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Original Article

Trends and demographic disparities in heart failure mortality rates in non-alcoholic fatty liver disease: a population-based retrospective study in the United States from 1999 to 2020

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Abstract: Objectives: This study aimed to analyze two decades heart failure (HF) mortality data in Non-Alcoholic Fatty Liver Disease (NAFLD), now known as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), in the United States (US), identifying patterns and disparities in mortality rates. Methods: A retrospective analysis was conducted using mortality data from the CDC WONDER database spanning 1999-2020. Age-adjusted mortality rates (AAMRs) per 1,000,000 persons were calculated, and trends were assessed using Average Annual Percentage Change (AAPC) and Annual Percent Change (APC) using Joinpoint 5.0.2. Data were stratified by year, sex, race/ethnicity, urbanization, and census regions. Results: From 1999-2020, 68,436 HF-related deaths occurred among US adults with NAFLD. The overall AAMR increased from 12.49 in 1999 to 24.30 in 2020, with an AAPC of 3.05 (95% CI: 2.80 to 3.31, P < 0.001), with a steep rise in AAMR from 2017-2020 and an APC of 12.35 (95% CI: 9.71 to 15.99). American Indian or Alaskan natives had the highest AAMRs (28.63), followed by Hispanics (20.05), and African Americans or Blacks (14.51). The highest mortality regionally was in the Southern region (AAMR: 16.05) and nonmetropolitan areas had higher AAMRs than metropolitan areas (16.63 vs. 13.76). Conclusions: This analysis demonstrated increasing mortality rates from HF in NAFLD, with a sharper increase in recent years. This also showed nonmetropolitan areas, the Southern region of the US, and minority populations had higher mortality rates, which highlights at-risk populations and opportunities for important public health interventions.

Keywords: Heart failure (HF), non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), healthcare disparities

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD), now known as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), is on the rise. NAFLD has become the most common cause of chronic liver disease worldwide and has been estimated to affect 25% of the global population and continues to increase [1, 2]. NAFLD refers to the presence of steatosis in greater than 5% of hepatocytes without significant alcohol exposure and is preferably detected via elastography or ultrasound [3]. When steatosis exists with hepatic inflammation the condition is termed Non-Alcoholic Steatohepatitis (NASH), which can present with elevated liver enzymes and lead to fibrosis, and is often asymptomatic until complications of cirrhosis develop if fibrosis progresses [3]. In 2024, resmetirom became an approved drug for various stages of fibrosis from NAFLD and can reverse fibrosis in ~25% of cases, though a total body weight loss of 10% has also shown to lead to a resolution in NASH in up to 90% of cases [4, 5]. The United

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States (US), which has the highest prevalence of overweight and obese individuals worldwide, is particularly impacted by NAFLD and is estimated to bear an annual cost of $103 billion from this condition alone [6, 7]. Projections estimate 100 million Americans will suffer from NAFLD by 2030 with no signs of improvement on the horizon given the epidemic of childhood obesity and diabetes [8].

While noting the increasing prevalence of NAFLD, parallel focus must be given to the heart, as adverse cardiovascular events are the leading cause of death in patients with liver disease [9]. HF has been repeatedly linked to NAFLD, as those with metabolic liver disease are 20% more likely to suffer from HF than those without [10]. NAFLD has been found to be an independent risk factor for diastolic dysfunction as well as a contributor to coronary disease which can further impact systolic function [11]. The pathophysiologic explanations of this linkage have largely been attributed to effects of metabolic disease, including the toxicity of lipid metabolism, inflammatory cascades from fatty deposition, and neurohormonal activation [11, 12].

Evidence suggests the burden of HF and NAFLD are not felt equally throughout the US. Lower household income, minority status, and South and West US regions have been shown to suffer from increased liver related mortality [7, 13]. In heart failure, minorities also suffer disproportionately, and these inequities are worsening rather than improving [14, 15]. However, data demonstrating population details of the specific impact of HF in NAFLD is limited and there remains a critical knowledge gap regarding the influence of demographic disparities on these mortality trends in the US. The aim of this study was to investigate the trends and disparities by sex, race, geography, and overall HF-related death in patients with NAFLD from 1999 to 2020.

Methods

Population and study setting

This comprehensive investigation used *the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER)* database to collect information from death certificates. The study focused on instances of persons with heart failure related mortality who held a concurrent diagnosis of NAFLD/NASH between the years 1999 to 2020. Inclusion criteria consisted of decedents aged 25 to 85 years whose death certificates included ICD-10 codes corresponding to both heart failure (I50.x) and NAFLD/NASH (K74.0, K74.6, K75.8, K76.0, K76.9) from the *10th version of the International Classification of Diseases and Related Health Problems (ICD-10)* [16-18]. Exclusion criteria included individuals outside this age range, and unrelated causes of mortality. The dataset comprises information regarding the causes of death from death certificates from all 50 states and the District of Columbia. At-death records from the Multiple Causes of Death Public Use registry were examined to find cases of NAFLD and HF. The research did not necessitate any approval from a regional institutional review board because it relied on deidentified public use data issued by the government. The *STROBE* standards for reporting observational research were followed in this study.

Data abstraction

NAFLD and HF-related deaths, population size, and location of death (including medical facilities [outpatient, emergency room, inpatient, death on arrival or status unknown], home, hospice, and nursing home/long-term care facility) were extracted. Demographics (sex, race and ethnicity, and age) and regional information (urban-rural and state) were extracted from 1999 to 2020. Races were defined as Non-Hispanic (NH) White, NH Black, Hispanic, Native American or Alaska Native, and NH Asian or Pacific Islander patients. These racial and ethnic categories have previously been used within analyses from the CDC WONDER database and rely on reported data on death certificates. Under the National Center for Health Statistics Urban-Rural Classification Scheme, the population was categorized into rural versus urban areas. Rural regions were defined as those with fewer than 50,000 people based on the 2013 U.S. Census. Urban areas were divided into medium/small metropolitan areas with a population ranging from 50,000 to 999,999, and large metropolitan areas claimed a population of 1 million or more. These areas were further divided into four main geographical categories: Northeast, Midwest, South, and West, using the United States Census Bureau.

