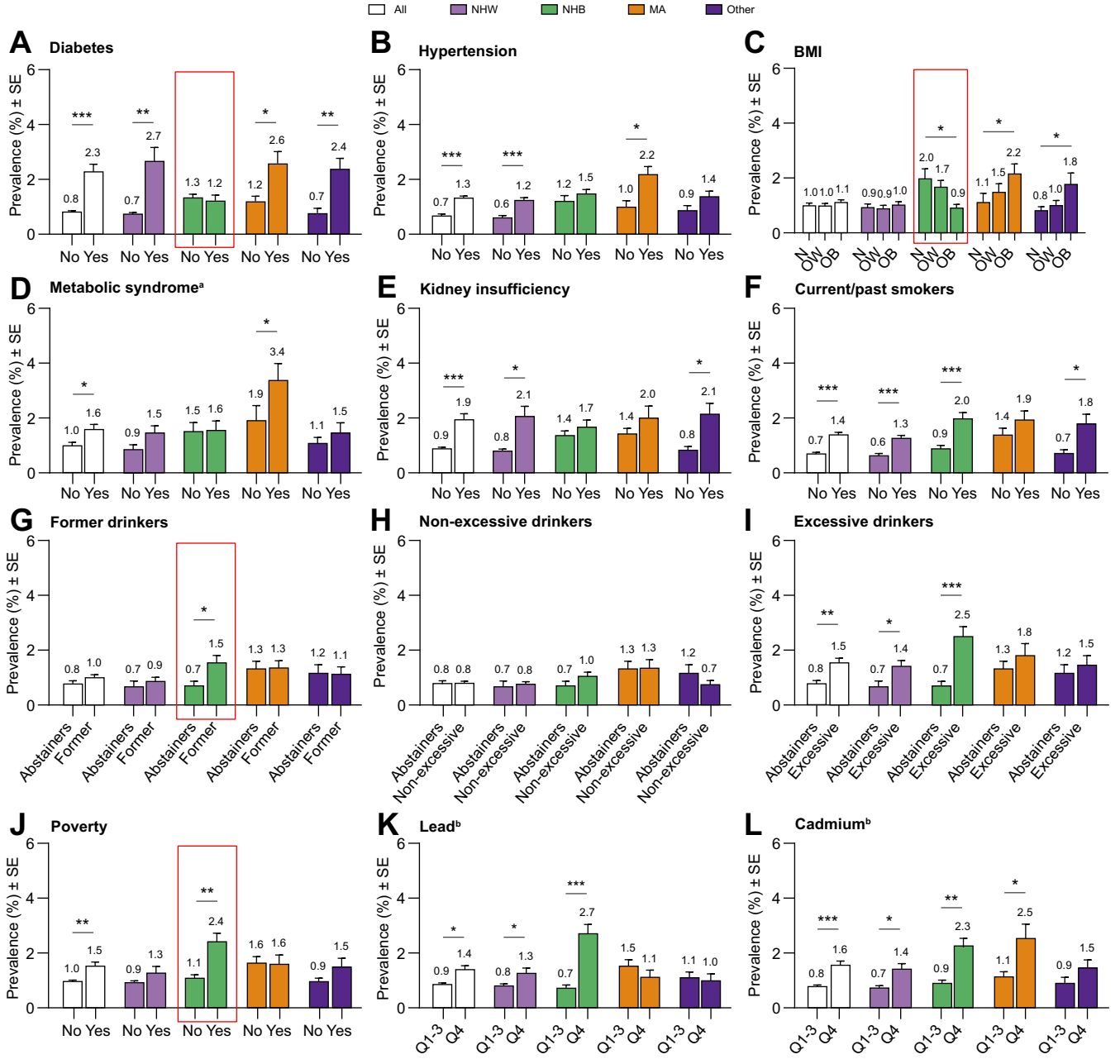

Fig. 3. Advanced fibrosis in participants aged 20–85 years, stratified by health conditions and race/ethnicity. The age-standardised weighted prevalence of advanced fibrosis among participants with and those without various health conditions were determined for the total cohort, NHW, NHB, MA, and other racial/ethnic groups. (A) Diabetes, (B) hypertension, (C) BMI categories (N, OW, and OB), (D) metabolic syndrome, (E) kidney insufficiency, (F) current/past smokers, (G) former drinkers *vs.* lifetime abstainers, (H) current non-excessive drinkers *vs.* lifetime abstainers, (I) current excessive drinkers *vs.* lifetime abstainers, (J) poverty, and blood levels of (K) lead and (L) cadmium (Q1–Q3 *vs.* Q4). Differences between groups were tested by univariate *t* statistics, **p* <0.05, ***p* <0.001, ****p* <0.0001. [a]Components of metabolic syndrome were only available for participants with fasting blood tests in NHANES 2007–2018 (n = 13,886). [b]Cadmium and lead analyses were based on participants with cadmium and lead measurements (N = 42,255). Red boxes marked variables whose association with advanced fibrosis differs qualitatively between NHW persons and members of all other race/ethnic groups. MA, Mexican American; N, normal; NHANES, National Health and Nutrition Examination Survey; NHB, non-Hispanic Black; NHW, non-Hispanic White; OB, obese; OW, overweight; Q1–Q4, quartiles 1–4.

