

Temporal Trends and Projected Mortality of Heart Failure and Interstitial Lung Disease among Adults Aged ≥ 55 Years in the United States, 1999–2040: A CDC WONDER Analysis

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Keywords: Heart failure, Interstitial lung disease, Mortality, CDC WONDER

Posted Date: August 27th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10192477/v1>

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Additional Declarations: No competing interests reported.

“Temporal Trends and Projected Mortality of Heart Failure and Interstitial Lung Disease among Adults Aged ≥ 55 Years in the United States, 1999–2040: A CDC WONDER Analysis”

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Abstract:

Background: Heart failure (HF) and interstitial lung disease (ILD) frequently coexist and may worsen outcomes through shared mechanisms, including fibrosis, inflammation, and cardiopulmonary dysfunction. However, long-term mortality trends associated with this comorbid phenotype remain poorly defined.

Methods: We analyzed mortality data from the CDC WONDER Multiple Cause of Death database (1999–2024). Adults aged ≥ 55 years with HF (ICD-10: I50) and ILD (ICD-10: J84) listed on death certificates were identified. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated. Joinpoint regression was used to assess temporal trends, and autoregressive integrated moving average (ARIMA) models projected mortality through 2040.

Results: Overall AAMRs increased from 4.12 to 7.37 per 100,000 between 1999 and 2024 (AAPC, 2.30%; 95% CI, 1.53–3.08; $p < 0.001$), with the steepest increase occurring during 2016–2021 (APC, 7.46%; 95% CI, 5.53–9.43). AAMRs were consistently higher among males (9.46), White individuals (8.09), older age adults (21.08), and non-metropolitan populations (7.49). Regionally, all U.S. Census regions showed rising mortality, with the South projected to experience the largest future increase. ARIMA projections indicate continued increases in mortality, reaching 8.67 per 100,000 by 2030 and 10.84 per 100,000 by 2040.

Conclusions: Mortality associated with coexisting HF and ILD increased substantially in the United States from 1999 to 2024 and is projected to continue rising through 2040. Older adults, males, White individuals, and non-metropolitan populations bear the greatest burden, highlighting the need for integrated cardiopulmonary care and targeted public health interventions.

KEYWORDS

Heart failure; Interstitial lung disease; Mortality; CDC WONDER.

Introduction

Heart failure (HF) is a major public health challenge and one of the leading causes of cardiovascular morbidity and mortality worldwide. It is a complex clinical syndrome characterized by structural or functional cardiac abnormalities that impair ventricular filling or blood ejection, resulting in reduced cardiac output and elevated intracardiac filling pressures. HF is associated with frequent hospitalizations, reduced quality of life, and substantial healthcare costs [1-3]. In the United States, the prevalence of HF continues to rise, largely driven by population aging and improved survival following cardiovascular disease. Consequently, HF disproportionately affects older adults and remains a significant contributor to mortality and healthcare utilization despite advances in contemporary medical therapy [1-4].

Interstitial lung disease (ILD) comprises a heterogeneous group of diffuse parenchymal lung disorders characterized by varying degrees of inflammation and fibrosis, ultimately leading to impaired gas exchange and progressive respiratory dysfunction [5,6]. ILD is a significant cause of chronic respiratory morbidity and mortality in the United States, with disease burden increasing

substantially with advancing age, particularly among adults aged 55 years and older[6,7]. Idiopathic pulmonary fibrosis, the most common fibrotic ILD, is associated with progressive lung function decline and poor long-term survival despite recent therapeutic advances [5,6].

HF and ILD often occur concurrently in older patients [8]. Cardiopulmonary interaction is also expected to complicate the condition even more [8,9], since HF exacerbates pulmonary congestion and remodeling of pulmonary interstitium as a result of increased pulmonary capillary pressure and inflammation [9], while advanced ILD results in pulmonary hypertension and dysfunction of right ventricle leading to heart failure [9-11]. Aging factor also adds to the interaction between HF and ILD and can affect the patient's prognosis negatively [8].

Despite the substantial clinical and public health burden of HF and ILD, national studies directly comparing their long-term mortality patterns remain limited. A comprehensive evaluation of temporal mortality trends is essential to better understand the evolving burden of these diseases and to guide healthcare planning for an aging population. Therefore, this study utilized the CDC WONDER database to examine temporal mortality trends and forecast future mortality among U.S. adults aged ≥ 55 years with HF and ILD.

