Mortality Related to Nonalcoholic Fatty Liver Disease Is Increasing in the United States

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Population-level nonalcoholic fatty liver disease (NAFLD) death rate data are sparse. We described death rates for adults with NAFLD in the United States using mortality data from the National Vital Statistics System multiple-cause mortality data (2007-2016). Decedents who had NAFLD were identified by International Classification of Diseases (ICD) codes K75.81, K76.0, K74.0, K74.6, and K76.9. Among NAFLD decedents, cause-specific deaths (e.g., cardiovascular disease [CVD], cirrhosis, hepatocellular carcinoma [HCC], non-liver cancer, diabetes mellitus [DM]) were identified by underlying cause of death ICD-10 codes. Trends were evaluated by average annual percentage change (AAPC) in age-standardized death rate (ASDR) per 100,000 persons. Among the 25,129,960 decedents aged ≥20 years, 353,234 (1.4%) decedents had NAFLD (212,322 men; 260,765 non-Hispanic whites, 32,868 non-Hispanic blacks, 46,530 Hispanics, 5,025 non-Hispanic American Indian or Alaska Natives [AIANs], 7,023 non-Hispanic Asian or Pacific Islanders [APIs]), with a mean age at death of 64.47 ± 13.17 years. During the study period, the ASDR for NAFLD increased by 15% (12.94 to 14.90; AAPC, 1.98%; *P* < 0.001]), while women (AAPC, 2.99% vs. 1.16% men; *P* = 0.003), non-Hispanic whites (AAPC, 2.48%), non-Hispanic AIANs (AAPC, 2.31%), and Hispanics (AAPC, 0.74%) experienced the highest annual increases. Stable trends were noted for non-Hispanic blacks and non-Hispanic APIs. Among subgroups, Mexican (AAPC, 1.75%) and Asian Indians (AAPC, 6.94%) experienced annual increases. The top six underlying causes of death (155,894 cirrhosis, 38,444 CVD, 19,466 non-liver cancer, 10,867 HCC, 8,113 DM, and 5,683 lung disease) accounted for 67.5% of NAFLD-related deaths. For cause-specific deaths, ASDR increased for HCC (AAPC, 3.82%), DM (AAPC, 2.23%), non-liver cancer (AAPC, 2.14%), CVD (AAPC, 1.59%), and cirrhosis (AAPC, 0.96%). *Conclusion:* NAFLD-related deaths in U.S. adults are increasing. Cirrhosis is the top cause-specific death, followed by CVD. Women, non-Hispanic whites, and non-Hispanic AIANs (subgroups Mexicans and Asian Indians) experienced the highest increases in deaths. Policies addressing the societal burden of NAFLD are needed. (*Hepatology Communications* 2019;3:1459-1471).

Nonalcoholic fatty liver disease (NAFLD) is a liver disease associated with components of metabolic syndrome, including insulin resistance, diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, and obesity. In 2016, using specific body mass index (BMI) cutoffs (overweight, BMI ≥25 and obesity, BMI ≥30; Asians with a BMI of 23-27.5 kg/m^2 are overweight, and those with a BMI ≥27.5 kg/m^2 are obese), the World Health Organization (WHO) determined that worldwide overweight and obesity rates have nearly tripled since 1975.[1] The WHO recently reported that 13% of the world's adult population is currently obese and 39% are overweight, with the United States leading the

way with the highest prevalence of adults with obesity.[2] Therefore, NAFLD and obesity are considered significant global health threats, garnering increasing interest among all stakeholders.[2]

Although most patients with NAFLD do not progress to end-stage liver disease, patients with nonalcoholic steatohepatitis (NASH), a subtype of NAFLD, can progress to cirrhosis and its complications.[3] On the other hand, given the very high prevalence of NAFLD, the projected number of patients with NAFLD facing adverse outcomes may be significant. In fact, a recent report using Markov modeling to forecast NAFLD disease by the year 2030 found the prevalence of NAFLD cases is forecasted to increase 21% and NASH cases will increase 63%, providing an overall NAFLD prevalence rate of 33.5% and a 27% prevalence rate of NASH in adults.[4] In addition, the incidence of adverse outcomes will significantly increase, with the incidence of decompensated cirrhosis increasing 168%, hepatocellular carcinoma (HCC) 137%, and liver-related mortality 178%.[4]

The magnitude of the burden of NAFLD is also seen in economic modeling and population-based studies.[5-9] NAFLD-associated costs over the next 10 years are projected to be an estimated $1.005 trillion in the United States and €334 billion in Europe.[8] Patients with NAFLD also report a decrease in their health-related quality of life, especially in the area of physical functioning, which affects their ability to work and perform activities of daily living.[9-11] Despite the significant burden posed by NAFLD, fully validated

noninvasive diagnostic tests are lacking and effective treatment for NASH is limited.[12,13] As a result, there may be an increasing number of deaths due to NAFLD and NASH. However, current NAFLD/NASH-related death data are lacking.[14] Thus, the aim of this study was to describe the NAFLD-related death rate among adults in the United States, using the National Vital Statistics System (NVSS) database for the years 2007-2016 to provide a better understanding of NAFLD-related mortality.

Materials and Methods

All death data were obtained from the NVSS database of the National Center for Health Statistics of the Centers for Disease Control and Prevention, with 2007-2016 data extracted from the NVSS multiple-cause of death files.[15,16] The NVSS annually provides public-use mortality data by multiple-cause of death, abstracted from death certificates filed in vital statistics offices of 50 states and the District of Columbia. Each record contains a single underlying cause of death, up to 20 contributing causes of death, and demographic characteristics. The underlying cause of death is defined by the WHO as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Underlying cause of death was selected from the conditions entered by the physician on the cause of death section of the death certificate.