categories for the 35- to 64-year age group. Differences between groups were tested by univariate *t* statistics.[25] To estimate the number of adults with advanced LF, prevalence was calculated and then multiplied by the estimated adult US population obtained from the Current Population Surveys or American Community Survey of each survey cycle.[26] Annual percent changes (APCs) were calculated using the Joinpoint Regression Program (Version 4.9.0.0, National Cancer Institute).[27] Univariable and multivariable survey logistic regression with appropriate sample weights were used to examine the

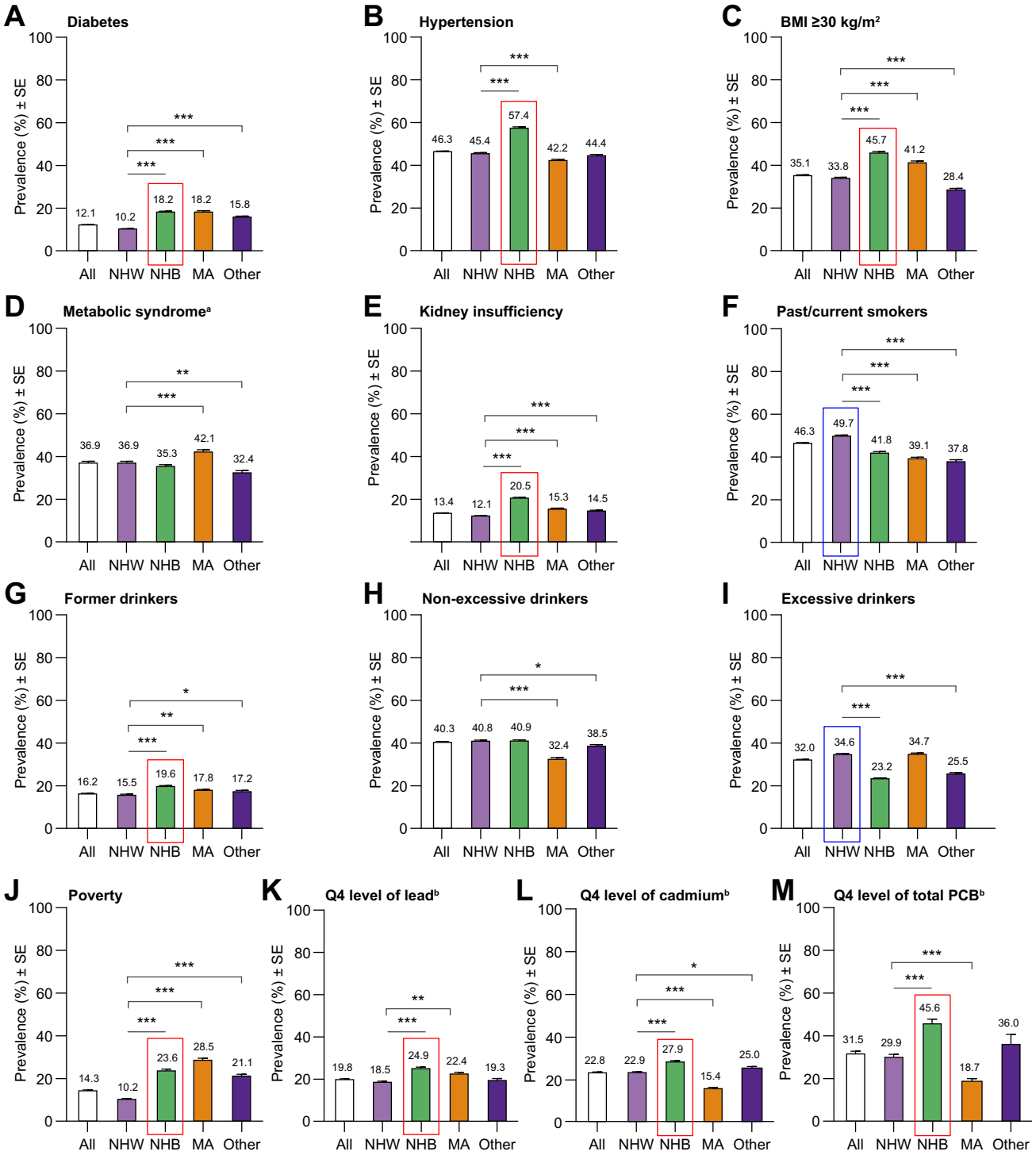

Fig. 4. Prevalence of heath conditions in participants aged 20–85 years, stratified by race/ethnicity. Age-standardised weighted prevalence of (A) diabetes, (B) hypertension, (C) obesity (BMI ≥30 kg/m^2), (D) metabolic syndrome, (E) kidney insufficiency, (F) past/current smokers, (G) former drinker, (H) current non-excessive drinker, (I) current excessive drinker, (J) poverty, and Q4 blood level of (K) lead, (L) cadmium, and (M) total PCBs among NHW (blue), NHB (red), MA, and other race groups. [a]Components of metabolic syndrome were only available for participants with fasting blood test in NHANES 2007–2018 (N = 13,886). [b]Cadmium and lead analyses were based on participants with cadmium and lead measurements (N = 42,255). [c]PCB data from NHANES 2003–2004 survey cycles included 1,242 participants. Differences between groups were tested by univariate *t* statistics, **p* <0.05, ***p* <0.001, ****p* <0.0001. Red boxes identified conditions more prevalent in NHB persons than in NHW persons; blue boxes identified the opposite. MA, Mexican American; NHANES, National Health and Nutrition Examination Survey; NHB, non-Hispanic Black; NHW, non-Hispanic White; PCB, polychlorinated biphenyl; Q4, quartile 4.