Methods

1. Study Design and Data Source

This descriptive, retrospective, population-based study analyzed mortality trends among U.S. residents aged 55 years and older from 1999 to 2024. The age threshold of ≥ 55 years was selected because mortality related to heart failure and interstitial lung disease begins to rise significantly from midlife, allowing a broader evaluation of disease burden across at-risk populations. Mortality data were obtained from the Centers for Disease Control and Prevention Wide-ranging Online

Data for Epidemiologic Research (CDC WONDER) Multiple Cause of Death database [12]. Deaths related to heart failure (HF) were identified using ICD-10 code I50, including its subcategories: I50.0 (congestive heart failure), I50.1 (left ventricular failure), and I50.9 (heart failure, unspecified) [13]. Interstitial lung disease (ILD) was identified using ICD-10 code J84, including J84.0 (alveolar and parietoalveolar conditions), J84.1 (other interstitial pulmonary diseases with fibrosis), J84.8 (other specified interstitial pulmonary diseases), and J84.9 (interstitial pulmonary disease, unspecified) [14]. Mortality data were extracted from the Multiple Cause of Death Public Use Record, where HF and ILD were recorded anywhere on the death certificate in the multiple cause-of-death fields, regardless of the underlying cause. Institutional review board approval was not required because CDC WONDER contains only de-identified, publicly available data. Study conduct and reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research [15].

2. Data Extraction

Data were extracted from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause of Death (MCD) database, covering all 50 U.S. states and the District of Columbia from 1999 to 2024. The dataset included annual mortality counts, population denominators, year of death, geographic location, and available demographic characteristics. Additional variables extracted included age at death, sex, race/ethnicity, U.S. Census region, urbanization level, and underlying and contributing causes of death as recorded on death certificates.

Age was categorized into 55–74 and ≥ 75 years. Sex was classified as male or female according to death certificate records. Race/ethnicity analyses were restricted to non-Hispanic White, non-Hispanic Black or African American, non-Hispanic Asian or Pacific Islander, and Hispanic or

Latino. Non-Hispanic American Indian or Alaska Native populations were excluded from subgroup analyses due to small case counts and consequently unreliable and statistically unstable mortality estimates in CDC WONDER. Geographic distribution was assessed using U.S. Census regions (Northeast, Midwest, South, and West). State-level mortality data were also extracted for regional comparisons where applicable. Place of death was categorized as medical facility inpatient, medical facility outpatient or emergency department, decedent's home, hospice facility, nursing home/long-term care facility, and other locations. Urbanization was assessed using the National Center for Health Statistics (NCHS) urban–rural classification scheme and categorized as metropolitan and non-metropolitan areas [16]. Analyses involving urbanization were restricted to 1999–2020 due to data availability limitations in the CDC WONDER database.

3. Statistical Analysis

Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated using CDC WONDER's standard methodology. AAMRs were directly standardized to the 2000 U.S. standard population to ensure comparability across time and demographic strata [17]. Temporal trends in mortality were evaluated using Joinpoint regression software (version 5.4.0, National Cancer Institute) [18], which identifies statistically significant changes in the direction and magnitude of the trend over time. The Monte Carlo permutation method was applied to select the optimal number of joinpoints and to test the statistical significance of trend changes. Annual Percent Change (APC) and Average Annual Percent Change (AAPC) were calculated for each segment and across the entire study period, respectively, along with corresponding 95% confidence intervals. Statistical significance was defined as a two-sided p-value <0.05 .

Time series forecasting

The autoregressive integrated moving average (ARIMA) models were used for time-series forecasting and implemented in R using the forecast package. Optimal parameters (p, d, q) were selected based on Akaike Information Criterion (AIC), with appropriate seasonal adjustments. Diagnostic validation was performed. The model was trained on data from 2000-2020, with data from 2021-2024 reserved for validation. The model performance was evaluated using a rolling one-step-ahead forecast approach. The predicted values were compared using root mean square error (RMSE). The model with the lowest RMSE was then applied to the full dataset (2000-2024) to generate projected AAMR for the years 2025-2040, along with the corresponding 95% confidence intervals. To summarize the projected trend over the forecast period, a forecast Average Annual Percent Change (forecast AAPC) was calculated from the ARIMA-projected AAMRs in R as the average annual percentage change between the beginning and end of the forecast period.[19].