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Cause of death was coded using the International Classification of Diseases (ICD) codes in use at the time of death (ICD-8 for 1969-1978, ICD-9 for 1979-1998, and ICD-10 for 1999-2016).[16] More than 99% of deaths in the United States are captured by this database.[17]

To evaluate trends in death rates among adults with NAFLD, NAFLD was identified from the death certificates using the following ICD-10 codes and categories: fatty liver not elsewhere classified (K76.0), NASH (K75.81), hepatic fibrosis (K74.0), or cryptogenic liver disease with or without cirrhosis (K76.9 and K74.6, respectively). In addition, NAFLD had to reside by itself; therefore, the absence of other chronic liver diseases, including hepatitis C, hepatitis B, alcoholic liver disease, chronic hepatitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, iron overload, alpha-1-antitrypsin deficiency, or excessive alcohol use, was assessed.[18] A flow diagram outlining the inclusion and exclusion of NAFLD-related deaths is shown in Fig. 1. Among decedents who had NAFLD, cause-specific

deaths (e.g., cardiovascular disease [CVD], cirrhosis, HCC, non-liver cancer, DM) were identified with the ICD-10 underlying cause of death codes. The ICD-10 codes that were used to identify NAFLD and other liver diseases as well as NAFLD-related extrahepatic manifestations, including CVD, DM, and non-liver cancer, are shown in Supporting Table S1.[19,20]

Sociodemographic variables gathered included age at the time of death (20-44, 45-54, 55-64, 65-74, and ≥75 years), sex, race, Hispanic origin, marital status, and education level. Because race and Hispanic origin are reported independently on the death certificate, race/ethnicity for the non-Hispanic population (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian or Pacific Islander [API], and other, which included American Indian or Alaska Native [AIAN]) was a combination of two questions; the first was answering "no" to the question of whether the decedent was of Hispanic origin and the second was a question of the decedent's race with the answer selected from a checklist.
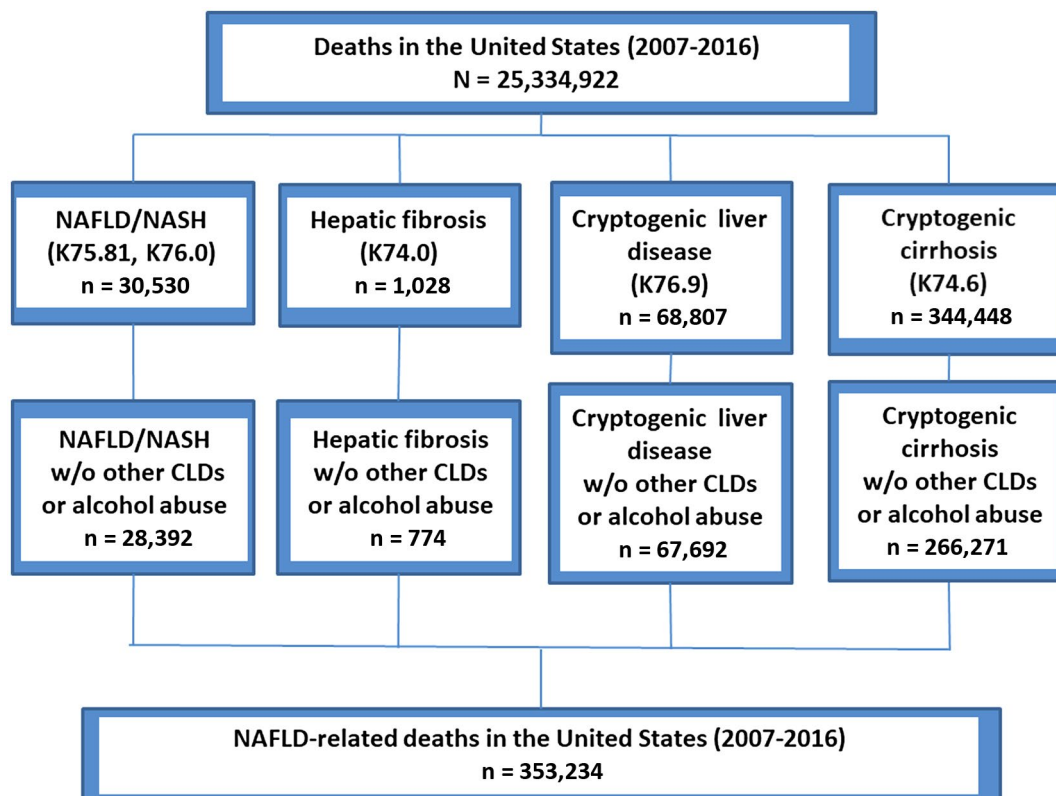

FIG. 1. Flow diagram. Abbreviations: CLD, chronic liver disease; w/o, without.

STATISTICAL METHODS

Age-specific death rates were calculated by sex and race/ethnicity from 2007 through 2016 based on the corresponding population estimates and adjusted for population shifts due to hurricanes Katrina and Rita, released by the Survey of Epidemiology and End Results (SEER).[21,22] Age-standardized death rates (ASDRs) per 100,000 with 95% confidence intervals (CIs) were then calculated by using the direct method based on the 2000 Census standard population, using 10-year age groups starting at 20 years and ending at ≥85 years. Temporal trends in ASDRs were analyzed by the joinpoint regression (JR) model. The JR model identified the best fit for joinpoints at which an apparent change in trend is statistically significant. A maximum number of 2 joinpoints was allowed, and a Monte Carlo permutation method was used for model selection.[23] From the selected models, the annual percentage change (APC) for each trend segment and the average annual percentage change (AAPC) for the entire period were reported with a 95% CI. An increasing or decreasing trend was defined if the APC or AAPC was significantly different from 0; otherwise, a stable or level trend was defined. For overall rates, annual death rates were averaged across the entire study period. ASDRs were graphed by sex and race/ethnicity group. Prevalence ratios (PRs) were estimated by modified Poisson regression models with sandwich error variance while adjusting for age, sex, and race/ethnicity. The population counts for Hispanic and Asian American subgroups in non-Census years were estimated by linear interpolation (2008-2009), U.S. Census data (2010), and extrapolation (2011-2016), using the 2000 and 2010 U.S. Census reports.[24-28] Joinpoint trend analysis was run with the JR Program, version 4.5.0.2, from SEER, and all other analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). Statistical tests were considered significant at $P < 0.05$ (two-tailed).