Table 1. ORs from multivariable logistic regression models with the outcome of advanced liver fibrosis.

Cohorts	Cohort aged 20–85 years, OR (95% CI)				
Sample size (n)	**Total (47,442)**	**NHW (21,167)**	**NHB (9,634)**	**MA (8,334)**	**O (8,307)**
Advanced fibrosis cases (n)	**642**	**259**	**149**	**127**	**107**
Age (unit 10 years)	**1.58 (1.47, 1.67)‡**	**1.54 (1.40, 1.69)‡**	**1.55 (1.36, 1.75)‡**	**1.78 (1.49, 2.13)‡**	**1.98 (1.70, 2.31)‡**
Sex					
Female					Reference
Male	**1.44 (1.15, 1.87)‡**	**1.47 (1.01, 2.13)***	1.43 (0.99, 2.06)	1.19 (0.69, 2.05)	1.34 (0.81, 2.22)
Kidney insufficiency					
No					Reference
Yes	1.30 (0.99, 1.71)	1.39 (0.94, 2.06)	1.00 (0.65, 1.54)	1.04 (0.57, 1.89)	1.47 (0.86, 2.54)
Diabetes					
No					Reference
Yes	**2.23 (1.75, 2.84)‡**	**2.58 (1.89, 3.52)‡**	0.88 (0.61, 1.27)	1.65 (0.93, 2.91)	**2.43 (1.33, 4.44)***
Hypertension					
No					Reference
Yes	**1.63 (1.21, 2.19)***	**1.70 (1.11, 2.59)***	1.25 (0.80, 1.94)	**2.03 (1.14, 3.61)***	1.21 (0.65, 2.23)
BMI					
Normal					Reference
Overweight	0.88 (0.63, 1.23)	0.81 (0.50, 1.32)	1.01 (0.61, 1.67)	1.33 (0.67, 2.68)	0.98 (0.57, 1.68)
Obese	0.93 (0.69, 1.27)	0.86 (0.56, 1.30)	0.68 (0.40, 1.14)	1.39 (0.67, 2.89)	1.74 (0.91, 3.32)
Alcohol use					
Lifetime abstainers					Reference
Former drinkers	0.86 (0.60, 1.24)	0.84 (0.48, 1.46)	1.60 (0.87, 2.93)	0.96 (0.57, 1.63)	0.67 (0.31, 1.45)
Non-excessive current drinkers	0.93 (0.65, 1.33)	1.02 (0.59, 1.74)	1.38 (0.74, 2.58)	0.89 (0.58, 1.36)	0.57 (0.28, 1.16)
Excessive current drinkers	**2.04 (1.38, 3.02)†**	**2.17 (1.19, 3.95)***	**2.65 (1.48, 4.73)†**	**2.36 (1.24, 4.49)***	1.47 (0.70, 3.09)
Smoking status					
Never					Reference
Past/current	**1.68 (1.30, 2.16)†**	**1.67 (1.17, 2.36)***	**1.79 (1.21, 2.64)***	1.41 (0.80, 2.47)	**2.03 (1.09, 3.80)***
Poverty					
No					Reference
Yes	**1.49 (1.19, 1.87)†**	1.25 (0.84, 1.87)	**2.09 (1.44, 3.03)†**	1.16 (0.69, 1.96)	1.13 (0.75, 1.71)

Multiple imputation was performed in univariate and multivariate logistic regression models. Variables with a p value of <0.1 in the univariate analysis in the total cohort were included into the multivariate analysis. *p <0.05, †p <0.001, ‡p <0.0001. The significant variables were labeled as bold front. MA, Mexican American; NHB, non-Hispanic Black; NHW, non-Hispanic White; O, other race; OR, odds ratio.

association between advanced LF and the independent variables. Survey-weighted adjusted multivariable Cox proportional models were used to investigate the association between advanced-LF and all-cause mortality. The minimal 10 events per variable rule was used to determine the minimal sample size required in models.[28] Missing values that ranged from 0.1% to 9.0% were addressed using multivariable imputation by chained equations.[29] Combined estimates using 10 imputed datasets were calculated. Statistical significance was a two-sided p value <0.05.

