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Original Article

Trends in Alcoholic Liver Disease and Nonalcoholic Fatty Liver Disease Underlying-Cause Mortality in the United States, 1999–2023

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ABSTRACT

Background: Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are major drivers of liver-related mortality in the United States, but comparative long-term trends remain unclear.
Methods: We analyzed U.S. mortality data (1999–2023) from the CDC WONDER Underlying Cause of Death database. ALD (ICD-10 K70.x) and NAFLD (K75.8, K76.0) deaths were identified. Age-adjusted mortality rates (AAMRs) per 100,000 were calculated, and Joinpoint regression estimated annual percent change (APC) with 95% confidence intervals (CI).
Results: ALD mortality rose from 6.71 in 1999 to 11.47 in 2023. Rates declined slightly in 1999–2006 (APC –0.51%; $p = 0.25$), then increased from 2006–2018 (APC 3.24%; $p < 0.001$) and 2018–2021 (APC 12.58%; $p < 0.001$), before declining after 2021 (APC –7.46%; $p = 0.002$). NAFLD mortality increased more than sixfold, from 0.24 to 1.69, with the steepest rise in 2004–2021 (APC 11.82%; $p < 0.001$). Men had higher ALD mortality, though women showed faster increases. ALD mortality surged among younger adults (25–44 years; APC 25.02% in 2018–2021; $p < 0.001$), while NAFLD was concentrated in older adults (≥65 years; AAMR 0.19 in 1999 vs 4.30 in 2023). State-level hotspots included New Mexico (ALD AAMR 19.49) and West Virginia (NAFLD AAMR 1.24); these are descriptive single-year (2023) rankings without confidence intervals and should not be interpreted as stable geographic estimates.
Conclusions: ALD and NAFLD mortality have risen substantially but with divergent patterns: men had higher absolute ALD mortality throughout the study period, while women experienced faster relative increases; ALD was also disproportionately concentrated among younger adults and rural residents, while NAFLD mainly impacts older adults in Southern and Midwestern states. These surveillance findings highlight priority subgroups for targeted public health action.

1. Introduction

Chronic liver disease represents a growing public health challenge worldwide, contributing to more than two million deaths annually [1]. In the United States, mortality from cirrhosis and related disorders has increased dramatically over the last two decades, reversing previous declines in liver-related deaths [2, 3]. Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are two of the most common causes of chronic liver disease.

ALD, the hepatic manifestation of chronic and excessive alcohol intake, is still a leading cause of cirrhosis, hepatocellular cancer, and liver-related mortality [4]. In recent years, the United States has seen an increase in alcohol use and high-intensity drinking, particularly among young adults and women [5]. These alterations, combined with the COVID-19 pandemic, have led to an increase in alcohol-related mortality [6].

Parallel to these trends, NAFLD has emerged as the most common chronic liver disease worldwide, affecting approximately 25-30% of adults in the United States [7]. NAFLD, which is strongly associated with obesity, diabetes, and metabolic syndrome, is currently the major cause of liver transplantation and hepatocellular cancer [8, 9]. NAFLD-related mortality is increasing, particularly among older persons, yet population-level mortality trends are still poorly understood.

Despite recognition of these parallel epidemics, direct comparisons of ALD and NAFLD mortality trends in the United States across demographic and geographic subgroups are limited. Previous research has examined liver disease mortality in general [2, 3], but few have examined the temporal dynamics of ALD versus NAFLD or analyzed differences by gender, age, area, and urbanization. Importantly, death-certificate capture is likely less sensitive for NAFLD than for ALD, because NAFLD is frequently underdiagnosed and undercoded; direct comparisons of apparent mortality burden should therefore be interpreted with this asymmetry in mind.

To address this gap, we conducted a comprehensive, population-based analysis of ALD and NAFLD mortality in the United States from 1999 to 2023, using nationally representative data from

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the CDC WONDER database. We aimed to quantify changes in age-adjusted mortality rates (AAMRs), evaluate temporal trends using joinpoint regression, and examine disparities by demographic, regional, and urban–rural characteristics. By contrasting ALD and NAFLD mortality, this study provides new insights into the evolving burden of liver disease in the U.S. and highlights opportunities for targeted interventions.

2. Methods

2.1. Study Design, Setting, and Population

We conducted a nationwide, population-based descriptive analysis of mortality from alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) in the United States between 1999 and 2023. Mortality data were obtained from the CDC Wide-Ranging Online Data for Epidemiologic Research (WONDER) Underlying Cause of Death database, which compiles information from death certificates for all 50 U.S. states and the District of Columbia [10]. We identified deaths attributable to ALD using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes K70.0, K70.1, K70.2-4, and K70.9 and deaths attributable to NAFLD using ICD-10 codes K75.8 and K76.0. These codes have been validated in prior epidemiologic studies of liver-related mortality [11, 12]. Case identification relied on the CDC WONDER underlying-cause-of-death framework, which assigns a single underlying cause per death certificate; no separate query-level exclusion of secondary etiologies was applied. This approach improves specificity but likely underestimates true NAFLD mortality, since NAFLD is more often a contributing than an underlying cause on death certificates; this limitation is discussed further below. Because this analysis utilized de-identified, publicly available data, institutional review board approval was not required. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2. Variables and Data Abstraction

We extracted mortality data stratified by sex, age group, state of residence, U.S. Census region, and urban–rural classification. Sex was categorized as male or female. Age was analyzed in three groups (25–44 years, 45–64 years, ≥65 years) to reflect meaningful epidemiologic thresholds; deaths below age 25 were excluded because they constitute a small and coding-variable proportion of liver disease mortality. Urban–rural status was defined using the 2013 National Center for Health Statistics (NCHS) Urban–Rural Classification Scheme for Counties [13], which classifies counties into six levels. For this analysis, the four metropolitan levels (large central metro, large fringe metro, medium metro, and small metro) were collapsed into a single "metropolitan" category, and micropolitan and noncore counties were collapsed into a single "nonmetropolitan" category. Geographic variations were assessed using the four U.S. Census regions (Northeast, Midwest, South, and West) [14].

2.3. Statistical Analysis

We calculated age-adjusted mortality rates (AAMRs) per 100,000 population as the primary analytic output; crude mortality rates were calculated for completeness but are not reported in the results. Age adjustment was performed using the direct method, standardized to the 2000 U.S. standard population [15]. Absolute death counts are reported for overall and major subgroup findings where available from CDC WONDER.

Temporal mortality trends were analyzed using the Joinpoint Regression Program (National Cancer Institute, version 4.9.0.0). Joinpoint regression fits log-linear models to detect statistically significant changes ("joinpoints") in trends over time [16]. We calculated the annual percent change (APC) for each trend segment, along with the corresponding 95% confidence intervals (CIs). Statistical significance was determined using a two-sided t-test, with $p < 0.05$ indicating significance. Where multiple joinpoints were identified, the model selected the optimal number of joinpoints using the permutation test approach, as recommended by the NCI for Joinpoint version 4.9.0.0 [16].