TABLE 1. AGE-STANDARDIZED DEATH RATE (PER 100,000) FOR NAFLD AMONG U.S. ADULTS AGED ≥20 YEARS BY AGE, SEX, AND RACE, UNITED STATES, 2007-2016

	All-Cause Deaths (Rate per 100,000)			
	2007-2016[†]	2007	2016	AAPC* (95% CI)
Total	353,234 (14.05)	29,339 (12.94)	40,895 (14.90)	1.98 (1.57-2.39)[§]
Age group, years[‡]				
20-44	20,317 (1.08)	2,069 (1.11)	2,023 (1.07)	−0.14 (−0.92-0.64)
45-54	61,259 (13.90)	6,200 (14.11)	5,259 (12.29)	−1.21 (−1.97 to −0.45)[§]
55-64	100,686 (26.49)	7,443 (22.47)	11,687 (28.19)	2.57 (2.11-3.04)[§]
65-74	84,752 (35.31)	6,300 (31.98)	11,393 (39.79)	2.67 (1.47-3.89)[§]
≥75	86,220 (44.85)	7,327 (40.42)	10,533 (51.10)	2.78 (1.60-3.96)[§]
Sex				
Female	140,912 (10.41)	11,374 (9.24)	16,970 (11.54)	2.99 (2.50-3.49)[§]
Male	212,322 (18.21)	17,965 (17.19)	23,925 (18.76)	1.16 (0.56-1.77)[§]
Race				
Non-Hispanic white	260,765 (13.87)	21,825 (12.51)	30,147 (15.04)	2.48 (2.07-2.88)[§]
Non-Hispanic black	32,868 (12.24)	2,942 (12.38)	3,456 (11.61)	−0.01 (−0.73-0.71)
Hispanic	46,530 (20.65)	3,546 (19.7)	5,668 (20.81)	0.74 (0.26-1.22)[§]
Non-Hispanic American Indian or Alaska Native	5,025 (30.68)	415 (28.71)	640 (35.19)	2.31 (1.24-3.38)[§]
Non-Hispanic Asian or Pacific Islander	7,023 (6.77)	564 (6.81)	865 (6.66)	−0.02 (−0.98-0.95)

*AAPC is a weighted average of the APCs (a maximum number of 2 joinpoints was allowed). Age standardization is based on the direct method to the Census 2000 population by 10-year age groups. NAFLD-related deaths are defined by ICD-10 codes using underlying or contributing cause of death certificates.
[†]Age-standardized death rates were averaged over the period 2007-2016.
[‡]Age-specific death rates.
[§]Significantly different from 0 ($P < 0.05$).

Results

DEMOGRAPHICS

Among the 25,129,960 decedents (aged ≥20 years) observed in the United States (2007-2016), there were 353,234 (1.4%) decedents who had NAFLD listed as a co-contributory cause of death (212,322 men; 260,765 non-Hispanic whites, 32,868 non-Hispanic blacks, 46,530 Hispanics, 5,025 non-Hispanic AIANs, 7,023 non-Hispanic APIs; mean age at death 64.47 ± 13.17 years). The age-specific all-cause death rate was the highest for decedents aged ≥75 years, followed by age groups 65-74, 55-64, 45-54, and 20-44 years. The ASDR for NAFLD was the highest among non-Hispanic AIANs (30.7), followed by Hispanics (20.7), non-Hispanic whites (13.9), non-Hispanic blacks (12.2), and non-Hispanic APIs (6.8) (Table 1; Supporting Table S2). Within the Hispanic subgroup, the ASDR was higher among Mexicans (25.6) and Puerto Ricans (23.4), whereas within the non-Hispanic API subgroup, the Vietnamese (11.9) had the highest ASDR, followed by the Japanese (8.0) (Tables 2 and 3).

The top six underlying causes (155,894 cirrhosis, 38,444 CVD, 19,466 non-liver cancer, 10,867 HCC, 8,113 DM, and 5,683 lung disease) accounted for 67.5% of the deaths among adults with NAFLD. CVD (n = 80,080) was the largest contributory cause of death, followed by renal disease (n = 36,726), DM (n = 31,132), and HTN (n = 28,222) (Table 4; Supporting Table S2).

TIME TRENDS IN ASDR BETWEEN 2007 AND 2016

Between 2007 and 2016, the ASDR for NAFLD increased by 15%, from 12.94 to 14.90 (AAPC, 1.98%; $P < 0.001$), with women experiencing the most significant annual increase (AAPC, 2.99% in women vs.