Results

Threefold increase in cases of advanced LF over 20 years

The selection of the study group is presented in Fig. 1, and the dynamic time trends of advanced LF are presented in Fig. 2. The estimated number of people with advanced LF increased from 1.3 million (95% CI 0.8–1.9) to 3.5 million (95% CI 2.8–4.2), a nearly threefold increase over 20 years (Fig. 2A). The age-standardised weighted prevalence approximately doubled (Fig. 2B). The APC was 8.7% (95% CI 6.7–10.9) (Table S1). The prevalence of advanced LF was about 1.6-fold higher in NHB persons than in NHW persons in the total group and in men and women when analysed separately (Fig. 2C and D). The HR for all-cause mortality among people with advanced LF was 2.42 (95% CI 1.96–2.97) in the 20- to 85-year age group and 3.86 (95% CI 2.78–5.37) in the 35- to 64-year age group (Fig. 1B and C).

Associated conditions

The age-standardised weighted prevalence of advanced LF was compared between people with and those without health conditions that might be considered as eligibility criteria in risk factor-based screening. Several conditions differed by race/ethnicity. The prevalence of advanced LF was about twofold higher in those with diabetes in the total population and in the NHW, MA, and O groups, but not in the NHB group (total, males, and females) (Fig. 3A and Figs. S1 and S2); similar results were obtained when alternative definitions of diabetes were used, underscoring the robustness of the finding (Fig. S3). Only 35% (95% CI 29.9–40.1) of participants with advanced LF had diabetes, and thus, 65% of cases would be missed if screening were limited to people with diabetes. Associations between obesity and advanced LF also differed by race/ethnicity. The prevalence of fibrosis was significantly higher in the MA and O groups with obesity than in those with normal BMI (Fig. 3C). Strikingly, however, among NHB persons, the prevalence was about twofold higher in those with *normal* BMI than in those with obesity, with similar results obtained for WC (Fig. S4). Poverty was associated with advanced LF in NHB persons, but not in any other racial/ethnic group. Of the six conditions that reflect exposure to exogenous toxins, four (smoking, current excessive drinking, cadmium exposure, and lead exposure) were associated with advanced LF in the total population, in NHW persons, and in NHB persons (Fig. 3F, I, K, and L). Former drinkers had a higher prevalence of advanced LF in NHB persons (Fig. 3G). In sensitivity analyses, similar results were obtained when a less restrictive

Table 2. ORs from multivariable logistic regression models with the outcome of advanced liver fibrosis with blood cadmium levels included in the models.

Cohorts	In participants aged 20–85 years with cadmium into models, OR (95% CI)				
Sample size (n)	**Total (42,255)**	**NHW (19,176)**	**NHB (8,585)**	**MA (7,508)**	**O (6,986)**
Advanced fibrosis cases (n)	**542**	**226**	**128**	**102**	**86**
Survey year	**1.07 (1.03, 1.11)‡**	**1.08 (1.03, 1.13)†**	1.01 (0.95, 1.08)	1.10 (0.99, 1.20)	1.03 (0.94, 1.13)
Age (unit 10 years)	**1.56 (1.44, 1.68)‡**	**1.51 (1.36, 1.69)‡**	**1.52 (1.31, 1.76)‡**	**1.79 (1.46, 2.21)‡**	**2.09 (1.75, 2.50)‡**
Sex					
Female					Reference
Male	**1.61 (1.24, 2.08)†**	**1.67 (1.16, 2.41)***	**1.61 (1.08, 2.40)***	1.30 (0.71, 2.36)	1.25 (0.65, 2.40)
Kidney insufficiency					
No					Reference
Yes	1.15 (0.85, 1.55)	1.16 (0.75, 1.79)	1.17 (0.74, 1.84)	**0.58 (0.36, 0.94)***	1.54 (0.83, 2.87)
Diabetes					
No					Reference
Yes	**2.38 (1.83, 3.11)‡**	**2.85 (2.05, 3.96)‡**	0.78 (0.50, 1.19)	**1.97 (1.04, 3.73)***	**2.60 (1.26, 5.35)***
Hypertension					
No					Reference
Yes	**1.86 (1.33, 2.58)†**	**2.04 (1.27, 3.27)***	1.32 (0.77, 2.24)	**2.37 (1.15, 4.86)***	1.13 (0.54, 2.35)
BMI					
Normal					Reference
Overweight	0.89 (0.60, 1.33)	0.85 (0.48, 1.49)	0.91 (0.52, 1.57)	1.15 (0.56, 2.34)	0.94 (0.43, 2.08)
Obese	0.92 (0.64, 1.32)	0.81 (0.49, 1.33)	0.80 (0.47, 1.39)	1.02 (0.46, 2.30)	2.00 (0.83, 4.85)
Alcohol use					
Lifetime abstainers					Reference
Former drinkers	0.92 (0.61, 1.38)	0.85 (0.49, 1.47)	1.91 (0.86, 4.25)	0.84 (0.30, 2.35)	0.87 (0.33, 2.29)
Non-excessive current drinkers	1.00 (0.66, 1.52)	1.06 (0.61, 1.85)	1.41 (0.59, 3.34)	0.81 (0.26, 2.50)	0.74 (0.30, 1.82)
Excessive current drinkers	**2.02 (1.30, 3.13)***	**2.08 (1.12, 3.85)***	**2.65 (1.19, 5.90)***	2.03 (0.63, 6.46)	1.70 (0.64, 4.57)
Smoking status					
Never					Reference
Past/current	**1.40 (1.03, 1.91)***	1.42 (0.94, 2.14)	1.23 (0.76, 2.00)	1.37 (0.67, 2.80)	1.71 (0.72, 4.06)
Poverty					
No					Reference
Yes	**1.36 (1.02, 1.80)***	1.00 (0.62, 1.62)	**1.95 (1.26, 3.02)***	1.11 (0.57, 2.19)	1.06 (0.56, 2.01)
Blood cadmium level					
Q1–Q3					Reference
Q4	**1.81 (1.30, 2.53)†**	**1.75 (1.08, 2.85)***	**2.01 (1.23, 3.30)***	**2.24 (1.21, 4.16)***	1.75 (0.83, 3.65)