All statistical analyses accounted for population denominators from the U.S. Census Bureau bridged-race intercensal and postcensal estimates to ensure consistency across years. Results were stratified and reported by demographic subgroups, region, and urbanization to identify disparities in ALD- and NAFLD-related mortality.

3. Results

3.1. Overall Trends

Between 1999 and 2023, age-adjusted mortality rates (AAMR) for alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) increased substantially in the United States. For ALD, the AAMR rose from 6.71 per 100,000 in 1999 to 11.47 per 100,000 in 2023, while NAFLD-related mortality increased more than sixfold, from 0.24 per 100,000 in 1999 to 1.69 per 100,000 in 2023, as shown in Figure 1. NAFLD deaths increased from 385 (1999) to 4,728 (2023), totaling 43,235 deaths. ALD deaths rose from 11,948 to 28,593, with a total of 465,407 deaths (1999–2023).

Joinpoint regression revealed distinct temporal patterns. For ALD, mortality initially declined between 1999 and 2006 (APC –0.51, 95% CI –1.41 to 0.41, $p = 0.253$), followed by a significant increase between 2006 and 2018 (APC 3.24, 95% CI 2.84 to 3.64, $p < 0.001$). The sharpest rise was observed between 2018 and 2021 (APC 12.58, 95% CI 7.23 to 18.19, corresponding to a peak of 33,051 ALD deaths in 2021; $p < 0.001$), after which mortality significantly declined from 2021 to 2023 (APC –7.46, 95% CI –11.43 to –3.31, $p = 0.002$), as shown in Figure 1.

For NAFLD, mortality remained relatively stable from 1999 to 2004 (APC 1.91, 95% CI –2.75 to 6.81, $p = 0.405$), followed by a steep increase between 2004 and 2021 (APC 11.82, 95% CI 11.35 to 12.29, $p < 0.001$). From 2021 to 2023, mortality remained flat (APC 2.54; 95% CI –4.78 to 10.41; $p = 0.485$), as shown in Figure 1.

3.2. Sex-Specific Trends

Among women with ALD, mortality rose from 3.25 in 1999 to 7.41 in 2023 per 100,000. Trends were stable from 1999 to 2006 (APC 0.53, 95% CI –0.71 to 1.78, $p = 0.377$), followed by a rapid increase from 2006 to 2018 (APC 4.48, 95% CI 3.96 to 5.00, $p <$ 0.001) and a pronounced surge from 2018 to 2021 (APC 14.03, 95% CI 7.80 to 20.62, $p < 0.001$). A significant decline was observed thereafter (APC –6.80, 95% CI –11.64 to –1.70, $p = 0.013$), as shown in Figure 1. Among females, ALD deaths increased from 3,034 in 1999 to 9,167 in 2023, peaking at 10,482 in 2021.

In men, ALD mortality was consistently higher, rising from 10.64 in 1999 to 15.81 in 2023 per 100,000. Mortality declined from 1999 to 2005 (APC –1.57, 95% CI –2.72 to –0.40, $p = 0.012$), then increased from 2005 to 2018 (APC 2.52, 95% CI 2.15 to 2.90, $p < 0.001$), and accelerated sharply between 2018 and 2021 (APC 11.90, 95% CI 6.35 to 17.74, $p < 0.001$). This was followed by a significant decline between 2021 and 2023 (APC –7.68, 95% CI –12.12 to –3.03, $p =$

0.004), as shown in Figure 1. In males, ALD deaths increased from 8,914 in 1999 to 19,426 in 2023, peaking at 22,569 in 2021.

For NAFLD, mortality among women increased from 0.19 in 1999 to 1.93 in 2023 per 100,000. Rates were stable between 1999 and 2002 (APC 1.86, 95% CI –13.87 to 20.47, $p = 0.819$), rose markedly between 2002 and 2021 (APC 12.68, 95% CI 12.06 to 13.31, $p < 0.001$), and then plateaued after 2021 (APC 0.96, 95% CI –8.41 to 11.28, $p = 0.839$), as shown in Figure 1. Female NAFLD deaths increased from 178 in 1999 to 2,956 in 2023.

In men, NAFLD mortality rose from 0.23 in 1999 to 1.37 in 2023 per 100,000. Mortality increased steadily from 1999 to 2013 (APC 6.78, 95% CI 5.17 to 8.40, $p < 0.001$), accelerated sharply from 2013 to 2018 (APC 16.63, 95% CI 10.20 to 23.45, $p < 0.001$), and continued to rise, though at a slower pace, from 2018 to 2023 (APC 6.17, 95% CI 3.36 to 9.06, $p < 0.001$), as shown in Figure 1. Male NAFLD deaths rose from 207 in 1999 to 1,772 in 2023.

3.3. Urban–Rural Disparities

Alcoholic Liver Disease (ALD).

Among metropolitan populations, the age-adjusted mortality rate (AAMR) for ALD increased from 6.77 per 100,000 in 1999 to 11.67 per 100,000 in 2020 (Note: Urban–rural-stratified data from CDC WONDER were available only through 2020 at the time of analysis; findings for this subgroup therefore reflect 1999–2020). Joinpoint analysis demonstrated an initial decline between 1999 and 2005 (APC –1.34, 95% CI –2.41 to –0.26, $p = 0.019$), followed by a significant rise during 2005–2018 (APC 2.92, 95% CI 2.58–3.25, $p < 0.001$) and an accelerated increase between 2018 and 2020 (APC 11.38, 95% CI 6.30–16.71, $p < 0.001$), as shown in Figure 2. ALD deaths in metropolitan areas increased from 9,955 in 1999 to 24,208 in 2020.

In nonmetropolitan areas, AAMR rose from 6.64 in 1999 to 15.22 in 2020. Mortality remained relatively stable from 1999–2006 (APC 0.48, 95% CI –1.13 to 2.11, $p = 0.538$) but increased sharply between 2006–2018 (APC 4.27, 95% CI 3.54–5.00, $p < 0.001$), with a further surge during 2018–2020 (APC 16.63, 95% CI 7.22–26.85, $p = 0.002$), as shown in Figure 2. ALD deaths in nonmetropolitan areas increased from 1,993 in 1999 to 5,267 in 2020.

Nonalcoholic Fatty Liver Disease (NAFLD).

In metropolitan populations, NAFLD-related mortality increased from 0.24 in 1999 to 1.32 in 2020. No significant change was observed in 1999–2004 (APC 0.38, 95% CI –3.62 to 4.55, $p = 0.845$), followed by a marked rise from 2004–2020 (APC 11.52, 95% CI 11.00–12.03, $p < 0.001$), as shown in Figure 2. NAFLD deaths increased in metropolitan areas from 340 in 1999 to 2,994 in 2020.