TABLE 2. AGE-STANDARDIZED CAUSE-SPECIFIC DEATH RATE (PER 100,000) FOR NAFLD AMONG U.S. ADULTS AGED ≥20 YEARS, 2007-2016

	Cause-Specific Deaths (Rate per 100,000)			
	2007-2016[†]	2007	2016	AAPC* (95% CI)
Cause-specific death[‡]				
Cardiovascular disease	38,444 (1.54)	3,353 (1.48)	4,627 (1.7)	1.59 (0.85-2.34)[∥]
Cirrhosis	155,894 (6.21)	13,401 (5.91)	17,174 (6.27)	0.96 (0.18-1.74)[∥]
Diabetes	8,113 (0.32)	704 (0.31)	1,027 (0.37)	2.23 (0.01-4.49)[∥]
Non-liver cancer	19,466 (0.76)	1,644 (0.72)	2,440 (0.86)	2.14 (0.25-4.06)[∥]
HCC	10,867 (0.42)	798 (0.35)	1,408 (0.49)	3.82 (3.20-4.44)[∥]
Lung disease	5,683 (0.22)	463 (0.20)	703 (0.25)	2.13 (1.08-3.20)[∥]
Contributory causes of death[§]				
Diabetes	31,132 (1.24)	2,461 (1.10)	4,045 (1.46)	2.80 (2.03-3.58)[∥]
Hypertension	28,222 (1.12)	2,040 (0.90)	3,876 (1.41)	5.21 (4.58-5.85)[∥]
Cardiovascular disease	80,080 (3.20)	6,573 (2.92)	9,802 (3.59)	2.27 (1.66-2.89)[∥]
Lung disease	21,116 (0.83)	1,608 (0.71)	2,647 (0.94)	3.10 (2.65-3.56)[∥]
Renal disease	36,726 (1.46)	3,219 (1.42)	4,169 (1.52)	1.19 (–1.00-3.43)
Neurological disorder	8,613 (0.34)	704 (0.31)	1,156 (0.42)	3.56 (–0.04-7.29)
Non-liver cancer	8,414 (0.33)	703 (0.31)	1,003 (0.36)	1.46 (0.75-2.17)[∥]
Dementia	5,035 (0.21)	390 (0.18)	667 (0.25)	4.26 (2.94-5.61)[∥]
Thyroid	2,327 (0.09)	207 (0.09)	332 (0.12)	2.78 (0.14-5.50)[∥]
Obstructive sleep apnea	1,315 (0.05)	44 (0.02)	211 (0.07)	16.78 (6.66-27.86)[∥]
Depression	1,033 (0.04)	65 (0.03)	137 (0.05)	5.55 (2.27-8.93)[∥]
Osteoporosis	461 (0.02)	39 (0.02)	46 (0.02)	–3.71 (–7.29-0.00)

*AAPC is a weighted average of the APCs (a maximum number of 2 joinpoints was allowed).
[†]Age-standardized death rates were averaged over the period 2007-2016.
[‡]Defined by using underlying cause of death.
[§]Defined by using contributory causes of death; because a decedent can have multiple contributory causes of death, a decedent could be counted multiple times.
[∥]Significantly different from 0 ($P < 0.05$).

TABLE 3. MORTALITY RATIOS AMONG DECEDENTS WITH NAFLD, UNITED STATES, 2007-2016

	Mortality Ratio* (95% CI)				
	Male to Female	Non-Hispanic Black to Non-Hispanic White	Hispanic to Non-Hispanic White	Non-Hispanic American Indian or Alaska Native to Non-Hispanic White	Non-Hispanic Asian to Non-Hispanic White
Cause-specific death[†]					
Cardiovascular disease	1.34 (1.31-1.36)	1.23 (1.19-1.26)	0.91 (0.88-0.94)	0.87 (0.79-0.95)	1.21 (1.14-1.29)
Cirrhosis	0.95 (0.94-0.96)	0.89 (0.88-0.90)	0.99 (0.98-1.00)	0.90 (0.87-0.93)	0.83 (0.81-0.86)
Diabetes	0.83 (0.80-0.87)	1.11 (1.03-1.20)	1.40 (1.32-1.48)	1.76 (1.52-2.04)	1.15 (0.99-1.33)
Non-liver cancer	1.11 (1.08-1.14)	0.96 (0.92-1.01)	0.87 (0.83-0.91)	0.80 (0.69-0.91)	1.11 (1.02-1.22)
HCC	2.39 (2.28-2.50)	1.39 (1.30-1.47)	1.67 (1.59-1.76)	1.39 (1.19-1.63)	2.53 (2.31-2.77)
Lung disease	1.12 (1.06-1.18)	0.70 (0.63-0.77)	0.41 (0.36-0.45)	0.71 (0.54-0.92)	0.42 (0.32-0.54)
Contributory causes of death[‡]					
Diabetes	0.84 (0.83-0.86)	0.85 (0.82-0.89)	1.34 (1.30-1.38)	1.34 (1.24-1.46)	1.20 (1.12-1.29)
Hypertension	0.96 (0.94-0.99)	1.39 (1.34-1.44)	1.23 (1.19-1.27)	1.09 (0.99-1.20)	1.23 (1.15-1.32)
Cardiovascular disease	1.08 (1.06-1.09)	1.09 (1.07-1.12)	1.16 (1.14-1.18)	1.08 (1.03-1.14)	1.22 (1.17-1.26)
Lung disease	1.04 (1.01-1.07)	0.77 (0.73-0.81)	0.52 (0.49-0.54)	0.72 (0.63-0.82)	0.61 (0.54-0.68)
Renal disease	1.05 (1.03-1.07)	1.52 (1.48-1.57)	1.29 (1.26-1.33)	1.33 (1.23-1.44)	1.30 (1.22-1.38)
Neurological disorder	0.90 (0.86-0.94)	1.19 (1.11-1.27)	1.03 (0.97-1.10)	1.29 (1.11-1.51)	0.97 (0.83-1.13)
Non-liver cancer	1.06 (1.01-1.10)	0.97 (0.89-1.05)	0.83 (0.77-0.89)	0.77 (0.61-0.96)	0.95 (0.82-1.10)
Dementia	0.75 (0.71-0.79)	1.46 (1.32-1.61)	1.02 (0.94-1.11)	1.18 (0.90-1.55)	0.82 (0.68-0.99)
Thyroid	0.40 (0.36-0.43)	0.61 (0.51-0.74)	0.94 (0.83-1.06)	0.94 (0.66-1.35)	0.96 (0.73-1.25)
Obstructive sleep disorder	1.04 (0.93-1.17)	0.52 (0.41-0.66)	0.60 (0.50-0.73)	0.57 (0.33-0.99)	0.74 (0.48-1.13)
Depression	0.52 (0.46-0.58)	0.47 (0.35-0.62)	0.65 (0.53-0.79)	0.43 (0.21-0.85)	0.73 (0.45-1.18)
Osteoporosis	0.19 (0.15-0.24)	0.29 (0.16-0.55)	0.53 (0.38-0.75)	1.00 (0.45-2.24)	0.86 (0.48-1.52)

*Robust Poisson models were used while adjusting for age, sex, and race.
[†]Defined by using underlying cause of death.
[‡]Defined by using contributory causes of death; because a decedent can have multiple contributory causes of death, a decedent could be counted multiple times.