Cadmium analysis based on participants with information of blood lead and cadmium measurements (N = 42,255). Multiple imputation was performed in univariate and multivariate logistic regression models. Variables with a *p* value of <0.1 in the univariate analysis in the total cohort were included into the multivariate analysis. *p <0.05, †p < 0.001, ‡p <0.0001. The significant variables were labeled as bold front. MA, Mexican American; NHB, non-Hispanic Black; NHW, non-Hispanic White; O, other race; OR, odds ratio; Q1–Q4, quartiles 1–4.

definition of LF (without the requirement for ALT elevation) was used (Fig. S5).

Prevalence of risk factors

Compared with NHW persons, NHB persons had a lower prevalence of smoking and excessive drinking; however, they had a higher prevalence of many other conditions, including diabetes. Thus, the disconnection between diabetes and advanced LF in NHB persons does not result from a low prevalence of diabetes. NHB persons also had a higher prevalence of KI, hypertension, obesity, poverty, and exposure to environmental pollutants, as indicated by higher blood levels of lead, cadmium, and PCBs (Fig. 4). Both heavy metals and organic chemicals are associated with liver disease.[21,30,31]

Conditions independently associated with advanced LF

Multivariable logistic regression was used to identify factors independently associated with advanced LF. Variables included age, sex, KI, diabetes, hypertension, BMI, alcohol use, smoking, and poverty. Two age groups were analysed (20–85 and 36–64 years). In the 20- to 85-year age group, smoking and current excessive drinking were risk factors in both NHW and NHB persons (Table 1). Diabetes and hypertension were independently associated with advanced LF in NHW persons, but not in NHB persons. Conversely, poverty was a risk factor in NHB persons, but not in NHW persons.

Six sensitivity analyses were conducted to confirm the robustness of the associations between the independent variables in Table 1 and advanced LF: (1) In a sensitivity analysis that excluded participants with VH, generally similar odds ratios (ORs) obtained. Among NHB persons, the OR for diabetes was 0.76 (95% CI 0.39–1.48), and the OR for smoking was 3.00 (95% CI 1.56–5.78) (Table S2). (2) Similarly, when participants with ALD (defined in the Materials and methods section) were excluded, diabetes was not significantly associated with advanced LF among NHB persons (OR 1.01; 95% CI 0.64–1.59), whereas poverty remained a risk factor (OR 2.10; 95% CI 1.29–3.42) (Table S3). (3) When metabolic syndrome was substituted for diabetes, hypertension, and obesity, it was associated with advanced LF in the total group (Table S4). (4) In an analysis of the 35- to 64-year age group, results were generally similar to those of the 20- to 85-year age group; however, in the 35- to 64-year age group, KI was a risk factor for advanced LF in NHW persons, and poverty was a risk factor in NHW persons, as well as in NHB persons (Table S5). (5) KI was an independent risk factor in all racial/ethnic groups in a sensitivity analysis that used the less

Table 3. ORs from multivariable logistic regression models with the outcome of advanced liver fibrosis with blood lead levels included in the models.