RESULTS

Overall:

Between 1999 and 2024, overall AAMR increased from 4.12 to 7.37. Joinpoint regression analysis demonstrated a significant overall increase, with an AAPC of 2.30% (95% CI: 1.53 to 3.08; $p < 0.001$). Trend analysis showed that AAMRs increased significantly from 1999 to 2004 (APC: 2.27%; 95% CI: 0.42 to 4.14; $p = 0.020$), followed by a non-significant decline between 2004 and 2009 (APC: -1.87%; 95% CI: -4.27 to 0.59; $p = 0.123$). A significant upward trend resumed from 2009 to 2016 (APC: 2.04%; 95% CI: 0.83 to 3.27; $p = 0.003$), with a marked acceleration from 2016 to 2021 (APC: 7.46%; 95% CI: 5.53 to 9.43; $p < 0.001$). The most recent period (2021–2024)

showed a non-significant increase (APC: 1.69%; 95% CI: -0.88 to 4.33; $p = 0.178$). Projections based on ARIMA models indicate that overall AAMRs may continue to rise, reaching 8.67 (95% CI: 6.75 to 10.59) per 100,000 by 2030 and 10.84 (95% CI: 5.33 to 16.35) by 2040. The projected trend corresponds to a forecast AAPC of 2.40%, suggesting a sustained increase consistent with historical patterns. Detailed APCs, p-values, historical AAPCs, and forecast AAPCs for all subgroups are provided in Supplementary Table 8 (Figure 1, Supplementary Table 1 and 8).

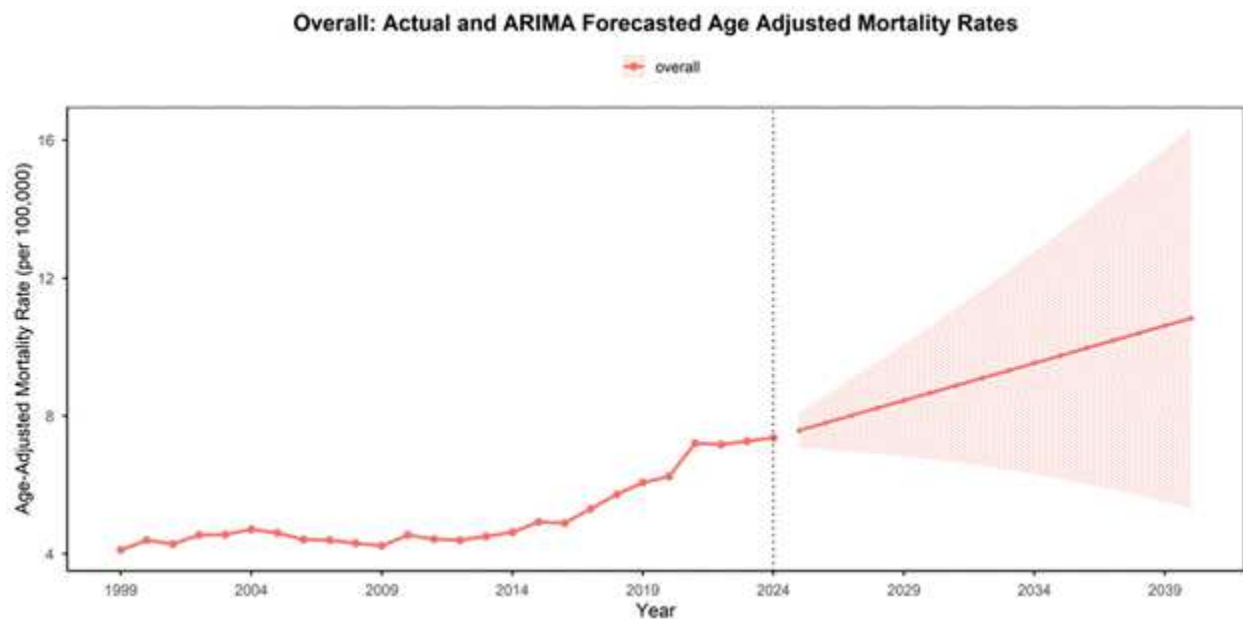


Figure 1. Overall age-adjusted mortality rates (AAMRs) for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years, 1999–2024, with ARIMA-based projections through 2040.

Stratified by Sex:

Among males, AAMRs increased from 5.07 in 1999 to 9.46 in 2024, with a significant overall rise (AAPC: 2.40%; 95% CI: 1.25 to 3.57; $p < 0.001$). A non-significant increase was observed from

1999 to 2004 (APC: 2.02%; 95% CI: -0.09 to 4.17; $p = 0.059$), followed by a non-significant decline between 2004 and 2007 (APC: -3.66%; 95% CI: -11.60 to 5.00; $p = 0.364$). A significant increasing trend was noted from 2007 to 2016 (APC: 2.11%; 95% CI: 1.25 to 2.97; $p < 0.001$), which further accelerated during 2016–2021 (APC: 7.93%; 95% CI: 5.84 to 10.06; $p < 0.001$). The trend stabilized during 2021–2024 (APC: 1.21%; 95% CI: -1.48 to 3.97; $p = 0.350$).