1.16% in men; P = 0.003) (Fig. 2A). The increase in the ASDR (per 100,000) for adults with NAFLD was most pronounced in those aged ≥75 years (AAPC, 2.78%; 95% CI, 1.60%-3.96%), followed by those aged 65-74 years (AAPC, 2.67%; 95% CI, 1.47%-3.89%) and those aged 55-64 years (AAPC, 2.57%; 95% CI, 2.11%-3.04%). On the other hand, the death rate decreased for those aged 45-54 years (AAPC, –1.21%; 95% CI, –1.97% to –0.45%) and remained stable for those aged 20-44 years. By ethnicity, the highest increase in the ASDR for NAFLD was seen in non-Hispanic whites (AAPC, 2.48%; 95% CI, 2.07%-2.88%), followed by non-Hispanic AIANs (AAPC, 2.31%; 95% CI, 1.24%-3.38%) and Hispanics (AAPC, 0.74%; 95% CI, 0.26%-1.22%), whereas the ASDR remained stable in non-Hispanic blacks and non-Hispanic APIs (Fig. 2B). However, there was substantial heterogeneity in the ASDR for NAFLD among the Hispanic and

non-Hispanic API subgroups. The pattern of change for ASDR between 2007 and 2016 shows a substantial increase among Mexicans (AAPC, 1.8%; 95% CI, 1.1%-2.4%) and Asian Indians (AAPC, 6.9%; 95% CI, 4.7%-9.3%), whereas the ASDR remained stable among other subgroups (Tables 2 and 3; Fig. 3).

For cause-specific deaths among adults with NAFLD, ASDRs increased in 2016 from 2007 for HCC (AAPC, 3.82%; 95% CI, 3.20%-4.44%), DM (AAPC, 2.23%; 95% CI, 0.01%-4.49%), non-liver cancer (AAPC, 2.14%; 95% CI, 0.25%-4.06%), CVD (AAPC, 1.59%; 95% CI, 0.85%-2.34%), and cirrhosis (AAPC, 0.96%; 95% CI, 0.18%-1.74%). Among the top six contributory causes of death, the ASDR increased for four: CVD (AAPC, 2.27%), DM (AAPC, 2.80%), HTN (AAPC, 5.21%), and lung disease (AAPC, 3.10%) (all P < 0.001). The remaining two contributory causes of death (renal disease

TABLE 4. AGE-STANDARDIZED DEATH RATES FOR NAFLD AMONG U.S. HISPANIC ADULTS AGED ≥20 YEARS BY AGE, SEX, AND ETHNICITY, UNITED STATES, 2007-2016

	All-Cause Deaths (Rate per 100,000)			
	2007-2016[†]	2007	2016	AAPC* (95% CI)
Total	46,530 (20.65)	3,546 (19.7)	5,668 (20.81)	0.74 (0.20 -1.22)[§]
Age group, years[‡]				
20-44	3,717 (0.94)	374 (1.03)	392 (0.93)	−1.35 (−2.69-0.02)
45-54	9,033 (15.74)	805 (16.89)	873 (13.06)	−2.28 (−3.93 to −0.60)[§]
55-64	12,512 (34.93)	831 (30.69)	1,565 (35.01)	1.14 (−0.49-2.81)
65-74	10,838 (57.89)	768 (53.64)	1,419 (59.09)	1.33 (0.43-2.25)[§]
≥75	10,430 (82.31)	768 (77.49)	1,419 (90.53)	1.80 (0.79-2.82)[§]
Sex				
Female	19,030 (16.4)	1,356 (14.89)	2,477 (17.52)	1.81 (1.03-2.60)[§]
Male	27,500 (25.25)	2,190 (25.04)	3,191 (24.29)	−0.04 (−0.73-0.64)
Race				
Mexican	3,0242 (25.61)	2,269 (23.38)	3,664 (26.92)	1.75 (1.14-2.37)[§]
Puerto Rican	5,565 (23.36)	449 (21.65)	621 (23.23)	0.62 (−0.37-1.62)
Cuban	1,993 (11.84)	173 (11.60)	222 (11.81)	−0.38 (−2.01-1.29)