Cohorts	In participants aged 20–85 years with blood lead level into models, OR (95% CI)				
Sample size (n)	**Total (42,255)**	**NHW (19,176)**	**NHB (8,585)**	**MA (7,508)**	**O (6,986)**
Advanced fibrosis cases (n)	**542**	**226**	**128**	**102**	**86**
Survey year	**1.08 (1.04, 1.12)**‡	**1.09 (1.04, 1.14)**‡	**1.07 (1.01, 1.14)***	1.06 (0.97, 1.17)	1.02 (0.92, 1.12)
Age (unit 10 years)	**1.52 (1.40, 1.65)**‡	**1.47 (1.31, 1.66)**‡	**1.35 (1.16, 1.59)**‡	**1.83 (1.49, 2.26)**‡	**2.12 (1.78, 2.53)**‡
Sex					
Female					Reference
Male	**1.46 (1.11, 1.92)***	**1.54 (1.04, 2.28)***	1.12 (0.72, 1.74)	1.24 (0.69, 2.22)	1.19 (0.67, 2.14)
Kidney insufficiency					
No					Reference
Yes	1.19 (0.88, 1.59)	1.20 (0.79, 1.84)	1.01 (0.46, 2.24)	0.63 (0.38, 1.05)	1.58 (0.85, 2.93)
Diabetes					
No					Reference
Yes	**2.37 (1.82, 3.10)**‡	**2.84 (2.04, 3.95)**‡	0.82 (0.53, 1.26)	1.85 (0.99, 3.44)	**2.56 (1.27, 5.14)**†
Hypertension					
No					Reference
Yes	**1.87 (1.34, 2.60)**†	**2.04 (1.27, 3.29)***	1.29 (0.76, 2.20)	**2.38 (1.16, 4.89)***	1.12 (0.53, 2.35)
BMI					
Normal					Reference
Overweight	0.85 (0.58, 1.25)	0.81 (0.47, 1.42)	0.89 (0.51, 1.56)	1.08 (0.51, 2.28)	0.87 (0.41, 1.87)
Obese	0.86 (0.61, 1.21)	0.76 (0.47, 1.22)	0.83 (0.48, 1.44)	0.93 (0.42, 2.09)	1.73 (0.70, 4.27)
Alcohol use					
Lifetime abstainers					Reference
Former drinkers	0.91 (0.61, 1.37)	0.87 (0.50, 1.50)	1.72 (0.77, 3.87)	0.84 (0.30, 2.30)	0.86 (0.34, 2.14)
Non-excessive current drinkers	0.97 (0.64, 1.46)	1.05 (0.61, 1.81)	1.33 (0.56, 3.14)	0.78 (0.25, 2.41)	0.75 (0.31, 1.77)
Excessive current drinkers	**1.96 (1.26, 3.05)***	**2.05 (1.10, 3.81)***	**2.38 (1.08, 5.25)***	2.07 (0.65, 6.55)	1.71 (0.66, 4.43)
Smoking status					
Never					Reference
Past/current	**1.68 (1.27, 2.22)**†	**1.68 (1.15, 2.45)***	1.44 (0.92, 2.25)	1.75 (0.92, 3.33)	1.96 (0.90, 4.24)
Poverty					
No					Reference
Yes	**1.36 (1.02, 1.80)***	1.07 (0.66, 1.73)	**1.86 (1.19, 2.90)***	1.21 (0.64, 2.31)	1.10 (0.59, 2.06)
Blood lead level					
Q1–Q3					Reference
Q4	1.32 (0.96, 1.80)	1.24 (0.79, 1.94)	**3.25 (1.95, 5.43)**‡	0.72 (0.40, 1.28)	0.84 (0.39, 1.83)

Lead analysis based on participants with information of blood lead and cadmium measurements (N = 42,255). Multiple imputation was performed in univariate and multivariate logistic regression models. Variables with a *p* value of <0.1 in the univariate analysis in the total cohort were included into the multivariate analysis. *p <0.05, †p <0.001, ‡p <0.0001. The significant variables were labeled as bold front. MA, Mexican American; NHB, non-Hispanic Black; NHW, non-Hispanic White; O, other race; OR, odds ratio; Q1–Q4, quartiles 1–4.

restrictive definition of LF (Table S6). (6) Finally, when FIB-4 ≥3.25, which has an overall accuracy of 86% in predicting advanced fibrosis,[32] was used as the dependent variable, results were similar to those in Table 1. Among NHB persons, the OR for diabetes was 0.74 (95% CI 0.51–1.08), whereas poverty and excessive alcohol use were strongly associated with FIB-4 ≥3.25 (Table S7).

Environmental exposures and advanced LF

High blood levels of cadmium, as indicated by measurements in Q4, were associated with advanced LF in the total population and in NHW, NHB, and MA persons in multivariable logistic regression analysis (Table 2). Blood levels of lead were strongly associated with advanced LF in NHB persons, but not significantly associated with advanced LF in NHW persons: OR 3.25 (95% CI 1.95–5.43) *vs.* OR 1.24 (95% CI 0.79–1.94; p = 0.34) (Table 3). Associations between advanced LF and heavy metal exposures were dose dependent for both cadmium and lead (Tables S8 and S9, respectively). Results were similar in sensitivity analysis in which participants with VH were excluded (Tables S10 and S11).

NHANES 2003–2004 measured lipid-adjusted plasma levels of PCBs in 1,242 adults (Fig. S6). Over 95% of the participants with advanced LF had high PCB exposure (Fig. 5). The small sample size precluded an analysis by race/ethnicity.

Time trends of health conditions from 1999–2000 to 2017–2018

To identify factors that might underlie the increase in advanced LF and to determine whether the 8.7% APC was typical of other diseases, we examined time trends for 13 other conditions (Table S1). The age-standardised weighted prevalence of high lead and cadmium exposure decreased, as did the percentage of former drinkers in the total population, in NHW persons, and in NHB persons. Smoking decreased in the total population, but the decrease was not significant among NHB persons. KI, hypertension, and current non-excessive drinking did not change significantly. Diabetes increased 1.6-fold in the total population (APC 4.9%) and in all groups except the NHB group. Obesity, as defined by either BMI or WC, increased; however, obesity was not associated with advanced LF in multivariable logistic regression analyses. LF without the requirement for ALT