In nonmetropolitan areas, the AAMR increased from 0.15 in 1999 to 2.01 in 2020, with a sustained and steep increase across the entire period (APC 14.27, 95% CI 13.58–14.96, $p < 0.001$), as shown in Figure 2. The number of deaths also increased in nonmetropolitan areas from 45 in 1999 to 861 in 2020.

3.4. Regional Trends

Alcoholic Liver Disease (ALD).

Regional disparities in ALD mortality were evident across the U.S. Census regions. In the Northeast, AAMR increased from 4.86 in 1999 to 7.34 in 2023. Mortality declined during 1999–2005 (APC –2.33, 95% CI –3.91 to –0.72, $p = 0.008$), followed by a significant rise in 2005–2018 (APC 3.07, 95% CI 2.54–3.59, $p < 0.001$) and a sharp surge during 2018–2021 (APC 11.84, 95% CI 3.97–20.30, $p = 0.005$), before a recent decline in 2021–2023 (APC –7.21, 95% CI –13.32 to –0.67, $p = 0.034$), as shown in Figure 3.

In the Midwest, AAMR rose from 5.35 to 11.27. Rates were stable in 1999–2006 (APC 0.37, 95% CI –0.89 to 1.65, $p = 0.541$), then increased sharply during 2006–2018 (APC 4.17, 95% CI 3.62–4.73, $p < 0.001$) and 2018–2021 (APC 15.81, 95% CI 8.54–23.57, $p < 0.001$), followed by a decline in 2021–2023 (APC –7.89, 95% CI –13.51 to –1.90, $p = 0.014$), as shown in Figure 3.

In the South, AAMR increased from 6.22 to 10.31. Mortality decreased in 1999–2008 (APC –1.19, 95% CI –1.99 to –0.38, $p = 0.007$), rose substantially during 2008–2018 (APC 4.28, 95% CI 3.57–5.01, $p < 0.001$) and 2018–2021 (APC 12.47, 95% CI 5.87–19.49, $p = 0.001$), then declined in 2021–2023 (APC –7.27, 95% CI –12.52 to –1.70, $p = 0.015$), as shown in Figure 3.

In the West, AAMR was the highest, increasing from 10.93 to 16.75. Mortality remained stable during 1999–2005 (APC –0.34, 95% CI –1.46 to 0.78, $p = 0.512$), rose during 2005–2015 (APC 2.75, 95% CI 2.22–3.28, $p < 0.001$), then plateaued in 2015–2018 (APC –1.19, 95% CI –6.00 to 3.87, $p = 0.608$), followed by a surge during 2018–2021 [APC 12.81, 95% CI 7.64 to 18.25, $p < 0.001$], before declining recently in 2021–2023 (APC –7.50, 95% CI –11.47 to –3.34, $p = 0.002$), as shown in Figure 3.

Nonalcoholic Fatty Liver Disease (NAFLD).

In the Northeast, NAFLD-related mortality rose from 0.20 in 1999 to 1.24 in 2023. No change was observed in 1999–2007 (APC –0.22, 95% CI –4.30 to 4.03, $p = 0.912$), but rates increased during 2007–2017 (APC 14.11, 95% CI 11.47–16.82, $p < 0.001$) and 2017–2023 (APC 6.71, 95% CI 3.70–9.80, $p < 0.001$), as shown in Figure 3.

In the Midwest, AAMR increased from 0.19 to 1.91. Mortality was stable in 1999–2004 (APC 1.58, 95% CI –6.12 to 9.91, $p = 0.670$), with a non-significant surge in 2004–2007 (APC 30.16, 95% CI –2.80 to 74.30, $p = 0.072$), then rose significantly in 2007–2012 (APC 7.95, 95% CI 1.45–14.87, $p = 0.020$) and 2012–2020 (APC 14.65, 95% CI 12.44–16.91, $p < 0.001$), before plateauing in 2020–2023 (APC 2.84, 95% CI –2.48 to 8.45, $p = 0.270$), as shown in Figure 3.

In the South, AAMR rose from 0.21 to 1.83. Mortality remained stable in 1999–2006 (APC 2.58, 95% CI –1.44 to 6.76, $p = 0.197$), followed by a steep increase in 2006–2021 (APC 13.44, 95% CI 12.69–14.19, $p < 0.001$), then stabilized in 2021–2023 (APC 0.85, 95% CI –6.79 to 9.12, $p = 0.823$), as shown in Figure 3.

In the West, AAMR increased from 0.30 to 1.55. Mortality showed no change during 1999–2001 (APC –9.51, 95% CI –37.69 to 31.41, $p = 0.582$), but rose steadily during 2001–2023 (APC 9.54, 95% CI 8.94–10.15, $p < 0.001$), as shown in Figure 3.

3.5. Age-Group Disparities

Alcoholic Liver Disease (ALD). Ages 25–44 years: The AAMR rose from 2.89 in 1999 to 6.11 in 2023. Mortality initially declined between 1999 and 2006 (APC: –2.95; 95% CI: –4.66 to –1.2; $p = 0.003$), followed by a significant increase from 2006 to 2018 (APC: 3.84; 95% CI: 2.97–4.72; $p < 0.001$). The most dramatic rise occurred from 2018 to 2021 (APC: 25.02; 95% CI: 14.12–36.96; $p < 0.001$), after which rates declined between 2021 and 2023 (APC: –9.48; 95% CI: –16.41 to –1.98; $p = 0.018$), as shown in Figure 4.

Ages 45–64 years: The AAMR increased from 11.03 in 1999 to 17.89 in 2023. Mortality remained stable from 1999 to 2005 (APC: 0.07; 95% CI: –0.83 to 0.99; $p = 0.861$), then rose significantly between 2005 and 2015 (APC: 3.51; 95% CI: 3.08–3.93; $p < 0.001$). A nonsignificant change was observed from 2015 to 2018 (APC:

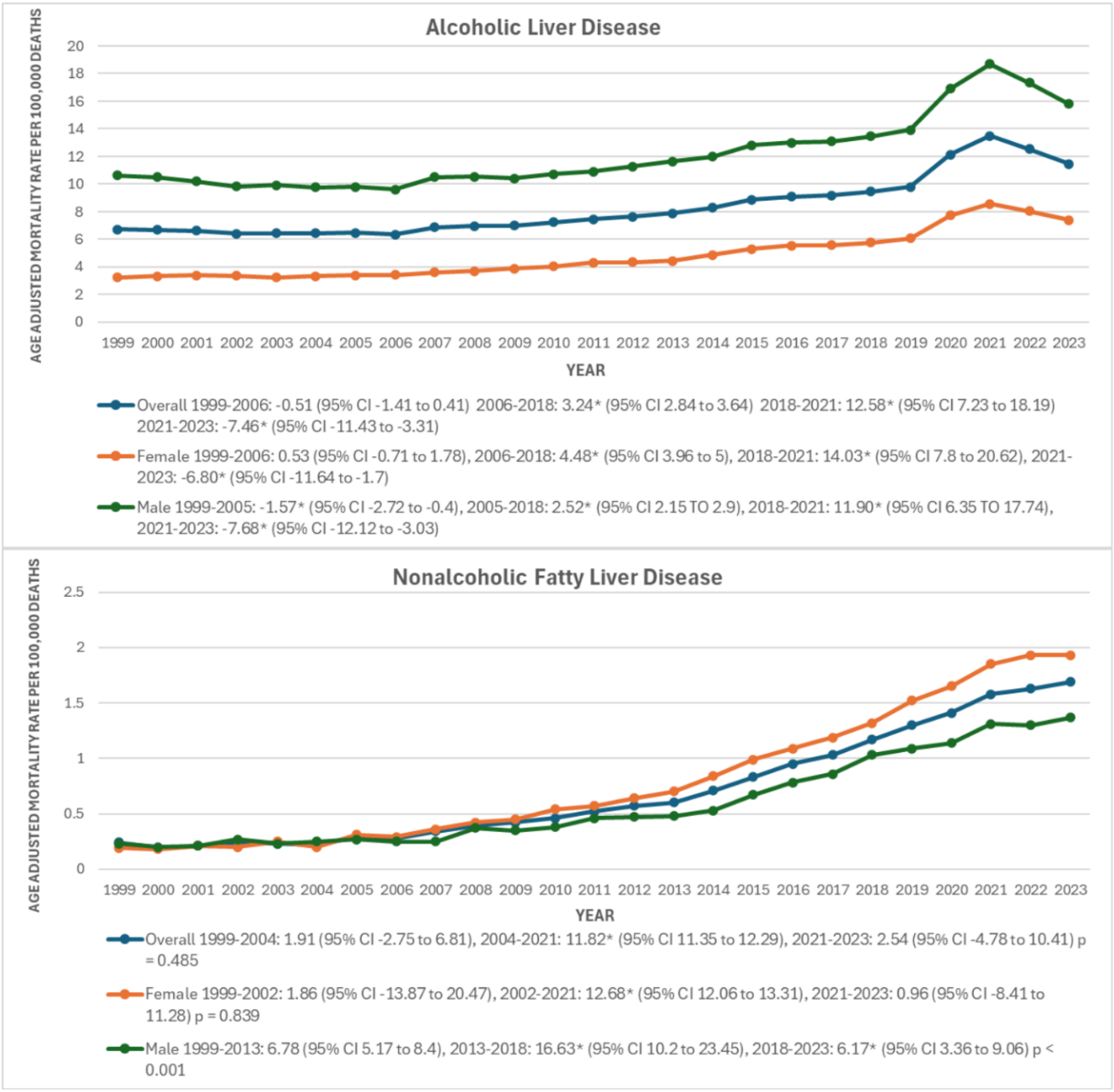

Figure 1: Sex-Stratified ALD and NAFLD-related AAMR per 100,000 in the United States from 1999 to 2023.

0.38; 95% CI: –3.59 to 4.52; $p = 0.839$), followed by a marked increase between 2018 and 2021 (APC: 11.17; 95% CI: 7.02–15.48; $p < 0.001$). Mortality then declined between 2021 and 2023 (APC: –9.04; 95% CI: –12.31 to –5.64; $p < 0.001$), as shown in Figure 4.

Ages ≥65 years: The AAMR rose from 8.14 in 1999 to 12.84 in 2023. Mortality was stable between 1999 and 2011 (APC: –0.47; 95% CI: –1.10 to 0.17; $p = 0.139$), followed by a sharp rise from 2011 to 2021 (APC: 5.88; 95% CI: 5.07–6.70; $p < 0.001$). No significant change was observed between 2021 and 2023 (APC: –0.01; 95% CI: –6.23 to 6.63; $p = 0.998$), as shown in Figure 4.

Nonalcoholic Fatty Liver Disease (NAFLD). Ages 25–44 years: AAMR remained stable (0.21 in 1999 vs. 0.21 in 2023). Mortality declined nonsignificantly from 1999 to 2019 (APC: –0.46; 95% CI: –1.11 to 0.19; $p = 0.157$) but rose sharply between 2019 and 2023 (APC: 11.30; 95% CI: 2.25–21.15; $p = 0.016$), as shown in Figure 4.

Ages 45–64 years: AAMR increased from 0.30 in 1999 to 1.27 in 2023, with a consistent rise throughout the study period (APC: 7.38; 95% CI: 6.96–7.80; $p < 0.001$), as shown in Figure 4.

Ages ≥65 years: AAMR rose steeply from 0.19 in 1999 to 4.30 in 2023. Mortality increased significantly between 1999 and 2019 (APC: 18.24; 95% CI: 16.90–19.60; $p < 0.001$), followed by a nonsignificant decline from 2019 to 2023 (APC: –3.51; 95% CI: –7.31 to 0.44; $p = 0.078$).