*AAPC is a weighted average of the APCs (a maximum number of 2 joinpoints was allowed). Age standardization is based on the direct method to the Census 2000 population by 10-year age groups. NAFLD-related deaths are defined by ICD-10 codes using underlying or contributing cause of death certificates.
[†]Age-standardized death rates were averaged over the period 2007-2016.
[‡]Age-specific death rates.
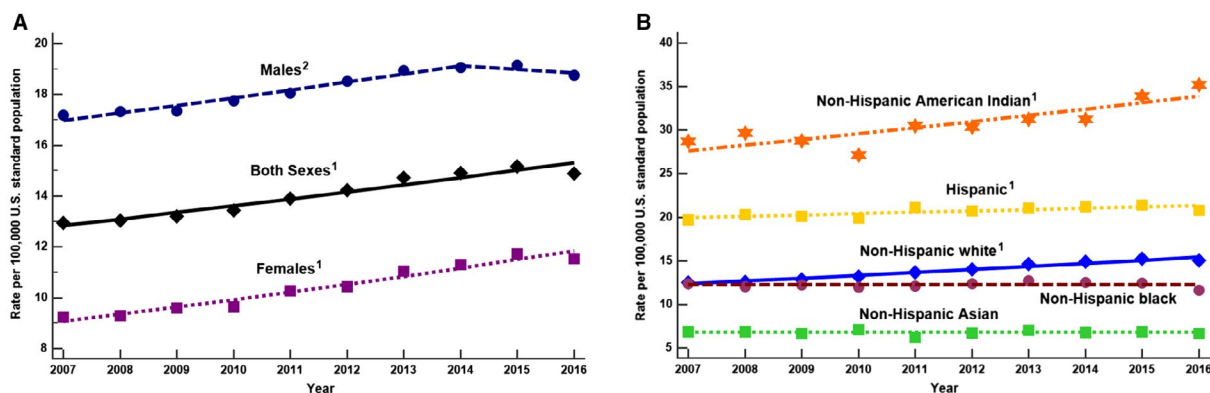[§]Significantly different from 0 ($P < 0.05$).

FIG. 2. Age-standardized death rates for NAFLD, United States, 2007-2016. (A) By sex; (B) by race/ethnicity. [1]Significant increasing trend from 2007 to 2016; [2]significant increasing trend from 2007 to 2014 and stable trend from 2014 to 2016. Data markers denote observed rates; lines are fitted based on joinpoint analysis. Age standardization is based on the direct method to the Census 2000 population by 10-year age groups. (From the National Center for Health Statistics, 2007-2016.)

and neurological disorders) remained stable. In a sensitivity test, we evaluated trends in ASDR for decedents coded for NAFLD/NASH compared to those coded with cryptogenic liver disease/cirrhosis to demonstrate homogeneity of our NAFLD group. The ASDR trends for death significantly increased for both groups (Supporting Table S3).

SEX AND RACE/ETHNICITY DIFFERENCES

The age–sex–race-adjusted mortality ratios for cause-specific deaths among decedents with NAFLD are described in Table 5. Among decedents with NAFLD, there were 139% more deaths due to HCC
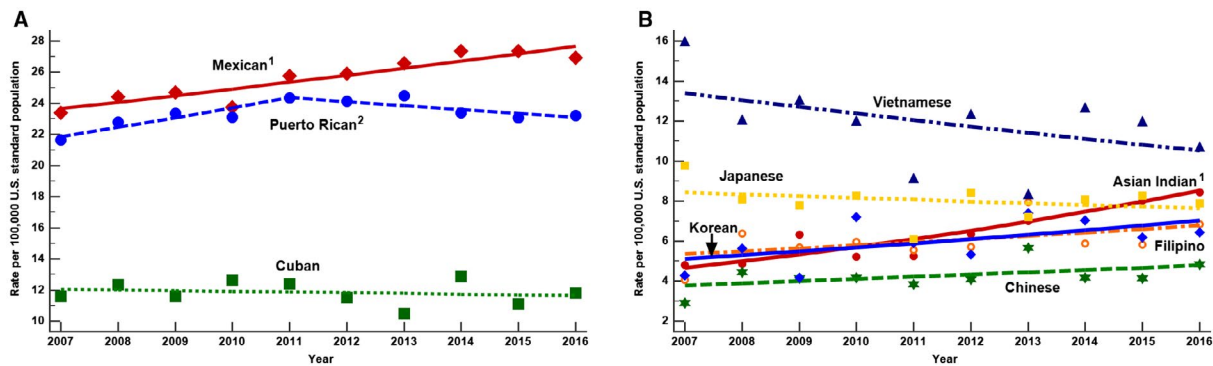
FIG. 3. Age-standardized death rates for NAFLD, United States, 2007-2016. (A) Hispanic subgroup; (B) Asian American subgroup. [1]Significant increasing trend from 2007 to 2016; [2]significant increasing trend from 2007 to 2011 and stable trend from 2011 to 2016. Data markers denote observed rates; lines are fitted based on joinpoint analysis. Age standardization is based on the direct method to the Census 2000 population by 10-year age groups. NAFLD-related deaths are defined by ICD-10 codes, using underlying or contributing cause of death noted on the death certificates. Because of small sample size and livability, an increasing or decreasing trend among Asian American subgroup are not statistically significant but among Asian Indians. See Table 5 AAPC column.

TABLE 5. AGE-STANDARDIZED DEATH RATES FOR NAFLD AMONG U.S. NON-HISPANIC ASIAN OR PACIFIC ISLANDER ADULTS AGED ≥20 YEARS BY AGE, SEX, AND ETHNICITY, UNITED STATES, 2007-2016

	All-Cause Deaths (Rate per 100,000)			
	2007-2016[†]	2007	2016	AAPC* (95% CI)
Total	7,023 (6.77)	564 (6.81)	865 (6.66)	−0.02 (−0.98-0.95)
Age group, years[‡]				
20-44	470 (0.42)	47 (0.46)	45 (0.36)	−2.70 (−6.29-1.02)
45-54	854 (3.73)	97 (4.78)	80 (3.05)	−5.34 (−7.97 to −2.64)[§]
55-64	1,439 (8.1)	111 (7.95)	187 (8.93)	1.36 (−0.36-3.11)
65-74	1,721 (16.83)	127 (16.65)	228 (16.93)	0.88 (−1.93-3.77)
≥75	2,539 (37.39)	182 (35.54)	325 (36.73)	0.62 (−0.65-1.90)
Sex				
Female	3,130 (5.59)	250 (5.73)	392 (5.5)	−0.19 (−1.46-1.10)
Male	3,893 (8.17)	314 (8.04)	473 (7.99)	0.18 (−2.01-2.41)
Race				
Asian Indian	159 (6.44)	12 (4.82)	23 (8.44)	6.94 (4.6 -9.27)[§]
Chinese	167 (4.25)	12 (2.92)	21 (4.84)	2.66 (−1.25-6.73)
Filipino	264 (5.99)	20 (4.08)	42 (6.85)	2.67 (−1.24-6.74)
Korean	84 (5.96)	7 (4.28)	9 (6.45)	3.60 (−0.74-8.13)
Japanese	155 (7.99)	14 (9.76)	22 (7.9)	−1.09 (−3.86-1.77)
Vietnamese	99 (11.85)	7 (16)	15 (10.74)	−2.64 (−6.50-1.38)