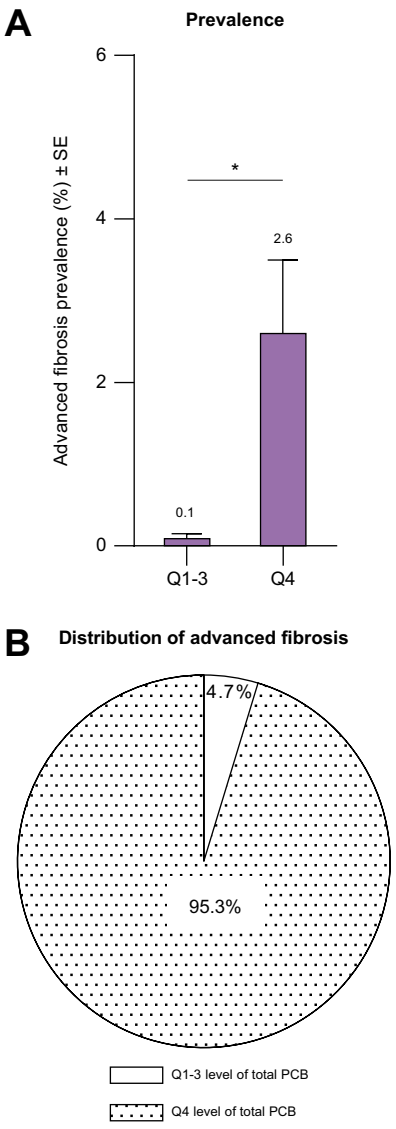

Fig. 5. Association between advanced fibrosis and PCBs (NHANES 2003–2004). (A) Age-standardised weighted prevalence of advanced liver fibrosis in people with low (Q1–Q3) and high (Q4) lipid-adjusted plasma measurements of total PCBs in participants in NHANES 2003–2004. (B) Distribution of advanced fibrosis cases in participants with Q1–Q3 (white) *vs.* Q4 (dotted) levels of total PCBs. Differences between groups were tested by univariate *t* statistics, $^{*}p$ <0.05, and by logistic regression with age adjustment, p = 0.0001. NHANES, National Health and Nutrition Examination Survey; PCB, polychlorinated biphenyl; Q1–Q4, quartiles 1–4.

elevation increased 2.0-fold in the total population (APC 10.7%), suggesting that advanced LF may continue to rise in the future (Table S1). Current excessive drinking increased significantly in the total population (APC 2.3%) and increased 1.8-fold in NHB persons (APC 5.8%), underscoring the importance of alcohol in LF.

Fibrosis in adults with NEI

Screening is often used to detect patients who have *specific* liver diseases. We investigated the percentage of people with advanced LF who might be missed if the population were screened for the three major liver diseases (namely, VH, ALD, and NAFLD), rather than for fibrosis. One analysis used the USFLI to define NAFLD (n = 20,388). The weighted prevalence of VH was 6.1% (95% CI 5.6–6.6%), that of ALD was 28.8% (95% CI, 27.8–29.8%), that of NAFLD was 18.7% (95% CI 17.8–19.5%), and that of the NEI category was 46.4% (95% CI 45.4–47.4%). Among the 285 participants with advanced LF, 36 (12.8%, 95% CI 7.5–18.0) did not meet criteria for VH, ALD, or NAFLD. A second analysis used ultrasound to define NAFLD (n = 12,811 NHANES III participants). Among the 84 participants with advanced LF, 10 (13.9%, 95% CI 3.6–24.2) did not meet criteria for VH, ALD, or NAFLD (Figs. S7 and S8). In sensitivity analyses that used LF without the requirement for ALT elevation, almost 40% of the cases were in the NEI category (Figs. S9 and S10). This corresponds to 3.24 million US adults averaged over the period analysed. Multivariable logistic regression identified KI as a risk factor for LF in the NEI category (Table S12). These findings suggest that a significant percentage of advanced LF occurs in individuals who could be missed in aetiology-based screening programmes.

Discussion

This study used nationally representative data to evaluate dynamic changes in the prevalence of advanced LF and to identify risk factors in the multi-ethnic US population. The results provide valuable information for the design of liver disease screening programmes. The study had three major findings.

First, during the past 20 years, the prevalence of advanced LF approximately doubled and increased more rapidly than that of 13 other conditions. The number of people with advanced LF increased nearly threefold, reaching about 3.5 million in the 2017–2018 NHANES cycle. Liver care services will need to expand to care for these patients. Only diabetes increased more than 1.5-fold in the total population (APC 4.9%), which makes the increase in advanced LF (APC 8.7%) especially noteworthy. Although diabetes rose among NHW persons, it did not increase significantly in NHB persons. Conversely, current excessive drinking increased 1.8-fold (APC 5.8%) among NHB persons and may be an important driver. Excessive current drinking increased about 1.2-fold in the total population (APC 2.3%), underscoring the need to reduce harmful drinking.