Forecasts suggest that male AAMRs may increase to 10.51 (95% CI: 8.83 to 12.19) by 2030 and further to 12.27 (95% CI: 9.53 to 15.01) by 2040, with a projected AAPC of 1.62%, indicating continued but slightly slower growth compared to historical trends.

Among females, AAMRs rose from 3.53 in 1999 to 5.82 in 2024, with a significant overall increase (AAPC: 2.01%; 95% CI: 0.95 to 3.09; $p < 0.001$). A non-significant increase occurred from 1999 to 2003 (APC: 3.05%; 95% CI: -0.17 to 6.37; $p = 0.061$), followed by a significant decline from 2003 to 2012 (APC: -1.19%; 95% CI: -2.20 to -0.16; $p = 0.027$). Although rates increased between 2012 and 2016 (APC: 2.75%; 95% CI: -1.68 to 7.38; $p = 0.204$), this change was not statistically significant. A sharp and significant rise was observed from 2016 to 2022 (APC: 6.45%; 95% CI: 4.65 to 8.28; $p < 0.001$), followed by a plateau from 2022 to 2024 (APC: 0.14%; 95% CI: -6.41 to 7.15; $p = 0.964$).

Forecasts suggest that female AAMRs may increase modestly to 6.37 (95% CI: 5.38 to 7.36) by 2030 and 7.29 (95% CI: 5.67 to 8.90) by 2040, with a forecasted AAPC of 1.40%, suggesting a continued upward trend at a slower pace than observed historically (**Figure 2, Supplementary**

Table 1 and 8)

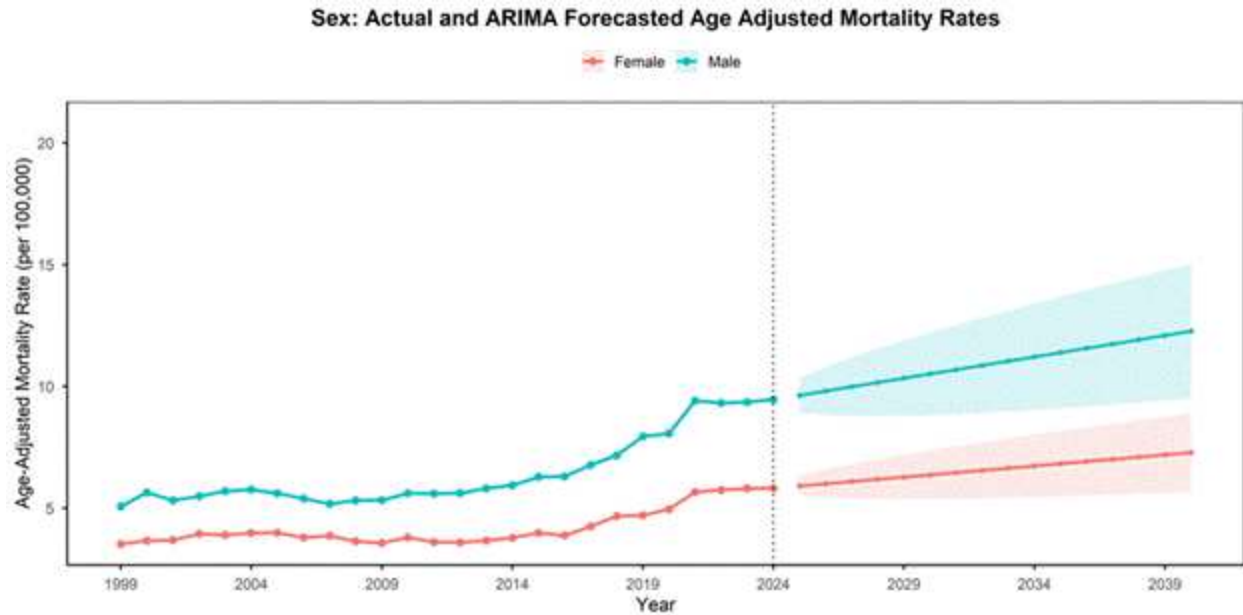


Figure 2. Sex-stratified age-adjusted mortality rates (AAMRs) for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years, 1999–2024, with ARIMA-based projections through 2040.