*AAPC is a weighted average of the APCs (a maximum number of 2 joinpoints was allowed). Age standardization is based on the direct method to the Census 2000 population by 10-year age groups. NAFLD-related deaths are defined by ICD-10 codes using underlying or contributing cause of death certificates.
[†]Age-standardized death rates were averaged over the period 2007-2016.
[‡]Age-specific death rates.
[§]Significantly different from 0 ($P < 0.05$).

in men than in women, whereas women experienced 5% more deaths due to cirrhosis than men (PR, 0.95; 95% CI, 0.80%-0.96%).

Compared to non-Hispanic whites, every ethnicity experienced more deaths due to HCC, with non-Hispanic Asians experiencing the highest

ratio of 2.53 (PR, 2.53; 95% CI, 2.31-2.77). On the other hand, non-Hispanic whites experienced more deaths due to cirrhosis and lung disease than all other ethnicities. Non-Hispanic AIANs experienced 76% more deaths due to DM (PR, 1.76; 95% CI, 1.52-2.04), which is similar for Hispanics, who had 40% more deaths due to DM (PR, 1.40; 95% CI, 1.32-1.48) compared to non-Hispanic whites. Non-Hispanic blacks and non-Hispanic APIs were more likely to die due to CVD (PR, 1.23; 95% CI, 1.19-1.26 and PR, 1.21; 95% CI, 1.14-1.29, respectively) than non-Hispanic whites. In contrast, the number of deaths due to CVD was lower among Hispanics (PR, 0.91; 95% CI, 0.88-0.94) and non-Hispanic AIANs (PR, 0.87; 95% CI, 0.79-0.95) than non-Hispanic whites (Table 5).

Among the contributory causes of death, men experienced more deaths from CVD, lung disease, renal disease, non-liver cancers, and obstructive sleep disorder but fewer deaths from DM, HTN, neurological disorders, dementia, thyroid, depression, and osteoporosis compared to women (Table 5). By ethnicity, non-Hispanic blacks incurred more deaths from HTN, renal disease, neurological disorders, and dementia compared to non-Hispanic whites, whereas Hispanics, non-Hispanic AIANs, and non-Hispanic APIs incurred more deaths from DM, HTN, renal disease, and CVD compared to non-Hispanic whites (Table 5). However, overall, CVD, renal disease, and DM were the top three contributory causes of death (Supporting Table S3).

Discussion

In this study, we categorized deaths among adults with NAFLD or NASH in the United States, using data from the NVSS multiple-cause of death files. Using these data, we found that NAFLD-related deaths in the United States significantly increased, with an average of almost 2% a year, from 2007 to 2016 (15% overall). The majority of all-cause deaths occurred in those aged ≥55 years (the highest ASDR was in those aged ≥75 years), non-Hispanic whites (the highest ASDR was for non-Hispanic AIANs), and men. Interestingly, although men accounted for the largest percentage of deaths, they only experienced a significant increasing trend from 2007 to 2014, followed by a steady trend from 2014 to 2016. In addition, non-Hispanic AIANs, non-Hispanic whites, and Hispanics experienced the most significant increases in deaths from 2007 to 2016, whereas the death rates for all other ethnicities remained stable.

Cirrhosis was the leading cause of death among adults with NAFLD (2007-2016), with a significant increasing trend. CVD remained the second leading specific cause of death but was fifth among the six leading causes of death for an increase in its trend. CVD was the main contributing cause of death, followed by DM and HTN; however, HTN had the most significant increasing trend. Combined, these findings point to a potential change in the main cause of death between 2007 and 2016. Earlier studies reported that the major cause of death among adults with NAFLD was CVD, but in this study, the major cause was liver related.[29,30] However, further research is warranted to corroborate our findings because we realize that our definition of NAFLD may have captured patients with cirrhosis as a result of other liver diseases rather than NAFLD, even though we tried to exclude all those with other known causes of liver disease. In addition, the difference in our findings may also be a result of how we obtained the cause of death. For this study, we took the underlying cause of death from the death certificate as the cause-specific death, and all other categories on the death certificate used were considered contributory causes of death.

Of note, HCC among adults with NAFLD was the fourth leading cause of death; however, HCC was found to have experienced the most significant increasing trend over the study time from 2007 through 2016. In fact, men and all ethnicities when compared to non-Hispanic whites experienced a higher ratio of deaths attributed to HCC; this was especially the case among non-Hispanic Asians. These findings are important, first, because they confirm findings from recent studies that the stage of fibrosis is the independent predictor for death among those with NAFLD/NASH.[29,30] Second, these findings further explain why NAFLD is now the second most common reason for liver transplant and that the rate of listing for NASH-related HCC is the highest in the United States.[31-35] Third, patients with NASH-related HCC have a higher rate of mortality following their HCC diagnosis,[36-39] which portends the necessity of developing screening and surveillance guidelines dedicated to patients with NAFLD and fibrosis in hopes of reversing this dismal trend. However, we

recognize that it is plausible that the current screening modalities for HCC fail to detect small-tumor HCC due to the presence of central obesity in many patients with NASH. As a result, patients with NASH with HCC may present with more invasive and complicated tumors, which are not conducive to treatment or liver transplant. Furthermore, we recognize that, due to the presence of many other metabolic diseases associated with NAFLD, patients may be too sick for transplant and/or die from CVD or their liver disease while awaiting transplant.[39] Yet, these reasons are also why earlier screening and surveillance for cirrhosis and HCC may need to be advocated for, especially as newer technology and serum biomarkers with better precision are being investigated.[12]