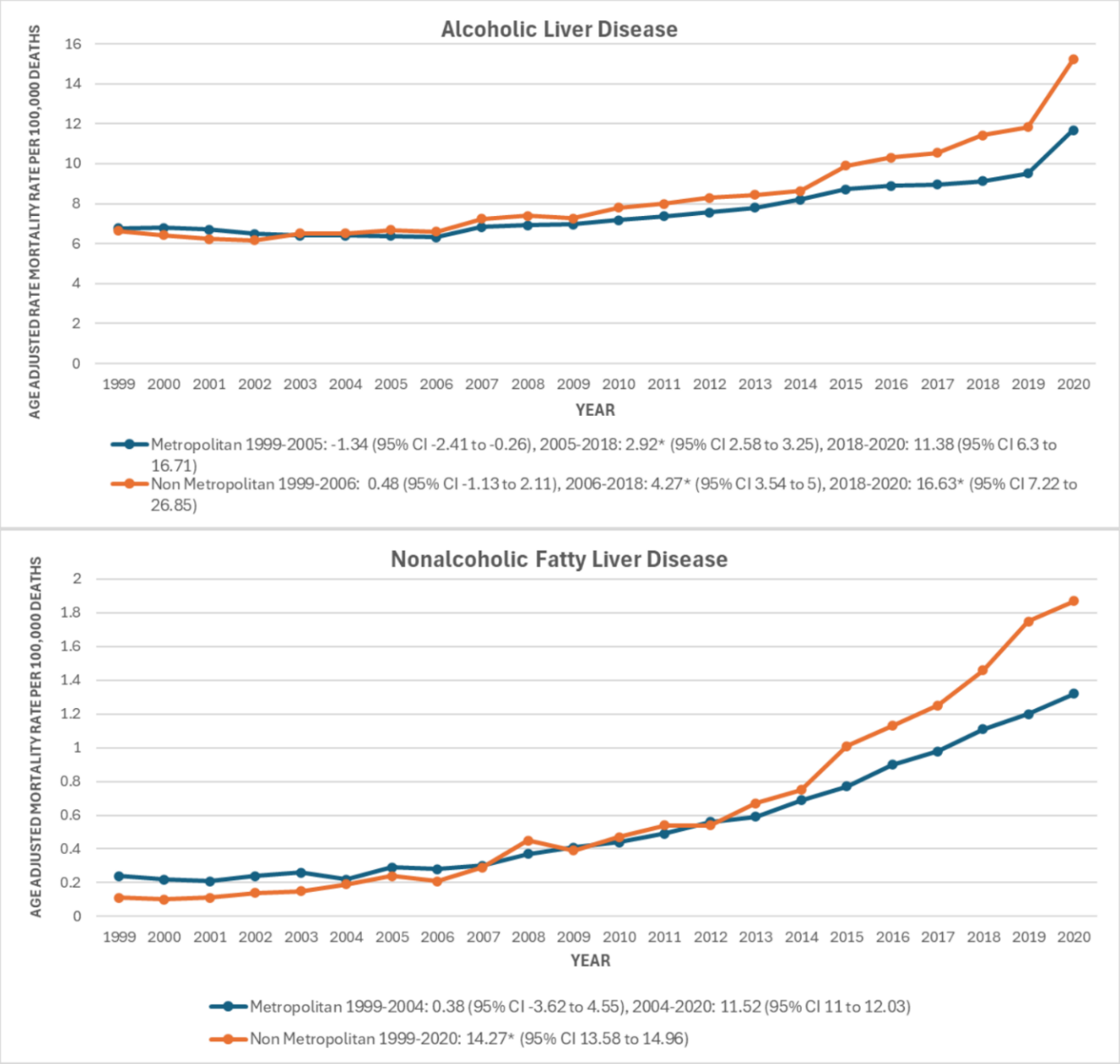

Figure 2: Urbanization-Stratified ALD and NAFLD-related AAMR per 100,000 in the United States from 1999 to 2020.

3.6. Geographic Variation

For ALD, the states with the highest age-adjusted mortality rates (AAMRs) in 2023 were New Mexico (19.49 per 100,000), Wyoming (15.67), South Dakota (15.66), Oregon (13.66), Arizona (13.43), Montana (13.08), and Alaska (12.99). These rankings are based on single-year (2023) estimates without confidence intervals or multi-year smoothing and should be interpreted as descriptive snapshots only.

For NAFLD, the highest AAMRs were observed in West Virginia (1.24 per 100,000), Kentucky (1.15), Tennessee (1.13), South Carolina (1.11), Oklahoma (1.09), Vermont (1.04), and North Carolina (0.97). These NAFLD state rankings are likewise single-year 2023 estimates and should be interpreted as descriptive and exploratory.

4. Discussion

In this large, population-based analysis of U.S. mortality data spanning 1999–2023, we found that both ALD and NAFLD demonstrated substantial and distinct increases in mortality. ALD mortality rose from 6.71 per 100,000 in 1999 to 11.47 per 100,000 in 2023, while NAFLD mortality increased more than sixfold during the same period. Importantly, our joinpoint analysis identified key inflection points that temporally coincide with previously reported shifts in alcohol consumption, obesity trends, and the COVID-19 pandemic; however, because this is a descriptive study, causal attribution cannot be made.

4.1. Trends in ALD Mortality

The trajectory of ALD mortality points to a serious public health crisis. Following a minor reduction in the early 2000s, rates rose

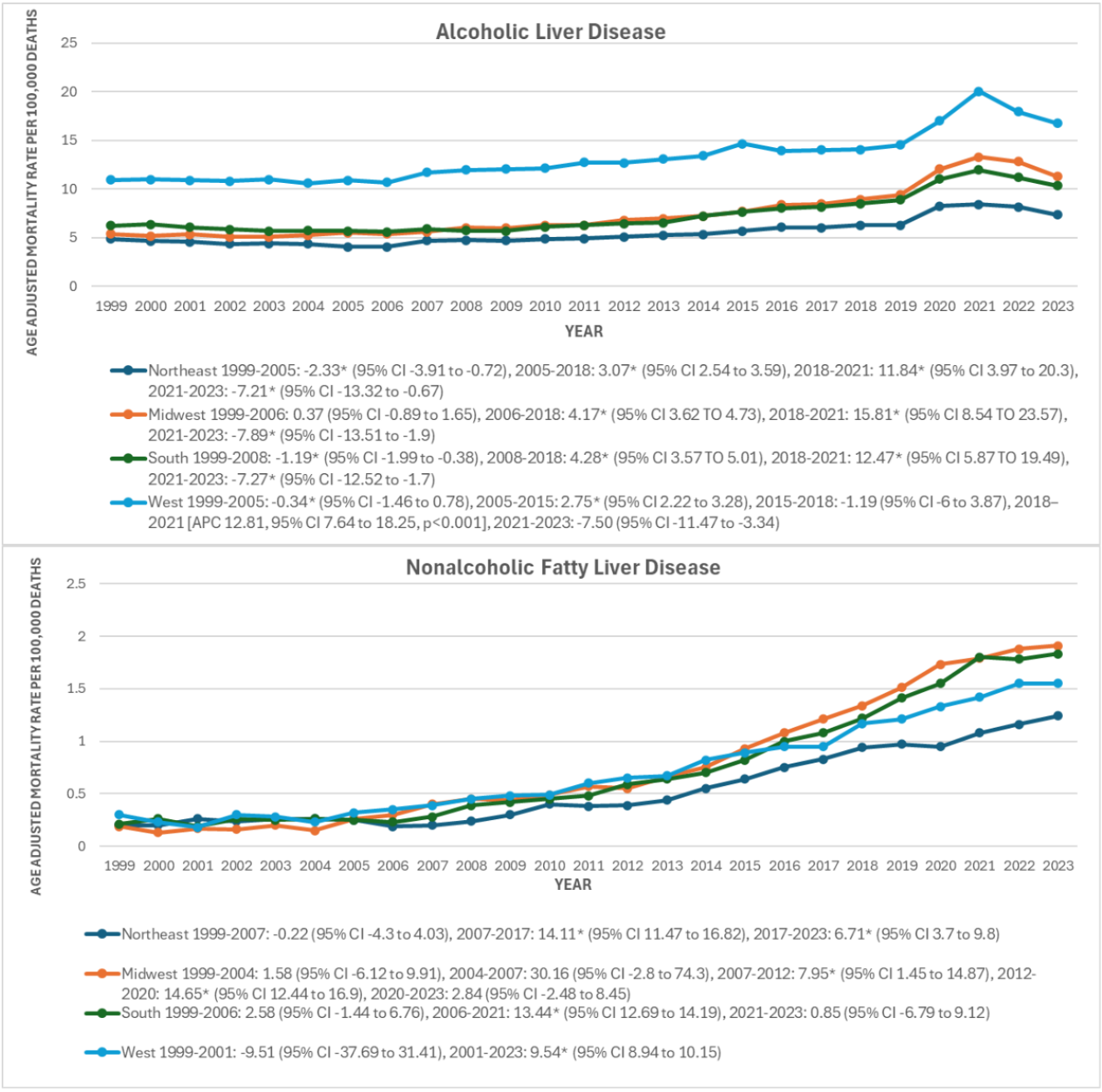

Figure 3: Region-Stratified ALD and NAFLD-related AAMR per 100,000 in the United States from 1999 to 2023.