Stratified by Race:

Among Hispanic or Latino populations, AAMRs increased from 3.81 in 1999 to 6.38 in 2024. Overall trends showed a significant increase (AAPC: 1.71%; 95% CI: 0.96 to 2.47; $p < 0.001$). Rates remained relatively stable from 1999 to 2014 (APC: -0.58% ; 95% CI: -1.61 to 0.46 ; $p = 0.257$), followed by a sharp and significant increase from 2014 to 2024 (APC: 5.24% ; 95% CI: 3.99 to 6.51 ; $p < 0.001$), indicating a recent acceleration. Forecasts suggest that AAMRs may remain relatively stable at approximately 6.38 through 2030 (95% CI: 4.19 to 8.57) and 2040 (95%CI: 2.80 to 9.96), with no projected change in trend (forecast AAPC: 0%), indicating a plateau following the recent increase.

208 Among Asian or Pacific Islander populations, AAMRs increased from 3.01 in 1999 to 4.01 in
 209 2024, with a significant overall rise (AAPC: 1.53%; 95% CI: 0.24 to 2.84; $p = 0.020$). A non-
 210 significant decline was observed from 1999 to 2013 (APC: -1.71% ; 95% CI: -3.67 to 0.30 ; $p =$
 211 0.091), followed by a marked and statistically significant increase from 2013 to 2024 (APC:
 212 5.80% ; 95% CI: 4.01 to 7.63 ; $p < 0.001$).
 213 Projections indicate that AAMRs may remain relatively stable at approximately 4.01 by 2030
 214 (95% CI: 2.22 to 5.80) and 2040 (95%CI: 1.08 to 6.94) with a forecast AAPC of 0%, suggesting
 215 no further increase after the recent rise.

216 Among Black or African American populations, AAMRs rose from 2.72 in 1999 to 4.79 in 2024.
 217 The overall trend demonstrated a significant increase (AAPC: 2.31% ; 95% CI: 1.47 to 3.15; $p <$
 218 0.001), Rates remained relatively stable between 1999 and 2013 (APC: -0.65% ; 95% CI: -1.85 to
 219 0.57 ; $p = 0.281$), followed by a pronounced and statistically significant increase from 2013 to 2024
 220 (APC: 6.19% ; 95% CI: 4.88 to 7.52; $p < 0.001$), representing the steepest recent rise among all
 221 groups. Forecasts suggest that AAMRs may remain relatively stable at approximately 4.79 through
 222 2030 and 2040, with (95% CI: 3.13 to 6.45) and (95%CI: 2.08 to 7.50), respectively. The forecast
 223 AAPC of 0% indicates a plateau after the recent increase.

224 Among White populations, AAMRs increased from 4.25 in 1999 to 8.09 in 2024, with a significant
 225 overall rise (AAPC: 2.54% ; 95% CI: 1.83 to 3.25; $p < 0.001$). A significant increase was observed
 226 from 1999 to 2004 (APC: 2.39% ; 95% CI: 0.73 to 4.07; $p = 0.008$), followed by a non-significant
 227 decline between 2004 and 2009 (APC: -1.66% ; 95% CI: -3.81 to 0.54 ; $p = 0.126$). Rates then
 228 increased significantly from 2009 to 2016 (APC: 2.30% ; 95% CI: 1.21 to 3.40; $p < 0.001$), with a
 229 sharp rise during 2016–2021 (APC: 7.84% ; 95% CI: 6.02 to 9.68; $p < 0.001$). The most recent
 230 period (2021–2024) showed a non-significant increase (APC: 1.87% ; 95% CI: -0.55 to 4.34 ; $p =$

0.119).

Projections indicate that AAMRs may continue to increase, reaching 9.64 (95% CI: 7.52 to 11.77) by 2030 and 12.23 (95% CI: 6.17 to 18.28) by 2040, with a forecast AAPC of 2.57%, suggesting sustained growth consistent with historical trends (Figure 3, Supplementary Table 2 and 8)