A somewhat surprising finding was the significant increasing trend of the underlying cause of death as a result of lung disease, especially in non-Hispanic whites, which is the group that comprises the largest number of deaths among adults with NAFLD. Lung disease incurred the second highest average APC as the underlying cause of death among adults with NAFLD, increasing 2% a year from 2007 to 2016. In fact, studies are now beginning to investigate the possible relationship between lung disease and NAFLD. One such study among a Korean population found that those with NAFLD were 33% more likely to have obstructive lung disease (OLD) and those with OLD were 55% more likely to have NAFLD after adjusting for age, sex, and smoking history.[40] Another study found similar results that, despite the presence or nonpresence of smoking, the incidence of NAFLD in those with OLD increased.[41] A recent study conducted in the United States also found that those with moderate or severe hepatic steatosis were 65% more likely to have a restrictive lung disease than those without steatosis. However, caution is needed in interpreting these findings because there are many environmental issues that may affect lung function. Nonetheless, combined with our results, further investigation is warranted into the link between NAFLD and lung disease; some have suggested that decreased lung function is related to an increase in low-grade inflammation associated with DM, CVD, and metabolic syndrome (all components also associated with NAFLD), suggesting that there is a pathobiological pathway between all disease entities.[42]

Our analysis found that across all ethnicities, CVD was the number one contributory cause of death among patients with NAFLD.[43-45] Among the top six contributory causes (CVD, DM, HTN, renal disease, lung disease, and neurological disorders), however, HTN had the highest AAPC (5.21%). This is an interesting finding and may help to decipher which components of metabolic syndrome have the most impact on NAFLD-related mortality and suggests that further study is needed, especially the impact of treating HTN and outcomes in patients with NAFLD.[45] In addition, many of the contributory causes of death are components of metabolic syndrome, which helps to confirm our prior work that reported an association between higher mortality and an increasing number of components of metabolic syndrome.[46]

Also of importance is that the death rate for adults with NAFLD is increasing significantly more in women than men.[3] Such a finding confirms another report that also found the mortality rate is increasing among women with NAFLD.[47] However, our study furthers this knowledge and notes that women encounter more deaths from cirrhosis when compared with men, suggestive that many women may have NASH rather than just NAFLD.[47-49] Furthermore, our work highlights that there is possibly a sex bias when diagnosing NAFLD and that attention should be directed toward educating the public and health care workers that women are at risk for NAFLD and its negative outcomes, including patient-reported outcomes and NAFLD-related mortality.

Finally, the results of our analysis for Hispanics and Asians represent another finding that may provide further insight into awareness of patients who may be at the highest risk for NAFLD-related mortality. Among Hispanics, Mexicans followed closely by Puerto Ricans accounted for the group with the most deaths among Hispanic adults with NAFLD. However, those aged ≥65 years, women, and Mexicans experienced a significantly increased mortality trend over the study period.[49] Therefore, public health outreach to educate these groups on their risk of this chronic liver disease as well as educating health care providers who deliver care to these populations must continue and may need to be further expanded to include a focus on these Hispanic subgroups.

Among non-Hispanic Asians with NAFLD, we found Vietnamese had the highest ASDR followed by Japanese. However, Asian Indians experienced a significant increase in their death rate trend, whereas

overall, Asians aged 45-54 years experienced a decreasing trend in their death rate.

We acknowledge limitations to this study. First, this study was conducted with a national database abstracted from death certification, which may not be accurate.[50] To our knowledge, the concordance between the underlying cause of death from death certificates and the leading cause of death among subjects with NAFLD had not been studied. Regardless of this inherent limitation of the NVSS database, this study provided us with the ability to understand nationally representative trends in mortality among NAFLD. Second, we restricted our analysis to NAFLD listed as the ICD-10 underlying or contributory cause of death codes on the death certification; therefore, true mortality rates for NAFLD might be underestimated. Because the coding of the underlying or contributory cause of death was not changed during the study period, we assumed something of a systematic underestimation of NAFLD mortality constant over time. Third, we relied on ICD codes to identify NAFLD and other diseases, but they can be miscoded, leading to either an undercoding or overcoding of the data we used. However, given the possibility for these coding errors in either direction, we feel that over time the miscoding balanced out so that there was neither a net gain nor a loss of data. Also, our extended definition of NAFLD including the ICD codes for cryptogenic cirrhosis may have led to an overestimation. However, NAFLD defined as the ICD-10 codes of K76.0 and K75.81 certainly underestimates the true prevalence of NAFLD. Our sensitivity analyses showed that trends in all-cause mortality due to NAFLD/NASH only and cryptogenic liver disease and cirrhosis both experienced a similar increasing trend. Therefore, we believe that our estimates of NAFLD in the United States reflect the true burden of this liver disease.

In summary, NAFLD-related deaths are increasing in the United States, especially among men, those aged ≥55 years, and non-Hispanic whites and Hispanics. However, attention must be drawn to the increasing rate of NAFLD-related deaths among women, non-Hispanic AIANs, Mexicans, and Asian Indians. Cirrhosis accounted for the majority of deaths, but CVD, DM, HCC, renal disease, lung disease, and HTN were all associated with the increase in deaths among adults with NAFLD, with HCC having the most significant increase in the trend for cause of death. Research efforts must continue to determine the best education, diagnostic, and treatment interventions as well as screening and surveillance guidelines in order to reverse this disease trajectory in addition to continuing endeavors investigating the mortality trends among adults with NAFLD.

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Supporting Information

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