Second, advanced LF was strongly associated with heavy metal (lead and cadmium) exposure, and over 95% of participants with advanced LF had high lipid-adjusted levels of PCBs. These findings add to published data[21,30,31,33–35] and should prompt a more extensive examination of toxic exposures in liver disease. Importantly, the World Health Organization classifies cadmium as a known human carcinogen.[36] Additional factors independently associated with advanced LF were older age, male sex, diabetes, hypertension, excessive current drinking, past/current smoking, and poverty. KI was independently associated with advanced LF in the 35- to 64-year age group, consistent with previous reports.[37] The association between LF and KI may reflect the shared roles of the liver and kidney in metabolism, detoxification, and excretion.

Third, NHB persons (both men and women) had a higher prevalence of advanced LF than their NHW counterparts and different risk factors. These results add to past evidence that NHB persons have a distinctive pattern of liver disease presentation and genomic risk factors.[34,38–40] A previous analysis of NHANES data also showed that NHB persons have a higher prevalence of

cirrhosis,[41] although other studies reported a lower prevalence of biopsy-defined advanced LF among NHB persons.[42] Because NHB persons are often under-represented in clinical trials,[43] and may have incomplete medical records and less access to healthcare,[44] nationally representative data, as provided by NHANES, are especially important. Diabetes was independently associated with advanced LF in NHW[45] and O persons, but not in NHB persons, as shown before,[45] or in MA persons, which is consistent with published data, as past studies did not adjust for hypertension and KI.[46] Among NHB persons, high blood levels of lead were strongly associated with advanced LF (OR 3.25), and poverty was also a risk factor. Poverty is associated with workplace and environmental toxic exposures.[47] High blood levels of PCBs were strongly associated with advanced LF, and NHB persons had higher blood levels than NHW persons. Compared with NHW persons, NHB persons have a higher prevalence of a polymorphism in the gene encoding arylsulfatase A, a metabolic regulator[34] associated with lead-mediated neurotoxicity,[35] and they develop lung cancer at younger ages and with fewer pack-years of smoking,[33] suggesting that they may be especially vulnerable to toxic injury. In this study, NHB persons had a higher prevalence of KI, hypertension, obesity, poverty, and exposure to environmental pollutants (lead, cadmium, and PCB). These disparities could be associated with their reduced longevity.[48]

The study provided intriguing evidence that even if everyone in the United States were fully screened for VH, ALD, and NAFLD, 12–40% of significant LF might be missed. These findings are consistent with data showing that about 20% of cirrhosis-related deaths occur in people without any of the major liver diseases,[49] and with results showing that liver disease aetiology was unspecified in 48% of cirrhosis- or hepatocellular carcinoma-related deaths in the United States.[50] These findings highlight the advantage of universal screening for advanced LF. At a negligible cost, electronic health records could flag patients with FIB-4 ≥2.67 and/or Forns ≥6.9 and ALT ≥ULN, providing a realistic backstop to risk factor-based and aetiology-based screening and offering a safety net for the high percentage of people without diabetes whose liver disease has not been diagnosed.

Limitations

The main limitations of this study are as follows: (1) the use of NHANES data, which are collected cross-sectionally at a single time point and are restricted to the housed noninstitutionalised population; (2) the use of the FIB-4/Forns scores and USFLI to define LF and NAFLD, rather than histopathology; and (3) the use of self-reported data to define race/ethnicity, alcohol use, and smoking habits. The study could not assess causality. To mitigate these limitations, we (1) acknowledge them here; (2) performed weighted and age-standardised analyses, which adjust for changes in the age and demographic structure of the population; and (3) used ultrasound to define NAFLD in confirmatory studies.

Conclusions

In the United States, the prevalence of advanced LF doubled over the past 20 years and was higher in NHB persons (total group and men and women) than in NHW persons (total group and men and women). Liver care services will need to expand to meet the increased liver disease burden. Toxic exposures had especially strong associations with LF in NHB persons, suggesting that NHB persons may be particularly vulnerable. Poverty, smoking, excessive drinking, and exposure to environmental toxins are potentially modifiable LF risk factors. Universal screening with FIB-4 ≥2.67 and/or Forns ≥6.9 and ALT ≥ULN would be a realistic backstop to risk factor-based screening.

Abbreviations

ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; APC, annual percent change; BMI, body mass index; CI, confidence interval; FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; KI, kidney insufficiency; LF, liver fibrosis; MA, Mexican American; NAFLD, non-alcoholic fatty liver disease; NEI, no exposure identified; NHANES, National Health and Nutrition Evaluation Survey; NHB, non-Hispanic Black; NHW, non-Hispanic White; O, other race; PCB, polychlorinated biphenyl; Q1–Q4, quartiles 1–4; ULN, upper limit of normal; USFLI, US Fatty Liver Index; VH, viral hepatitis; WC, waist circumference.

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Conflicts of interest

All authors declare no relevant or material financial interests that relate to the research described in this paper.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Formal analysis: NM, RY. Methodology: NM, RY, SL, AD, CW, MC, AJ, LL, CA, MBB, DD, BW, DY, CH, ADB. Funding acquisition: ADB. Manuscript draft: NM, ADB. Manuscript review and editing: all authors.

Data availability statement

The data that support the findings of this study are openly available at the National Health and Nutrition Examination Survey website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100696.

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