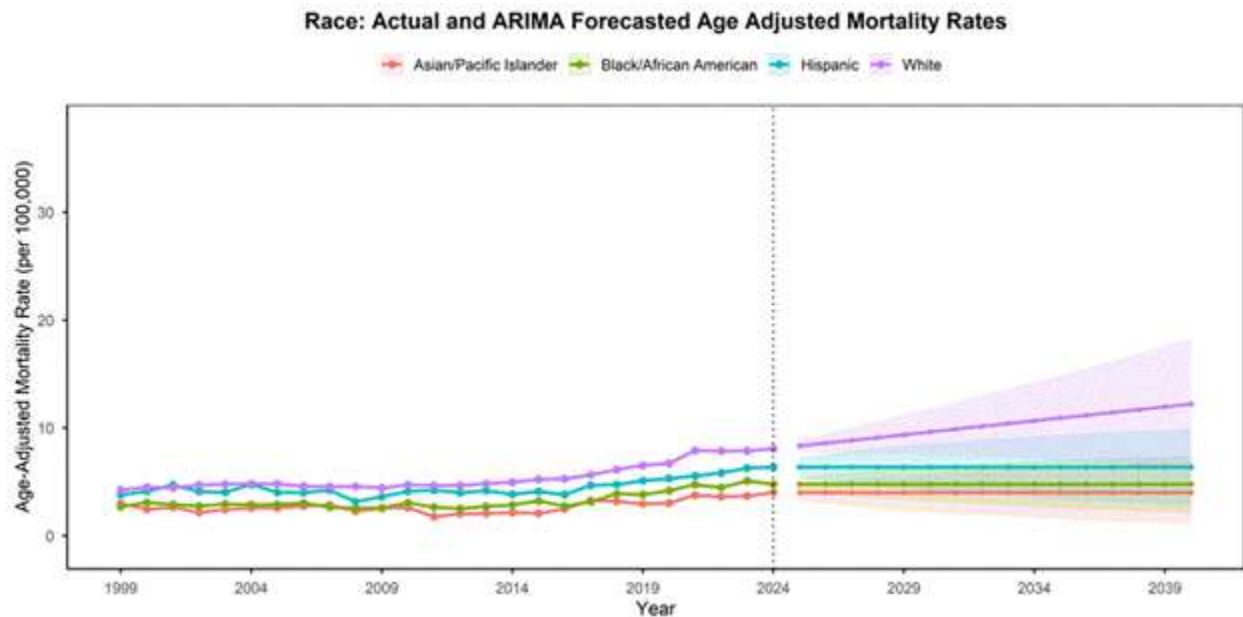


Figure 3. Race/ethnicity-stratified age-adjusted mortality rates (AAMRs) for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years, 1999–2024, with ARIMA-based projections through 2040.

Stratified by Age-Group:

Among individuals aged 55–74 years, AAMRs increased from 1.23 in 1999 to 1.98 in 2024, with a significant overall increase (AAPC: 1.73%; 95% CI: 0.32 to 3.15; $p = 0.016$). Trend analysis showed a non-significant increase from 1999 to 2003 (APC: 3.16%; 95% CI: -0.99 to 7.48 ; $p =$

0.124), followed by a significant decline between 2003 and 2009 (APC: -4.22% ; 95% CI: -6.99 to -1.38 ; $p = 0.007$). Rates then remained relatively stable from 2009 to 2013 (APC: 1.32% ; 95% CI: -4.59 to 7.60 ; $p = 0.643$), before a marked and significant increase from 2013 to 2022 (APC: 6.42% ; 95% CI: 5.36 to 7.49 ; $p < 0.001$). A non-significant decline was observed during 2022–2024 (APC: -2.48% ; 95% CI: -9.96 to 5.61 ; $p = 0.505$). ARIMA-based projections suggest that AAMRs may remain relatively stable at approximately 1.98 per 100,000 through 2030 (95% CI: 1.49 – 2.47) and 2040 (95% CI: 1.18 – 2.78). The forecast AAPC is 0% , suggesting no sustained long-term increase in this age group.

Among individuals aged ≥ 75 years, AAMRs increased substantially from 11.46 in 1999 to 21.08 in 2024, with a significant overall increase (AAPC: 2.30% ; 95% CI: 1.79 to 2.81 ; $p < 0.001$). A modest but significant increase was observed from 1999 to 2015 (APC: 0.62% ; 95% CI: 0.30 to 0.94 ; $p = 0.001$), followed by a sharp and accelerated increase between 2015 and 2021 (APC: 6.86% ; 95% CI: 5.28 to 8.47 ; $p < 0.001$). The most recent period (2021–2024) showed a continued but non-significant increase (APC: 2.41% ; 95% CI: -0.44 to 5.35 ; $p = 0.094$).