Statistical analysis

Mortality rates per 1,000,000 individuals were computed for both crude and age-adjusted data across the period from 1999 to 2020 as the main indicators of trend. These rates were divided into categories by year, gender, race/ethnicity, state, and urban/rural status, with 95% confidence intervals (CIs). The crude mortality rates were determined by dividing the total number of HF-related deaths in patients with NAFLD by the corresponding U.S. population each year. *Age-adjusted mortality rates (AAMRs)* were calculated by standardizing HF-related deaths in NAFLD patients to the United States population in 2000. The annual percent change (APC) and its associated 95% CI in AAMR were calculated using the *Join-Point Regression Program (Version 5.0.2, National Cancer Institute).* This method identifies significant changes in AAMR over time by fitting a series of joined straight lines on a log scale where temporal variation occurred. The Joinpoint regression statistical software was set to determine a maximum of 3 Joinpoints (21 years of analysis were included) where significant temporal variation existed in the trend. APCs with 95% CI for the AAMR were calculated at the identified line segments linking Joinpoints using the Monte Carlo permutation test. The weighted average of the APCs was calculated and reported as average APCs (AAPCs) and corresponding 95% CIs as a summary of the reported mortality trend for the entire study period. APC was classified as increasing or decreasing based on whether the slope reflected changes in mortality significantly differed from zero when assessed via two-tailed t-testing at a significance level of $P < 0.05$.

Results

Overall and annual trends for HF-related AAMR in NAFLD

From 1999 to 2020, HF was reported as a contributing cause for 68,436 deaths among adults with NAFLD aged 25 and older in the United States (Supplementary Data). The overall AAMR for HF-related deaths in NAFLD ranged between 12.49 (95% CI 11.97 to 13.01) per 1 million individuals in 1999 to 24.30 (95% CI 23.71 to 24.9) per 1 million individuals in 2020 (**Figure 1A**), with an Average Annual Percentage Change (AAPC) of 3.05 (95% CI 2.80-3.31) (p value < 0.001). AAMR experienced an initial decline from 1999 to 2010 (APC: -1.49, 95% CI -2.23 to -0.89) (p value = 0.003), followed by a notable upward slope from 2010 to 2017 (APC: 6.58, 95% CI 3.92 to 7.86) (p value = 0.01) and a drastic rise from 2017 to 2020 (APC 12.35, 95% CI 9.71 to 15.99) (p value < 0.001).

HF-related AAMR in NAFLD stratified by sex

HF in NAFLD resulted in 40,777 deaths in the male population in the last two decades while 27,659 deaths were reported in the female population. Adult males exhibited higher overall AAMRs consistently over the study period compared to adult females (overall AAMR for males: 19.33, 95% CI: 19.14 to 19.52; for females: 10.26, 95% CI: 10.14 to 10.38). The AAMRs of both male and female cohorts increased in the two decades with a more prominent rise in females [Males: AAPC: 2.72, 95% CI: 2.46 to 2.99 (p value < 0.001); Females: AAPC: 3.27, 95% CI: 2.90 to 3.67 (p value < 0.001)] (**Figure 1B**).

The AAMR for adult males decreased steadily from 17.24 (95% CI: 16.28 to 18.19) in 1999 to 15.30 (95% CI: 14.50 to 16.11) in 2010 (APC: -1.80; 95% CI: -2.59 to -1.11) (p value = 0.02), succeeded by a substantial increase to 23.09 by 2017 (APC: 6.66; 95% CI: -0.3 to 7.68) (p value = 0.055); and a sharp incline to 31.29 in 2020 (APC: 10.93; 95% CI: 8.24 to 14.34) (p value < 0.001). Similarly, the AAMR for adult females, decreased from 8.87 in 1999 to 7.56 in 2009 (APC: -1.60; 95% CI: -3.31 to -0.59) (p value < 0.006), followed by an increase to 11.49 by 2016 (APC: 5.18; 95% CI: 1.73 to 7.48) (p value < 0.01) and a steep ascent to 18.54 by 2020 (APC: 12.85; 95% CI: 10.09 to 18.57) (p value < 0.001).

HF-related AAMR in NAFLD stratified by race/ethnicity

Pronounced differences were found when examining deaths among different racial/ethnic groups. The highest number of deaths occurring in Non-Hispanic (NH) White individuals (51,581; 75.4%), followed by Hispanic individuals (7,468; 10.9%), NH Black individuals (6,956; 10.2%), NH Asian or Pacific Islanders (1,455; 2.1%), and the lowest number was in