sharply from 2006 onwards, with the most drastic spike occurring between 2018 and 2021. This spike temporally coincides with reports of rising alcohol consumption, particularly binge drinking, among young adults and women in the United States [5, 17], though this study cannot establish causation. The COVID-19 pandemic has been associated with worsened risky drinking habits, and the 2020–2021 acceleration in ALD mortality is consistent with this hypothesis. However, causal attribution cannot be established from these descriptive data [6]. Although we saw a drop after 2021, rates remain significantly higher than 25 years ago, highlighting ongoing hazards. Our findings are consistent with previous research indicating that alcohol-related liver disease mortality is increasing in younger cohorts and among women [2, 3].

4.2. Trends in NAFLD Mortality

In contrast, NAFLD mortality increased continuously over the study period, with the largest increase occurring between 2004 and 2021. This pattern mirrors the concurrent rise of obesity, metabolic syndrome, and type 2 diabetes in the US population [7, 18]. Since 1999, NAFLD mortality in older persons (≥65 years) has grown about 20-fold, making this group the epicenter of the disease burden. While ALD mortality decreased after 2021, NAFLD mortality plateaued rather than declining, suggesting a stronger association with long-term metabolic risk factors than with acute behavioral changes. Previous research has identified NAFLD as the fastest-growing indication for liver transplantation, particularly among women and the elderly [8, 9], which aligns with our findings.

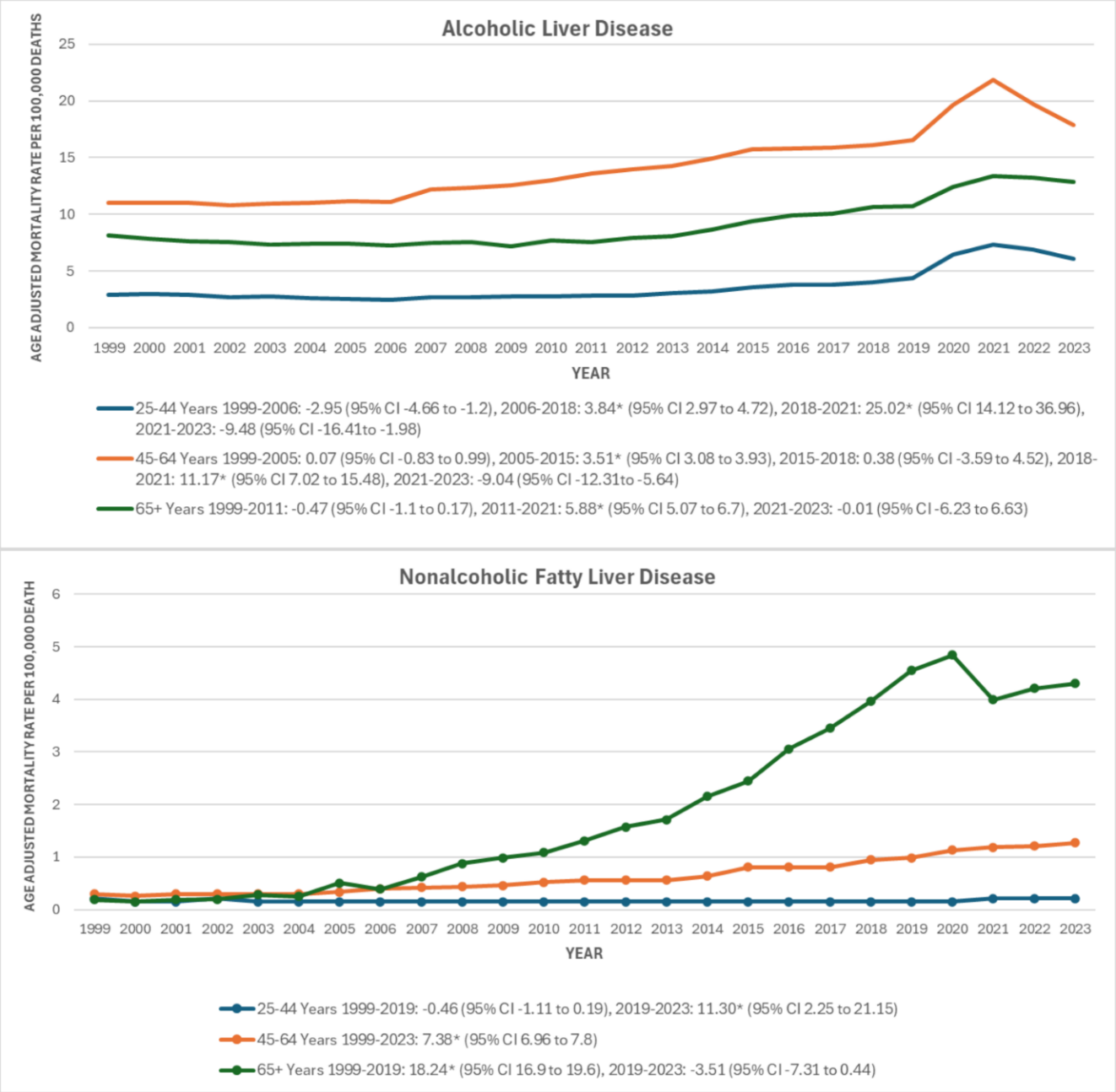

Figure 4: Age Group-Stratified ALD and NAFLD-related AAMR per 100,000 in the United States from 1999 to 2023.

4.3. Sex- and Age-Specific Patterns

Men consistently exhibited higher ALD mortality than women, although women had a faster relative rise, particularly after 2006. Biological vulnerability to alcohol's hepatotoxic effects, together with reducing gender disparities in alcohol intake, are likely contributing factors [19, 20]. Younger adults (25–44 years) had the greatest relative increases in ALD mortality, which is consistent with recent evidence of worsening alcohol use and cirrhosis deaths in younger cohorts [21, 22]. In contrast, NAFLD mortality was concentrated among older persons, indicating the combined burden of obesity and diabetes [23]. These findings emphasize the importance of interventions tailored to participants' age and gender.

4.4. Urban–Rural and Regional Disparities

We found marked urban-rural disparities, with non-metropolitan locations having disproportionately greater ALD mortality, especially after 2006. Rural populations confront distinct issues, such as greater rates of heavy drinking, poverty, and limited access to hepatology care [24, 25]. NAFLD mortality also increased faster in non-metropolitan areas, most likely reflecting similar rises in obesity and diabetes [26].