Projections indicate continued growth in this age group, with AAMRs reaching 24.86 (95% CI: 19.53 to 30.19) by 2030 and 30.97 (95% CI: 13.47 to 48.47) by 2040. The forecast AAPC of 2.35% suggests sustained long-term increases consistent with historical trends (**Figure 4, Supplementary Table 7 and 8**)

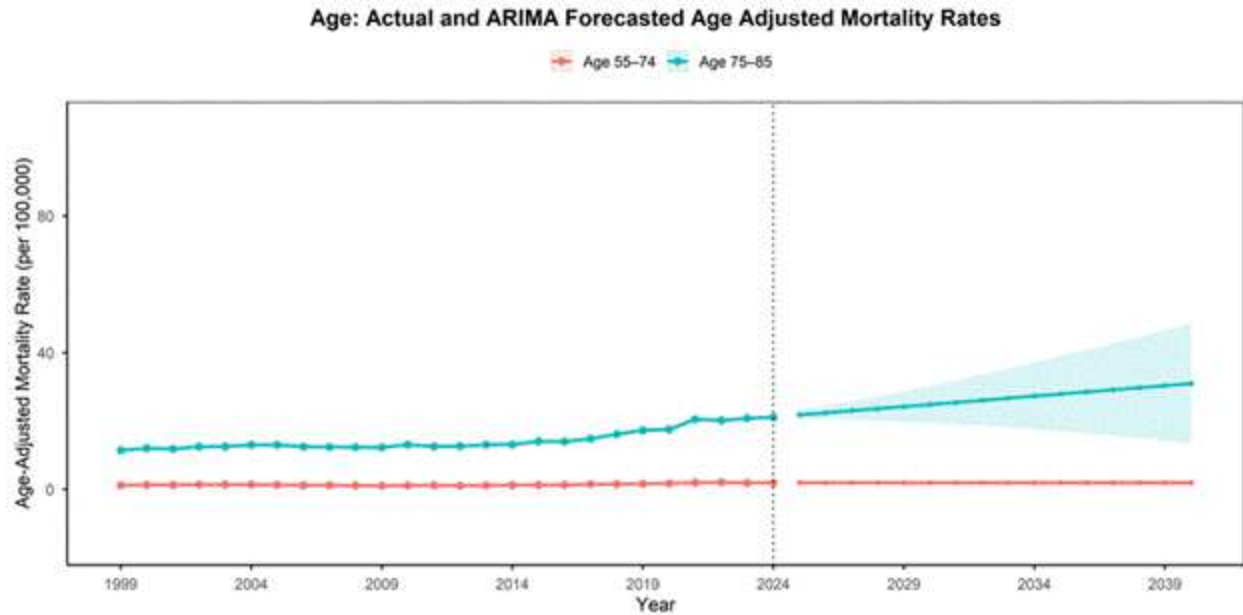


Figure 4. Age group–stratified mortality rates for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years, 1999–2024, with ARIMA-based projections through 2040.

Stratified by Urbanization:

Among metropolitan populations, AAMRs increased from 3.93 in 1999 to 5.99 in 2020, with a significant overall increase (AAPC: 1.95%; 95% CI: 1.33 to 2.58; $p < 0.001$). Trend analysis showed a non-significant increase from 1999 to 2004 (APC: 1.76%; 95% CI: -0.15 to 3.70 ; $p = 0.069$), followed by a non-significant decline between 2004 and 2012 (APC: -0.65% ; 95% CI: -1.72 to 0.44 ; $p = 0.220$). A marked and statistically significant increase was observed from 2012 to 2020 (APC: 4.74%; 95% CI: 3.99 to 5.51; $p < 0.001$), indicating an acceleration in recent years. ARIMA-based projections suggest continued gradual increases in metropolitan AAMRs, reaching

6.97 (95% CI: 5.88 to 8.05) in 2030 and 7.95 (95% CI: 6.41 to 9.45)) by 2040. The forecast AAPC (1.45%) indicates a sustained but slower upward trend compared with historical estimates.

Among non-metropolitan populations, AAMRs increased from 4.88 in 1999 to 7.49 in 2020, with a significant overall increase (AAPC: 1.54%; 95% CI: 0.79 to 2.29; $p < 0.001$). Rates remained relatively stable from 1999 to 2014 (APC: -0.37% ; 95% CI: -1.03 to 0.29 ; $p = 0.252$), followed by a sharp and significant increase between 2014 and 2020 (APC: 6.48% ; 95% CI: 4.12 to 8.89 ; $p < 0.001$), indicating a pronounced recent rise in rural mortality trends. Forecasts suggest that AAMRs may remain relatively stable at approximately 7.49 through 2030 (95% CI: 5.02 to 9.95) in 2030 and 2040 (95% CI: 4.0 to 10.97). The forecast AAPC of 0% suggests stabilization after the recent increase, although uncertainty intervals remain wide (**Figure 5, Supplementary Table 4 and 8**)