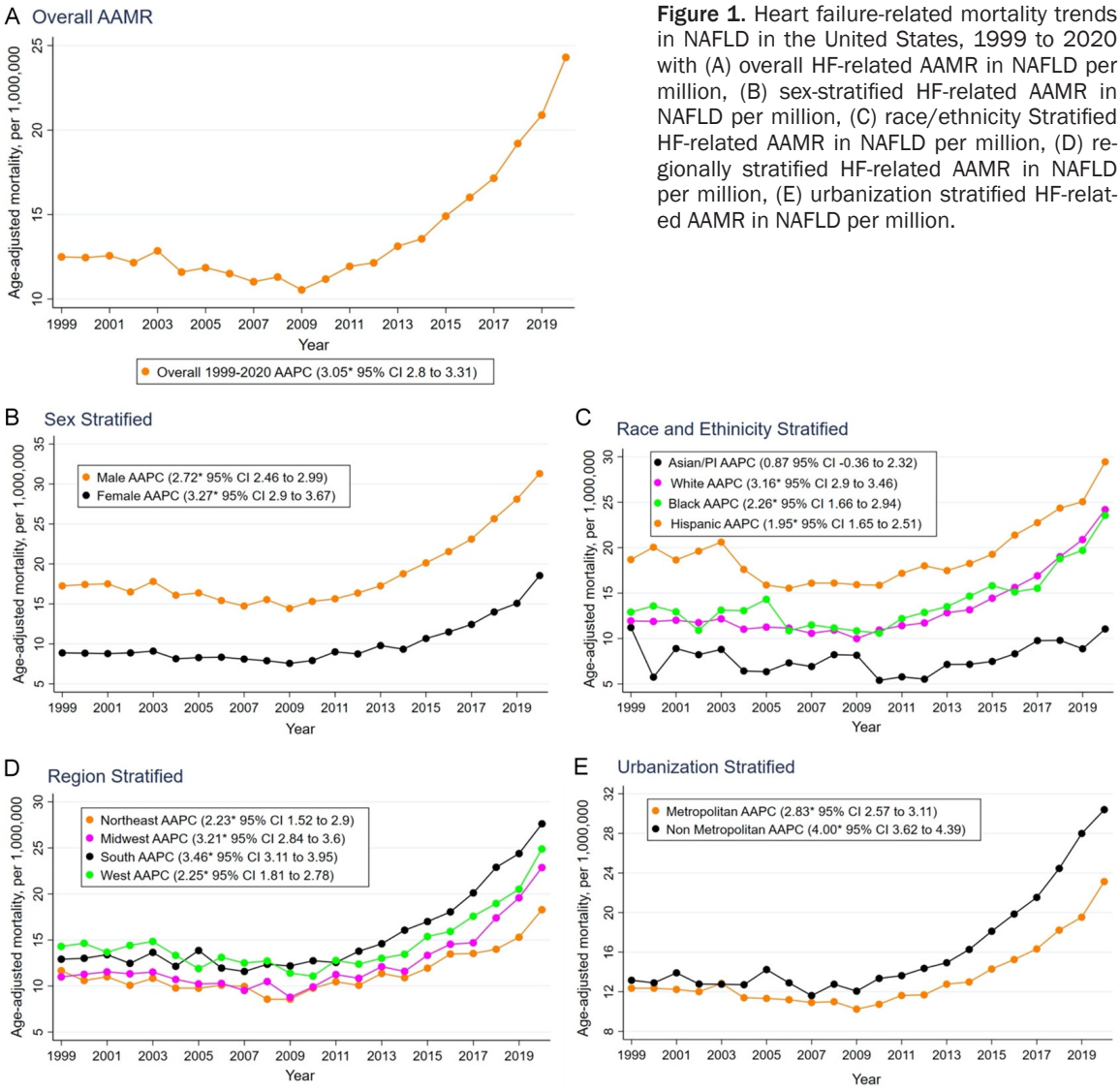

Figure 1. Heart failure-related mortality trends in NAFLD in the United States, 1999 to 2020 with (A) overall HF-related AAMR in NAFLD per million, (B) sex-stratified HF-related AAMR in NAFLD per million, (C) race/ethnicity Stratified HF-related AAMR in NAFLD per million, (D) regionally stratified HF-related AAMR in NAFLD per million, (E) urbanization stratified HF-related AAMR in NAFLD per million.

NH American Indian or Alaska Native individuals (807; 1.2%). AAMRs were highest among NH American Indian or Alaska Natives, followed by Hispanic or Latinos, NH Black or African Americans, NH Whites, and NH Asian or Pacific Islander populations (overall AAMR: NH American Indian or Alaska Native: 28.63, 95% CI: 26.56 to 30.7; Hispanic or Latino: 20.05, 95% CI: 19.57 to 20.52; NH Black or African American: 14.51, 95% CI: 14.16-14.86; NH White: 13.71, 95% CI: 13.59 to 13.83; NH Asian or Pacific Islander: 8.02, 95% CI: 7.60 to 8.44).

The AAMR of all the races increased to variable degrees from 1999 to 2020, with the incline most pronounced in NH White cohort [NH White: AAPC: 3.16, 95% CI: 2.90 to 3.46 (p value < 0.001); NH Black: AAPC: 2.26, 95% CI: 1.66 to 2.94 (p value < 0.001); Hispanic: AAPC: 1.95 95% CI: 1.65 to 2.51 (p value < 0.001); NH Asian or Pacific Islander: AAPC: 0.87, 95% CI: -0.36 to 2.32) (p value = 0.13)] (**Figure 1C**). Trend analysis of NH American Indian or Alaskan Native was not possible due to unreliable data.

HF-related AAMR in NAFLD stratified by geography

Disparities in AAMRs were observed among different states, with AAMRs ranging from as low as 9.23 (95% CI: 8.89 to 9.57) in New York to 25.08 (95% CI: 23.39 to 26.77) in West Virginia. States falling within the top 90th per-

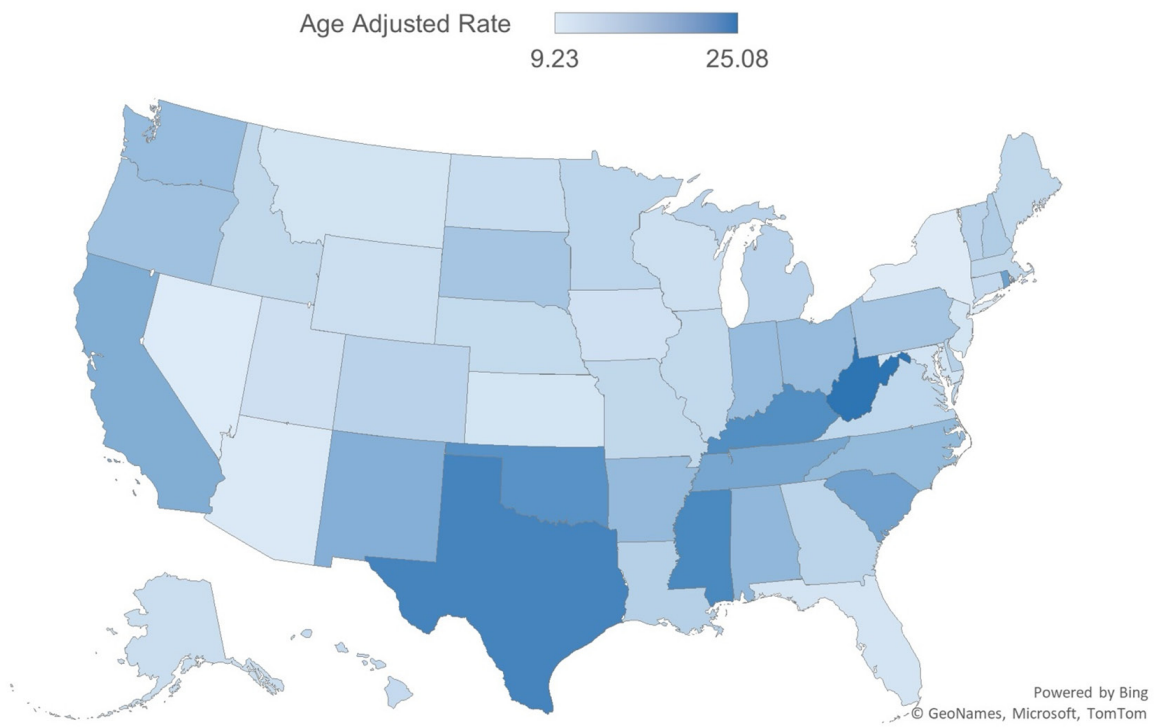

Figure 2. State-Stratified HF-related AAMRs in NAFLD per 1,000,000 in the United States from 1999 to 2020.

centile included West Virginia, Texas (23.04), Mississippi (22.46), Kentucky (21.62), and Oklahoma (21.19), while states in the lower 10th percentile included New York, Nevada (9.34), Arizona (9.48), Florida (10.11) and District of Columbia (10.14) (**Figure 2**).

For the census regions, highest mortality rates were observed in the South (16.05, 95% CI: 15.86 to 16.24), followed by the West (15.07, 95% CI: 14.83 to 15.30), Midwest (12.73, 95% CI: 12.52 to 12.94), and Northeast (11.53, 95% CI: 11.31 to 11.75). The AAMRs of all regions increased over the course of the study with greatest rise in the South [South: AAPC: 3.46, 95% CI: 3.11 to 3.95 (p value < 0.001); Midwest: AAPC: 3.21, 95% CI: 2.84 to 3.60 (p value < 0.001); West: AAPC: 2.25, 95% CI: 1.81 to 2.78 (p value < 0.001); Northeast: AAPC: 2.23, 95% CI: 1.52 to 2.90 (p value < 0.001)] (**Figure 1D**).