Regional disparities were also striking: the West always had the largest ALD burden, whereas the Midwest and South experienced the fastest recent rises. NAFLD mortality was highest in the South and Midwest, which have the highest obesity and diabetes rates [27, 28]. These findings are consistent with previous research indicating

a geographic clustering of advanced liver disease and transplant requirements [29].

4.5. State-Level Hotspots

The states with the greatest ALD death rates in 2023 were New Mexico, Wyoming, and South Dakota. Prior research has revealed that New Mexico, in particular, has persistently high alcohol-related mortality [30, 31]. NAFLD mortality was highest in West Virginia, Kentucky, and Tennessee [32]. These state-level rankings reflect single-year (2023) descriptive estimates without confidence intervals and should be interpreted as hypothesis-generating observations rather than findings from this analysis. Prior literature documents associations with socioeconomic and geographic factors in these states, but such variables were not analyzed here. Targeted, state-level public health initiatives remain important regardless of year-to-year ranking variation.

4.6. Public Health and Clinical Implications

Our findings underscore the urgent need for dual interventions to reduce liver-related mortality. Interventions for ALD, such as alcohol taxation, lower outlet density, and greater access to alcohol use disorder treatment, have been shown to lessen harm [33, 34]. Comprehensive metabolic risk reduction will be critical for NAFLD, including obesity avoidance, diabetes control, and pharmaceutical advancements in NASH treatment [35, 36]. Screening measures, including non-invasive fibrosis testing, should be prioritized in high-risk groups [37]. These findings have significant implications for health equity, particularly regarding the sex, age, geographic, and urban–rural disparities identified in this analysis. Addressing these disparities will require targeted public health strategies that account for differential access to care and regional variation in the burden of metabolic and behavioral risks.

4.7. Strengths and Limitations

This study has several important strengths. First, it draws on nearly 25 years of nationally representative mortality data from the CDC's WONDER database, assuring broad coverage while minimizing selection bias. Second, we used joinpoint regression analysis to identify temporal inflection points in mortality patterns, thereby providing a more detailed understanding of acceleration and decline. Third, stratification by sex, age group, urbanization, and census region allowed us to identify major demographic and geographic inequalities, highlighting those most at risk. Finally, by studying both alcoholic and nonalcoholic fatty liver disease, our study offers a comparative view on two of the most significant and expanding causes of liver-related death. Nevertheless, several limitations must be acknowledged. First, misclassification and underreporting on death certificates are still possible; ALD may be miscoded as nonspecific cirrhosis, but NAFLD is frequently underdiagnosed and undercoded when compared to ALD. Second, NAFLD cannot be consistently separated from nonalcoholic steatohepatitis (NASH) in death certificate data, restricting our capacity to evaluate severity-specific patterns. Third, changes in coding techniques and diagnostic awareness over time may have contributed to observed increases in mortality, notably for NAFLD. Fourth, mortality statistics do not include individual-level risk factors such as alcohol usage, BMI, diabetes status, or socioeconomic indicators, preventing causal inferences. Fifth, while our research finds urban-rural and regional discrepancies, it does not account for migratory patterns, healthcare availability, or cultural variables that could explain these differences. Sixth, because this is an ecological analysis, caution is warranted in attributing observed patterns to specific individual-level exposures. Seventh, restricting analyses to underlying-cause deaths likely underascertains liver disease mortality, particularly for NAFLD; this asymmetry probably biases apparent NAFLD estimates downward relative to ALD. Eighth, the NAFLD case definition (K75.8 or K76.0) may differ from that used in studies that use K76.0 alone; sensitivity analyses were not feasible but are recommended for future work. Ninth, urban–rural data were limited to 1999–2020 due to availability constraints. Tenth, state-level estimates are single-year 2023 snapshots without confidence intervals. Eleventh, underlying-cause coding does not capture mixed alcohol–metabolic liver disease, making the boundary between ALD and NAFLD less distinct than implied.

5. Conclusion

ALD and NAFLD mortality have risen markedly in the United States over the past quarter-century, but with divergent demographic and geographic patterns. Men had higher absolute ALD mortality throughout the study period, while women experienced faster relative increases; ALD mortality was also disproportionately concentrated among younger adults and rural residents, while NAFLD primarily impacts older adults and the Southern U.S. states. These findings underscore the urgent need for enhanced surveillance and targeted public health action in high-burden demographic and geographic subgroups. Future analytical studies with individual-level data are needed to evaluate causal pathways driving these trends.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this work.

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Informed Consent

Informed consent was not required. This analysis used publicly available, de-identified, aggregate mortality data from CDC WONDER, and no individual participants were involved.

Institutional Review Board (IRB)

Ethical approval was not required for this study as it used publicly available, de-identified data from the CDC WONDER database. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Large Language Model

The authors declare that no generative artificial intelligence tools were used in the preparation of this manuscript. The authors take full responsibility for the content of the publication.

Authors Contribution

AAK contributed to the conceptualization of the study, while AAK, SS, and FS were responsible for investigation and data collection. AAK and SS contributed to the methodology, and AAK and RS

performed the statistical analysis, with RS responsible for the software and visualization. SS and RS contributed to the interpretation of results, while AAK assisted in drafting the manuscript. AAK supervised the study, and FS was responsible for resources and project administration. All authors reviewed and approved the final manuscript.

Data Availability

The data underlying this study are publicly available from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Underlying Cause of Death database (https://wonder.cdc.gov/ucd-icd10.html). All analyses were performed using de-identified, aggregated data, and no individual-level data were accessed.

Clinical Trial Registration

Not applicable. This study is an analysis of publicly available aggregate mortality data and is not a clinical trial.