Regarding urbanization, nonmetropolitan areas exhibited higher AAMRs than metropolitan areas throughout the study period, with overall AAMRs of 16.63 (95% CI: 16.35 to 16.91) and 13.76 (95% CI: 13.64 to 13.88), respectively. The AAMR of both, Metropolitan and Nonmetropolitan areas increased from 1999 to 2020, with a greater increase in Nonmetropolitan areas [Nonmetropolitan: AAPC: 4.00, 95% CI: 3.62 to 4.39 (p value < 0.001); Metropolitan: AAPC: 2.83, 95% CI: 2.57 to 3.11 (p value < 0.001)] (**Figure 1E**).

Discussion

This analysis showed a concerning increase in HF-related mortality in NAFLD patients across recent years. Trends demonstrated significant gender, racial (**Figure 3**), and geographic disparities in HF mortality. Higher mortality rates were seen in males, though with a steeper increase in females, in non-metropolitan areas, the southern US, and in minorities, specifically with Non-Hispanic Alaska Natives and Hispanics experiencing the highest mortality rates.

Overall trends

In this study, the overall AAMR for HF deaths in those with NAFLD decreased from 1999 to 2010 but showed an increase from 2010 to 2017 and a sharp rise from 2017 to 2020. This initial decline in mortality could be attributed to several factors, including improvement in

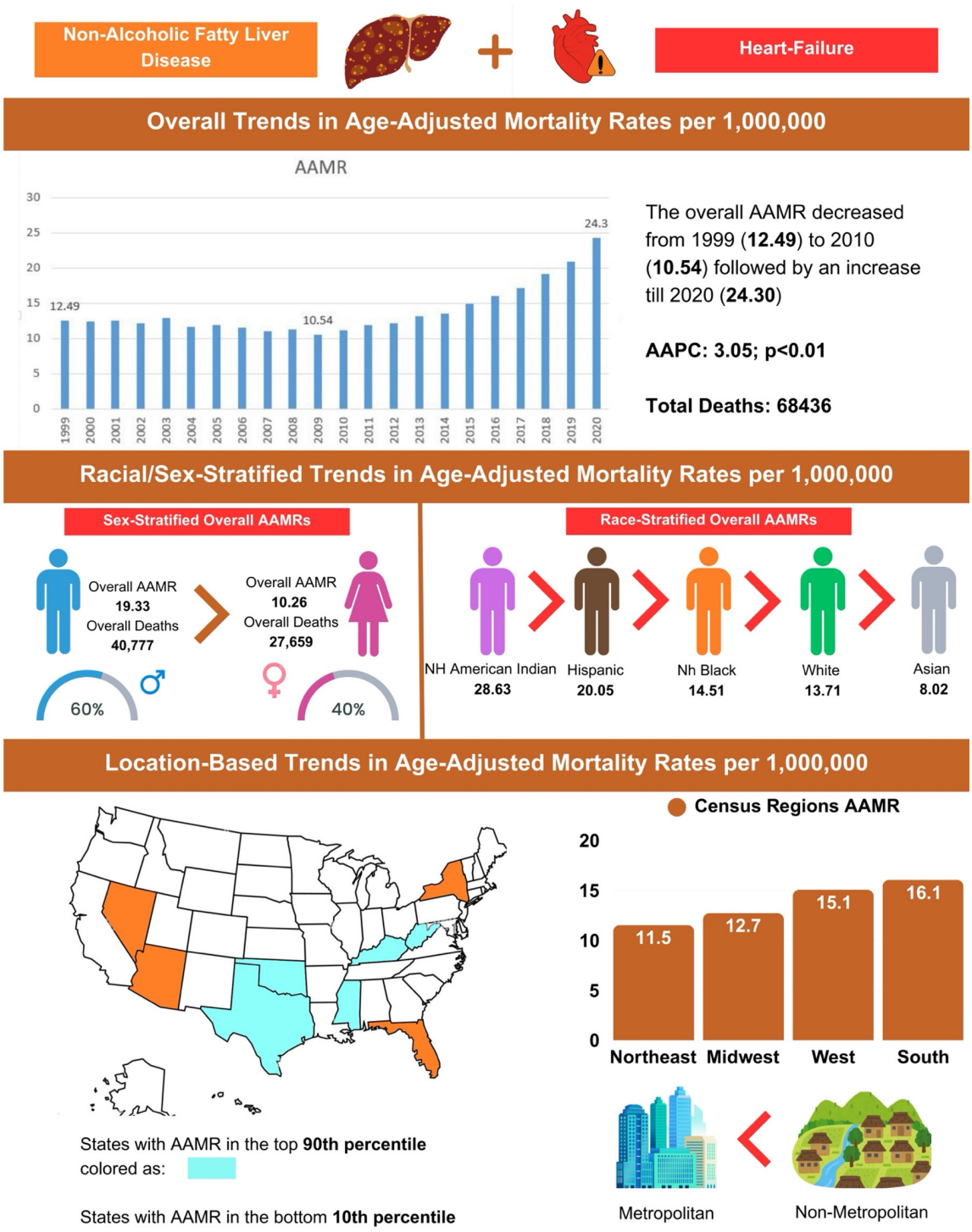

Figure 3. CENTRAL ILLUSTRATION: Demographic profiles of heart failure-related mortality among adults with NAFLD Aged 25 to 85+ in the United States, 1999 to 2020.

healthcare resources, improved detection of clinically significant liver disease, more effective antihypertensive and lipid lowering medications, and public health efforts such as limiting tobacco use. Similar studies on HF mortality trends in the US have suggested the latter exacerbation of mortality, however, can likely be attributed to impacts of the worsening obe-

sity epidemic and metabolic dysfunction [14]. These metabolic risk factors, including insulin resistance and impaired glucose and lipid metabolism, are primary contributors to cardiometabolic disease, and result in decreased myocardial energy metabolism leading to cardiac dysfunction [19-21]. Particular attention should be given to 2020, the peak of mortality in our study, in which the impact of COVID-19 must be considered as the virus' severity and outcomes was worse in obese individuals [7, 11].

Disparities by sex

Our study showed a higher AAMR for HF-related deaths in those with NAFLD in males compared to females, though with a steeper increase in the rates of female deaths. This is concordant with prior studies which found lifetime risk of HF and HF mortality to be higher in men than women. Cardiometabolic risk factors are a necessary link between these two diseases and can be further affected hormonally, as, for example, estrogen production can impact lipid metabolism and possibly lead to reduction of cardiac fibrosis in females [22]. The increasing rates of female mortality are notable, as evidence has found diabetes to be more strongly associated with HF in women than in men, planting a logical hypothesis that the obesity epidemic could disproportionately afflict women in relation to HF [23].

Disparities by race and ethnicity

The results of our study show a racial gap in HF-NAFLD mortality, with Non-Hispanic (NH) American Indian or Alaska Native individuals suffering from the highest mortality rates followed by other minorities. This correlates with prior demographic data in both hepatic and cardiac literature. Higher rates of liver-related mortality are reported in minorities, with the highest prevalence of NAFLD in Hispanic populations, and HF prevalence and mortality more heavily impact those who identify as American Indian, African American, or Hispanic [7, 24, 25]. An American Heart Association 2020 report echoed similar findings, showing the highest HF-related mortality rates in African American men [26]. A likely culprit for these racial disparities could be social determinants of health, as low socioeconomic status has been found to be independently associated with inpatient HF-related mortality [25, 27]. These factors include socioeconomic position, social support, reduced access to healthcare, poor residential environments, and food deserts - all of which have a negative association with HF morbidity and mortality [25].

Geographic disparities

Our study found that mortality events were highest in the Southern and non-metropolitan areas. In terms of geographical presentation, the South exhibited the highest mortality followed by the West, a trend also elicited when studying regional tendencies in liver disease mortality [13]. Furthermore, states across the US have also shown variation in NAFLD and HF mortality. The states in the top 90th percentile were West Virginia, Texas, Mississippi, Kentucky, and Oklahoma; while the states in the bottom 10th percentile were New York, Nevada, Arizona, Florida, and District of Columbia. Prior data has also demonstrated that from 1999-2017 the South and Midwest regions had higher HF AAMRs than other geographic regions, most notably Oklahoma and Mississippi [22]. This geographic disparity has been so historically prevalent, the southern states have at times been referred to as "the Heart Failure Belt" though this has been contested, with recent trends showing mortality may be more closely linked to urbanization than region [28]. When studying population density in relation to HF, rural counties have consistently been found to have higher mortality rates compared to urban counties [29]. Ultimately, the variation in public health investment and infrastructure, lack of access to both primary and specialty care in rural areas, and sociodemographic factors, and sociocultural attitudes all influence these disparities observed among regions and states [13, 29].

Limitations

Several limitations should be acknowledged in this study. Firstly, reliance on the CDC WONDER database introduces potential errors or omissions in the data. Moreover, the study's focus on individuals aged 25 and older may overlook variations in younger age groups, potentially biasing trend interpretations. The lack of detailed clinical data, such as biomarkers, treatment modalities, and interventions inhibits comprehensive understanding of mortality driv-

ers. The absence of granular analyses for distinct cases of NAFLD and HF further complicates causal inference, hindering targeted investigations. Furthermore, socioeconomic factors, which can profoundly influence health outcomes, were not accounted for in this study.

Conclusion

Main conclusion

HF-related mortality in patients with NAFLD, now known as MASLD, has increased from 1999 to 2020. Most notably, our study underscores a significant recent mortality increase from 2017 to 2020. Particularly high mortality rates were observed among NH American Indians or Alaska Natives, residents in the Southern US regions, and in non-metropolitan areas. HF in NAFLD significantly impacts cost and mortality for Americans and is a serious healthcare problem with a worsening trajectory. This data shows the disparities felt by Americans with these conditions and understanding these disparities is essential for guiding healthcare policies and developing targeted public health interventions to better serve at-risk populations.

Future studies

Future work on this subject should continue to focus on connections and interventions involving the interrelatedness of NAFLD and HF. As treatment options increase for metabolic disease, such as the use of glucagon-like peptide-1 receptor agonists, these mortality trends should continue to be studied to monitor for population level impacts.

Disclosure of conflict of interest

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Abbreviations

HF, Heart Failure; NAFLD, Non-Alcoholic Fatty Liver Disease; NASH, Non-Alcoholic Steatohepatitis; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; AAMRs, Age-adjusted mortality rates; AAPC, Average Annual Percentage Change; APC, Annual Percent Change; CDC WONDER, the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research; NH, Non-Hispanic.

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Supplementary Data

Supplementary Table 1. Number of NAFLD and HF-related deaths, stratified by sex and race in adults in the United States 1999-2020

Year	Overall	Women	Men	NH White	NH Black or African American	NH Asian or Pacific Islander	NH American Indian or Alaska Native	Hispanic or Latino	Population
1999	2214	919	1295	1754	205	48	25	175	180408769
2000	2230	917	1313	1758	224	23	18	200	181984640
2001	2288	930	1358	1797	219	41	21	203	184305128
2002	2255	947	1308	1772	193	41	19	222	186208028
2003	2421	983	1438	1861	237	48	28	242	188090429
2004	2232	895	1337	1709	243	34	24	217	190205384
2005	2321	919	1402	1771	274	37	17	215	192551384
2006	2288	942	1346	1774	213	51	29	215	195019359
2007	2240	929	1311	1705	236	45	25	228	197403777
2008	2350	924	1426	1792	232	60	23	240	199795090
2009	2242	898	1344	1670	233	59	28	249	202107016
2010	2416	964	1452	1861	234	42	24	253	203891983
2011	2627	1107	1520	1951	275	49	35	309	206592936
2012	2761	1105	1656	2059	301	50	22	322	208826037
2013	3052	1269	1783	2294	322	67	30	333	211085314
2014	3230	1227	2003	2381	353	73	28	384	213809280
2015	3639	1443	2196	2681	394	82	62	410	216553817
2016	4002	1595	2407	2964	402	95	47	482	218641417
2017	4387	1746	2641	3251	414	114	56	542	221447331
2018	5023	2000	3023	3710	517	125	65	596	223311190
2019	5589	2212	3377	4180	559	118	81	635	224981167
2020	6629	2788	3841	4886	676	153	100	796	226635013
Total	68436	27659	40777	51581	6956	1455	807	7468	4473854489

Supplementary Table 2. Annual Percent Change (APC) and Average Annual Percent Change (AAPC) of NAFLD and HF-related age-adjusted mortality rates per 1,000,000 in adults in the United States 1999-2020

Year Interval	APC (95% CI)	Year Interval	AAPC (95% CI)
Overall			
1999-2010	-1.49* (-2.23 to -0.89)	1999-2020	3.05* (2.8 to 3.31)
2010-2017	6.58* (3.92 to 7.86)		
2017-2020	12.35* (9.71 to 15.99)		
Men			
1999-2010	-1.8* (-2.59 to -1.11)	1999-2020	2.72* (2.46 to 2.99)
2010-2017	6.66 (-0.3 to 7.68)		
2017-2020	10.93* (8.24 to 14.34)		
Women			
1999-2009	-1.6* (-3.31 to -0.59)	1999-2020	3.27* (2.9 to 3.67)
2009-2016	5.18* (1.73 to 7.48)		
2016-2020	12.85* (10.09 to 18.57)		