References

1. Asrani S, Devarbhavi H, Eaton J, Kamath P. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151-71. [https://doi.org/10.1016/j.jhep.2018.09.014].
2. Tapper E, Parikh N. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ. 2018;362:k2817. [https://doi.org/10.1136/bmj.k2817].
3. Kim D, Li A, Perumpail B, Gadiparthi C, Kim W, Cholankeril G. Changing Trends in Etiology-Based and Ethnicity-Based Annual Mortality Rates of Cirrhosis and Hepatocellular Carcinoma in the United States. Hepatology. 2019;69(3):1064-74. [https://doi.org/10.1002/hep.30161].
4. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011;141(5):1572-85. [https://doi.org/10.1053/j.gastro.2011.09.002].
5. White A, Castle I, Powell P, Hingson R, Koob G. Alcohol-Related Deaths During the COVID-19 Pandemic. JAMA. 2022;327(17):1704-6. [https://doi.org/10.1001/jama.2022.4308].
6. Barbosa C, Cowell A, Dowd W. Alcohol Consumption in Response to the COVID-19 Pandemic in the United States. J Addict Med. 2021;15(4):341-4. [https://doi.org/10.1097/ADM.0000000000000767].
7. Younossi Z, Koenig A, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. [https://doi.org/10.1002/hep.28431].
8. Wong R, Aguilar M, Cheung R, Perumpail R, Harrison S, Younossi Z. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148(3):547-55. [https://doi.org/10.1053/j.gastro.2014.11.039].
9. Younossi Z, Stepanova M, Ong J, Jacobson I, Bugianesi E, Duseja A. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. Clin Gastroenterol Hepatol. 2019;17(4):748-55. [https://doi.org/10.1016/j.cgh.2018.05.057].
10. Heron M. Deaths: Leading Causes for 2019. Natl Vital Stat Rep. 2021;70(9):1-114.
11. Ilyas F, Ali H, Patel P, Sarfraz S, Basuli D, Giammarino A. Increasing nonalcoholic fatty liver disease-related mortality rates in the United States from 1999 to 2022. Hepatol Commun. 2023;7(7):e00207. [https://doi.org/10.1097/HC9.0000000000000207].
12. Paik J, Golabi P, Biswas R, Alqahtani S, Venkatesan C, Younossi Z. Nonalcoholic Fatty Liver Disease and Alcoholic Liver Disease are Major Drivers of Liver Mortality in the United States. Hepatol Commun. 2020;4(6):890-903. [https://doi.org/10.1002/hep4.1510].
13. Ingram D, Franco S. 2013 NCHS Urban-Rural Classification Scheme for Counties. Vital Health Stat 2. 2014;(166):1-73. [PMID: 24776070].
14. United States Census Bureau. Census regions and divisions of the United States. US Department of Commerce Economics and Statistics Administration. 2021.
15. Klein R, Schoenborn C. Age adjustment using the 2000 projected U.S. population. Healthy People 2010 Stat Notes. 2001;(20):1-10. [PMID: 11676466].
16. National Cancer Institute. Joinpoint Regression Program, Version 4.9.0.0; 2025. Accessed July 14, 2025. Surveillance Research Program.
17. Esser M, Sherk A, Liu Y, Naimi T, Stockwell T, Stahre M. Deaths and Years of Potential Life Lost From Excessive Alcohol Use - United States, 2011-2015. MMWR Morb Mortal Wkly Rep. 2020;69(30):981-7. [https://doi.org/10.15585/mmwr.mm6930a1].
18. Adams L, Anstee Q, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66(6):1138-53. [https://doi.org/10.1136/gutjnl-2017-313884].
19. Becker U, Deis A, Sørensen T, Grønbaek M, Borch-Johnsen K, Müller C. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology. 1996;23(5):1025-9. [https://doi.org/10.1002/hep.510230513].
20. Guy J, Peters M. Liver disease in women: the influence of gender on epidemiology, natural history, and patient outcomes. Gastroenterol Hepatol. 2013;9(10):633-9. [PMID: 24764777, PMCID: PMC3992057].
21. Julien J, Ayer T, Bethea E, Tapper E, Chhatwal J. Projected prevalence and mortality associated with alcohol-related liver disease in the USA, 2019-40: a modeling study. Lancet Public Health. 2020;5(6):e316-23. [PMID: 32504584, https://doi.org/10.1016/S2468-2667(20)30062-1].
22. Asrani S, Mellinger J, Arab J, Shah V. Reducing the Global Burden of Alcohol-Associated Liver Disease: A Blueprint for Action. Hepatology. 2021;73(5):2039-50. [https://doi.org/10.1002/hep.31583].
23. Noureddin M, Vipani A, Bresee C, Todo T, Kim I, Alkhouri N. NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. Am J Gastroenterol. 2018;113(11):1649-59. [https://doi.org/10.1038/s41395-018-0088-6].
24. Roskilly A, Rowe I. Surveillance for hepatocellular cancer. Clin Med (Lond). 2018;18(Suppl 2):s66-9. [https://doi.org/10.7861/clinmedicine.18-2-s66].
25. Andrilla C, Patterson D, Garberson L, Coulthard C, Larson E. Geographic Variation in the Supply of Selected Behavioral Health Providers. Am J Prev Med. 2018;54(6 Suppl 3):S199-207. [https://doi.org/10.1016/j.amepre.2018.01.004].
26. Singh G, Siahpush M. Widening rural-urban disparities in all-cause mortality and mortality from major causes of death in the USA, 1969-2009. J Urban Health. 2014;91(2):272-92. [https://doi.org/10.1007/s11524-013-9847-2].
27. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020; 2020. Atlanta, GA: CDC.
28. Hales C, Carroll M, Fryar C, Ogden C. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. NCHS Data Brief. 2020.
29. Yilma M, Dalal N, Wadhwani S, Hirose R, Mehta N. Geographic disparities in access to liver transplantation. Liver Transpl. 2023;29(9):987-97. [https://doi.org/10.1097/LVT.0000000000000182].
30. Chartier K, Caetano R. Ethnicity and health disparities in alcohol research. Alcohol Res Health. 2010;33(1-2):152-60. [PMID: 21209793, PMCID: PMC3887493].
31. Esser M, Sherk A, Liu Y, Naimi T. Deaths from Excessive Alcohol Use — United States, 2016–2021. MMWR Morb Mortal Wkly Rep. 2024;73:154-61. [https://doi.org/10.15585/mmwr.mm7308a1].
32. Ufere N, Patzer R, Kavalieratos D, Louissaint J, Kaplan A, Cross S. Rural-Urban Disparities in Mortality From Cirrhosis in the United States From 1999 to 2019. Am J Gastroenterol. 2022;117(7):1162-5. [https://doi.org/10.14309/ajg.0000000000001712].
33. Babor T. Alcohol: No Ordinary Commodity: Research and Public Policy. 2nd ed. Oxford: Oxford Academic; 2010. [https://doi.org/10.1093/acprof:oso/9780199551149.001.0001].
34. Elder R, Lawrence B, Ferguson A, Naimi T, Brewer R, Chattopadhyay S. The effectiveness of tax policy interventions for reducing excessive alcohol consumption and related harms. Am J Prev Med. 2010;38(2):217-29.

[https://doi.org/10.1016/j.amepre.2009.11.005].

35. Younossi Z, Ratziu V, Loomba R, Rinella M, Anstee Q, Goodman Z. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomized, placebo-controlled phase 3 trial. Lancet. 2019;394(10215):2184-96. [PMID: 31813633, https://doi.org/10.1016/S0140-6736(19)33041-7].
36. Friedman S, Neuschwander-Tetri B, Rinella M, Sanyal A. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24(7):908-22. [https://doi.org/10.1038/s41591-018-0104-9].
37. Chalasani N, Younossi Z, Lavine J, Charlton M, Cusi K, Rinella M. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57. [https://doi.org/10.1002/hep.29367].