NH White			
1999-2009	-1.68* (-2.89 to -0.91)	1999-2020	3.16* (2.9 to 3.46)
2009-2015	5.06* (1.54 to 7.32)		
2015-2020	11.11* (9.58 to 14.77)		
NH Asian or Pacific Islander			
1999-2012	-2.91* (-8.42 to -0.21)	1999-2020	0.87 (-0.36 to 2.32)
2012-2020	7.32* (3.81 to 16.75)		
NH Black or African American			
1999-2010	-1.95* (-4 to -0.33)	1999-2020	2.26* (1.66 to 2.94)
2010-2020	7.09* (5.7 to 9.15)		
Hispanic or Latino			
1999-2003	1.1 (-1.42 to 7.38)	1999-2020	1.95* (1.65 to 2.51)
20003-2006	-8.42* (-10.73 to -3.76)		
2006-2014	2.19* (0.55 to 4.29)		
2014-2020	7.84* (6.6 to 10.27)		
Census Region 1 - Northeast			
1999-2009	-2.26 (-7.47 to 6.81)	1999-2020	2.23* (1.52 to 2.9)
2009-2018	5.08 (-8.04 to 9.52)		
2018-2020	13.02* (5.23 to 18.29)		
Census Region 2 - Midwest			
1999-2009	-2.08* (-3.3 to -1.09)	1999-2020	3.21* (2.84 to 3.6)
2009-2017	5.69* (3.61 to 7.31)		
2017-2020	15.47* (11.52 to 21.57)		
Census Region 3 - South			
1999-2011	-0.61 (-1.79 to 0.43)	1999-2020	3.46* (3.11 to 3.95)
2011-2020	9.16* (8.09 to 10.82)		
Census Region 4 - West			
1999-2012	-1.79* (-3.01 to -0.79)	1999-2020	2.25* (1.81 to 2.78)
2012-2020	9.16* (7.64 to 11.43)		
Metropolitan			
1999-2010	-1.65* (-2.41 to -1.03)	1999-2020	2.83* (2.57 to 3.11)
2010-2017	6.26* (3.8 to 7.51)		
2017-2020	12.16* (9.49 to 16.06)		
Non-Metropolitan			
1999-2009	-0.77 (-3.27 to 0.25)	1999-2020	4.00* (3.62 to 4.39)
2009-2014	5.21* (0.5 to 9.1)		
2014-2020	11.37* (9.96 to 15.16)		

*indicates statistically significant value ($P < 0.05$).

Supplementary Table 3. NAFLD and HF-related age-adjusted mortality rates per 1,000,000, stratified by race in adults in the United States 1999-2020

Age-Adjusted Rate (95% CI)					
Year	NH White	NH Black or African American	NH American Indian or Alaska Native	Hispanic or Latino	NH Asian or Pacific Islander
1999	11.94 (11.38-12.5)	12.9 (11.11-14.69)	28.01 (17.76-42.04)	18.68 (15.77-21.59)	11.21 (8.11-15.1)
2000	11.87 (11.31-12.42)	13.57 (11.77-15.37)	Unreliable (11.56-32.85)	20.04 (17.12-22.95)	5.75 (3.56-8.78)
2001	12.01 (11.45-12.56)	12.93 (11.19-14.67)	20.18 (11.96-31.9)	18.64 (15.95-21.33)	8.9 (6.29-12.21)
2002	11.74 (11.19-12.28)	10.9 (9.34-12.46)	Unreliable (10.82-30.74)	19.61 (16.89-22.33)	8.22 (5.79-11.33)
2003	12.16 (11.61-12.72)	13.11 (11.4-14.81)	27.23 (17.45-40.52)	20.6 (17.86-23.33)	8.8 (6.39-11.81)

2004	11.02 (10.49-11.54)	13.06 (11.38-14.74)	24.29 (14.84-37.52)	17.6 (15.14-20.06)	6.43 (4.4-9.08)
2005	11.25 (10.73-11.78)	14.3 (12.57-16.04)	Unreliable (7.84-23.11)	15.88 (13.63-18.13)	6.35 (4.43-8.84)
2006	11.14 (10.62-11.66)	10.86 (9.36-12.35)	27.89 (18.05-41.17)	15.53 (13.35-17.71)	7.32 (5.38-9.73)
2007	10.57 (10.06-11.07)	11.48 (9.98-12.99)	20.37 (12.77-30.84)	16.09 (13.89-18.28)	6.92 (4.99-9.35)
2008	10.92 (10.41-11.43)	11.15 (9.68-12.63)	19.16 (11.7-29.59)	16.1 (13.96-18.23)	8.22 (6.21-10.68)
2009	9.98 (9.49-10.46)	10.83 (9.39-12.26)	23.06 (14.78-34.32)	15.92 (13.85-17.99)	8.16 (6.17-10.6)
2010	10.93 (10.43-11.43)	10.59 (9.18-11.99)	20.69 (12.81-31.63)	15.86 (13.82-17.9)	5.4 (3.86-7.36)
2011	11.41 (10.9-11.93)	12.18 (10.69-13.67)	28.93 (19.66-41.07)	17.17 (15.17-19.18)	5.78 (4.23-7.71)
2012	11.71 (11.19-12.22)	12.86 (11.36-14.37)	16.05 (9.8-24.79)	18 (15.95-20.04)	5.53 (4.08-7.33)
2013	12.83 (12.3-13.36)	13.5 (11.98-15.03)	21.93 (14.45-31.9)	17.47 (15.52-19.42)	7.15 (5.51-9.14)
2014	13.15 (12.61-13.69)	14.66 (13.08-16.24)	19.19 (12.42-28.33)	18.25 (16.35-20.16)	7.16 (5.58-9.05)
2015	14.43 (13.88-14.99)	15.8 (14.18-17.41)	38.77 (29.37-50.24)	19.26 (17.32-21.2)	7.48 (5.92-9.32)
2016	15.61 (15.04-16.18)	15.12 (13.59-16.65)	28.53 (20.65-38.43)	21.38 (19.39-23.36)	8.32 (6.71-10.21)
2017	16.9 (16.31-17.49)	15.51 (13.96-17.05)	34.5 (25.76-45.24)	22.74 (20.75-24.72)	9.77 (7.94-11.59)
2018	19 (18.38-19.63)	18.78 (17.12-20.45)	37.32 (28.48-48.04)	24.35 (22.33-26.38)	9.8 (8.05-11.54)
2019	20.88 (20.23-21.53)	19.68 (18.01-21.36)	46.4 (36.56-58.08)	25.05 (23.04-27.07)	8.87 (7.25-10.5)
2020	24.18 (23.49-24.87)	23.54 (21.71-25.36)	55.62 (44.37-66.86)	29.44 (27.33-31.56)	11.05 (9.28-12.82)
Total	13.71 (13.59-13.83)	14.51 (14.16-14.86)	28.63 (26.56-30.7)	20.05 (19.57-20.52)	8.02 (7.6-8.44)

Supplementary Table 4. Overall and sex-stratified NAFLD and HF-related age-adjusted mortality rates per 1,000,000 in adults in the United States 1999-202

Age-Adjusted Rate (95% CI)			
Year	Men	Women	Overall
1999	17.24 (16.28-18.19)	8.87 (8.3-9.45)	12.49 (11.97-13.01)
2000	17.42 (16.46-18.38)	8.83 (8.26-9.41)	12.45 (11.93-12.97)
2001	17.5 (16.55-18.44)	8.78 (8.22-9.35)	12.56 (12.04-13.07)
2002	16.49 (15.58-17.4)	8.87 (8.31-9.44)	12.15 (11.65-12.65)
2003	17.79 (16.85-18.72)	9.09 (8.52-9.66)	12.85 (12.34-13.36)
2004	16.08 (15.21-16.96)	8.14 (7.61-8.68)	11.59 (11.11-12.07)
2005	16.37 (15.5-17.24)	8.28 (7.74-8.82)	11.85 (11.36-12.33)
2006	15.41 (14.58-16.25)	8.33 (7.8-8.87)	11.5 (11.03-11.97)
2007	14.73 (13.92-15.54)	8.1 (7.58-8.63)	11.02 (10.56-11.48)
2008	15.53 (14.71-16.35)	7.89 (7.38-8.4)	11.3 (10.84-11.76)
2009	14.42 (13.64-15.21)	7.56 (7.06-8.06)	10.54 (10.1-10.98)
2010	15.3 (14.5-16.11)	7.91 (7.41-8.42)	11.18 (10.73-11.63)
2011	15.63 (14.83-16.43)	9 (8.46-9.54)	11.93 (11.47-12.39)
2012	16.35 (15.55-17.15)	8.74 (8.21-9.26)	12.14 (11.68-12.6)
2013	17.25 (16.44-18.07)	9.79 (9.25-10.34)	13.12 (12.65-13.59)
2014	18.76 (17.92-19.6)	9.33 (8.8-9.86)	13.56 (13.09-14.03)
2015	20.12 (19.26-20.98)	10.67 (10.11-11.23)	14.9 (14.41-15.39)
2016	21.53 (20.65-22.41)	11.49 (10.92-12.06)	16.01 (15.5-16.51)
2017	23.09 (22.19-23.99)	12.43 (11.84-13.03)	17.15 (16.64-17.67)
2018	25.64 (24.71-26.57)	13.99 (13.37-14.62)	19.2 (18.66-19.74)
2019	28.09 (27.12-29.05)	15.07 (14.43-15.71)	20.88 (20.32-21.43)
2020	31.29 (30.28-32.29)	18.54 (17.84-19.25)	24.3 (23.71-24.9)
Total	19.33 (19.14-19.52)	10.26 (10.14-10.38)	14.26 (14.15-14.37)

Supplementary Table 5. NAFLD and HF-related age-adjusted mortality rate per 1,000,000 stratified by census region in adults in the United States 1999-2020

Age-Adjusted Rate (95% CI)				
Year	Northeast	Midwest	South	West
1999	11.66 (10.56-12.76)	10.98 (9.98-11.99)	12.91 (12.02-13.8)	14.29 (13.05-15.53)
2000	10.59 (9.55-11.63)	11.27 (10.25-12.28)	13.01 (12.12-13.9)	14.63 (13.39-15.87)
2001	11 (9.94-12.06)	11.53 (10.51-12.55)	13.4 (12.51-14.3)	13.66 (12.47-14.84)
2002	10.07 (9.06-11.07)	11.32 (10.31-12.32)	12.46 (11.61-13.32)	14.4 (13.2-15.6)
2003	10.83 (9.79-11.88)	11.51 (10.51-12.52)	13.65 (12.77-14.54)	14.83 (13.62-16.04)
2004	9.77 (8.78-10.75)	10.71 (9.75-11.67)	12.14 (11.32-12.96)	13.32 (12.19-14.45)
2005	9.75 (8.77-10.72)	10.22 (9.29-11.16)	13.86 (12.99-14.73)	11.88 (10.83-12.93)
2006	10.08 (9.09-11.08)	10.28 (9.35-11.22)	11.95 (11.15-12.75)	13.1 (12-14.2)
2007	9.95 (8.97-10.93)	9.51 (8.62-10.4)	11.58 (10.8-12.36)	12.49 (11.43-13.55)
2008	8.56 (7.66-9.46)	10.48 (9.55-11.41)	12.36 (11.57-13.16)	12.71 (11.65-13.77)
2009	8.56 (7.66-9.45)	8.77 (7.92-9.61)	12.18 (11.4-12.96)	11.39 (10.4-12.38)
2010	9.76 (8.81-10.71)	9.89 (9-10.79)	12.74 (11.95-13.53)	11.06 (10.09-12.03)
2011	10.46 (9.48-11.44)	11.24 (10.29-12.18)	12.56 (11.79-13.34)	12.76 (11.73-13.79)
2012	10.07 (9.12-11.02)	10.83 (9.91-11.76)	13.78 (12.98-14.58)	12.37 (11.38-13.37)
2013	11.36 (10.35-12.37)	12.09 (11.13-13.05)	14.59 (13.78-15.4)	13 (12-14)
2014	10.9 (9.91-11.88)	11.58 (10.64-12.52)	16.06 (15.22-16.91)	13.44 (12.44-14.44)
2015	11.93 (10.92-12.94)	13.33 (12.33-14.34)	17 (16.14-17.85)	15.36 (14.3-16.42)
2016	13.47 (12.39-14.54)	14.53 (13.5-15.57)	18.05 (17.18-18.92)	15.91 (14.85-16.97)
2017	13.53 (12.46-14.6)	14.69 (13.67-15.72)	20.11 (19.2-21.02)	17.57 (16.47-18.67)
2018	13.99 (12.91-15.06)	17.39 (16.28-18.5)	22.89 (21.93-23.85)	18.95 (17.82-20.08)
2019	15.29 (14.18-16.39)	19.57 (18.41-20.72)	24.39 (23.42-25.37)	20.5 (19.34-21.66)
2020	18.28 (17.07-19.49)	22.86 (21.6-24.12)	27.62 (26.6-28.64)	24.87 (23.6-26.13)
Total	11.53 (11.31-11.75)	12.73 (12.52-12.94)	16.05 (15.86-16.24)	15.07 (14.83-15.3)

Supplementary Table 6. NAFLD and HF related age-adjusted mortality rates per 1,000,000 in the metropolitan and non-metropolitan areas in adults in the United States 1999-2020

Age-Adjusted Rate (95% CI)		
Year	Metropolitan	Nonmetropolitan
1999	12.35 (11.78-12.93)	13.16 (11.92-14.4)
2000	12.35 (11.78-12.92)	12.9 (11.68-14.13)
2001	12.23 (11.67-12.79)	13.91 (12.64-15.17)
2002	12 (11.45-12.55)	12.78 (11.57-13.98)
2003	12.84 (12.28-13.41)	12.76 (11.55-13.96)
2004	11.39 (10.86-11.91)	12.71 (11.51-13.9)
2005	11.32 (10.8-11.85)	14.24 (12.99-15.49)
2006	11.19 (10.68-11.71)	12.9 (11.72-14.08)
2007	10.91 (10.41-11.42)	11.61 (10.49-12.73)
2008	10.99 (10.49-11.49)	12.76 (11.6-13.92)
2009	10.24 (9.77-10.72)	12.06 (10.94-13.18)
2010	10.73 (10.24-11.22)	13.35 (12.18-14.52)
2011	11.62 (11.12-12.12)	13.63 (12.45-14.8)
2012	11.68 (11.19-12.18)	14.36 (13.16-15.55)
2013	12.76 (12.25-13.27)	14.93 (13.71-16.16)
2014	12.98 (12.47-13.49)	16.27 (15.01-17.53)
2015	14.29 (13.76-14.82)	18.11 (16.79-19.44)

2016	15.25 (14.71-15.79)	19.85 (18.47-21.23)
2017	16.32 (15.77-16.87)	21.53 (20.1-22.96)
2018	18.22 (17.64-18.79)	24.46 (22.94-25.99)
2019	19.53 (18.94-20.12)	27.99 (26.38-29.6)
2020	23.13 (22.5-23.77)	30.4 (28.74-32.06)
Total	13.76 (13.64-13.88)	16.63 (16.35-16.91)

Supplementary Table 7. NAFLD and HF-related age-adjusted mortality rates per 1,000,000, stratified by states in adults in the United States 1999-2020

State	Age-Adjusted Rate (95% CI)
Alabama	16.18 (15.27-17.08)
Alaska	11.04 (8.67-13.86)
Arizona	9.48 (8.88-10.09)
Arkansas	15.78 (14.64-16.91)
California	17.54 (17.17-17.9)
Colorado	12.5 (11.65-13.35)
Connecticut	11.61 (10.74-12.47)
Delaware	12.86 (11.03-14.69)
District of Columbia	10.14 (8.12-12.51)
Florida	10.11 (9.78-10.44)
Georgia	12.35 (11.73-12.97)
Hawaii	11.46 (10.05-12.86)
Idaho	11.82 (10.4-13.24)
Illinois	11.72 (11.24-12.21)
Indiana	15.5 (14.72-16.27)
Iowa	10.66 (9.77-11.55)
Kansas	10.23 (9.29-11.17)
Kentucky	21.62 (20.51-22.73)
Louisiana	12.84 (11.99-13.7)
Maine	11.93 (10.56-13.3)
Maryland	10.3 (9.61-10.98)
Massachusetts	12.06 (11.4-12.72)
Michigan	12.39 (11.84-12.93)
Minnesota	12.21 (11.44-12.97)
Mississippi	22.46 (21.07-23.85)
Missouri	11.86 (11.18-12.55)
Montana	10.34 (8.8-11.87)
Nebraska	11.58 (10.34-12.83)
Nevada	9.34 (8.35-10.33)
New Hampshire	13.28 (11.72-14.84)
New Jersey	10.22 (9.69-10.74)
New Mexico	17.29 (15.81-18.77)
New York	9.23 (8.89-9.57)
North Carolina	15.99 (15.34-16.65)
North Dakota	11.3 (9.34-13.27)
Ohio	15.64 (15.07-16.2)
Oklahoma	21.19 (20.01-22.37)
Oregon	14.78 (13.82-15.73)

Pennsylvania	14.28 (13.79-14.77)
Rhode Island	19.29 (17.27-21.31)
South Carolina	19.09 (18.08-20.1)
South Dakota	14.35 (12.32-16.37)
Tennessee	18.51 (17.66-19.37)
Texas	23.04 (22.51-23.57)
Utah	10.79 (9.6-11.97)
Vermont	12.6 (10.45-14.75)
Virginia	11.98 (11.35-12.61)
Washington	15.61 (14.84-16.39)
West Virginia	25.08 (23.39-26.77)
Wisconsin	10.83 (10.15-11.5)
Wyoming	10.85 (8.73-13.34)
Total	14.26 (14.15-14.37)

Supplementary Table 8. NAFLD and HF-related age-adjusted mortality rates per 1,000,000, stratified by states in adults in the United States 1999-2020 ranked according to percentiles

State	Age Adjusted Rate	Percentile	Rank
West Virginia	25.08	98	1
Texas	23.04	96	2
Mississippi	22.46	94	3
Kentucky	21.62	92	4
Oklahoma	21.19	90	5
Rhode Island	19.29	88	6
South Carolina	19.09	86	7
Tennessee	18.51	84	8
California	17.54	82	9
New Mexico	17.29	80	10
Alabama	16.18	78	11
North Carolina	15.99	76	12
Arkansas	15.78	75	13
Ohio	15.64	73	14
Washington	15.61	71	15
Indiana	15.5	69	16
Oregon	14.78	67	17
South Dakota	14.35	65	18
Pennsylvania	14.28	63	19
New Hampshire	13.28	61	20
Delaware	12.86	59	21
Louisiana	12.84	57	22
Vermont	12.6	55	23
Colorado	12.5	53	24
Michigan	12.39	51	25
Georgia	12.35	50	26
Minnesota	12.21	48	27
Massachusetts	12.06	46	28
Virginia	11.98	44	29
Maine	11.93	42	30

Missouri	11.86	40	31
Idaho	11.82	38	32
Illinois	11.72	36	33
Connecticut	11.61	34	34
Nebraska	11.58	32	35
Hawaii	11.46	30	36
North Dakota	11.3	28	37
Alaska	11.04	26	38
Wyoming	10.85	25	39
Wisconsin	10.83	23	40
Utah	10.79	21	41
Iowa	10.66	19	42
Montana	10.34	17	43
Maryland	10.3	15	44
Kansas	10.23	13	45
New Jersey	10.22	11	46
District of Columbia	10.14	9	47
Florida	10.11	7	48
Arizona	9.48	5	49
Nevada	9.34	3	50
New York	9.23	1	51