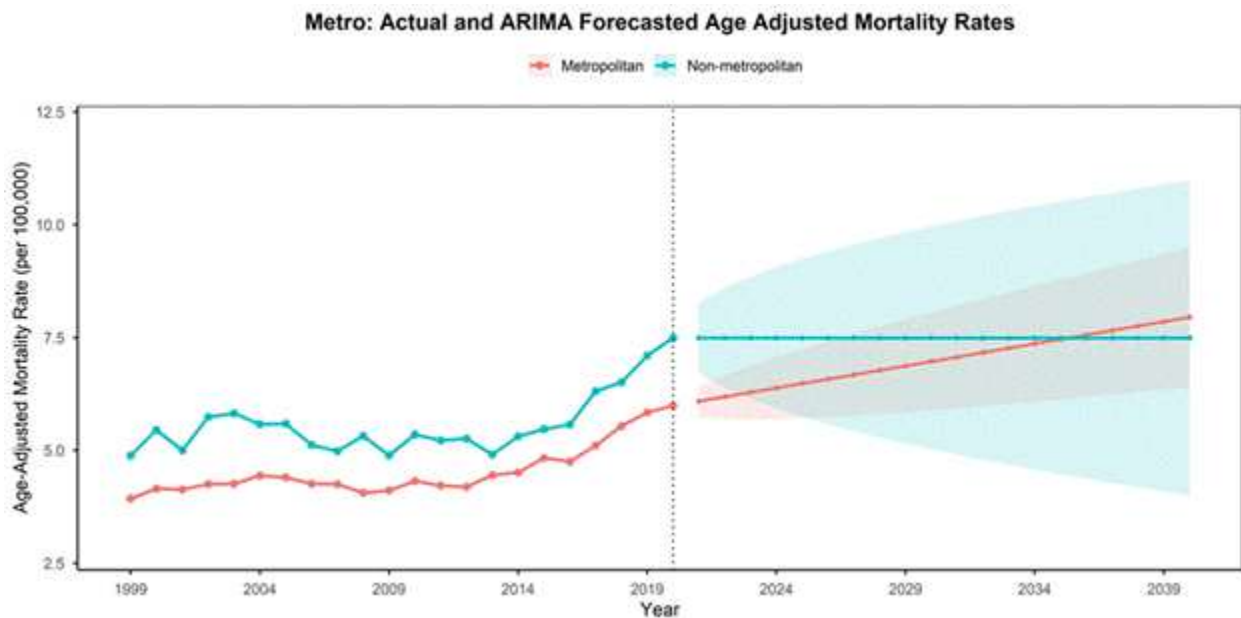


Figure 5. Urbanization-stratified age-adjusted mortality rates (AAMRs) for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years, 1999–2024, with ARIMA-based projections through 2040.

Stratified by Census Region:

Between 1999 and 2024, AAMR increased significantly across all U.S. Census regions, although the magnitude and temporal patterns varied.

In the Northeast, AAMRs rose from 3.48 to 6.33, with a significant overall increase (AAPC: 2.40%; 95% CI: 1.79 to 3.01; $p < 0.001$). Rates increased modestly from 1999 to 2014 (APC: 0.94%; 95% CI: 0.17 to 1.71; $p = 0.019$), followed by a sharper rise during 2014–2024 (APC: 4.63%; 95% CI: 3.50 to 5.77; $p < 0.001$).

In the Midwest, AAMRs increased from 4.75 to 8.44 (AAPC: 2.17%; 95% CI: 1.58 to 2.76; $p < 0.001$), with a non-significant decline from 1999 to 2013 (APC: -0.36% ; 95% CI: -1.19 to 0.46 ; $p = 0.370$) preceding a marked increase during 2013–2024 (APC: 5.48% ; 95% CI: 4.51 to 6.46 ; $p < 0.001$).

In the South, AAMRs increased from 3.83 to 7.09, with a significant overall trend (AAPC: 2.34% ; 95% CI: 1.19 to 3.50 ; $p < 0.001$). Trends included a non-significant increase from 1999 to 2003 (APC: 2.66% ; 95% CI: -1.29 to 6.77 ; $p = 0.171$), a borderline non-significant decline from 2003 to 2009 (APC: -2.55% ; 95% CI: -5.12 to 0.08 ; $p = 0.056$), a significant rise during 2009–2016 (APC: 2.52% ; 95% CI: 0.65 to 4.42 ; $p = 0.012$), and a pronounced acceleration in 2016–2021 (APC: 8.40% ; 95% CI: 5.40 to 11.48 ; $p < 0.001$), followed by a non-significant increase in 2021–2024 (APC: 1.73% ; 95% CI: -1.88 to 5.47 ; $p = 0.322$).

In the West, AAMRs increased from 4.48 to 7.74 (AAPC: 2.37%; 95% CI: 1.80 to 2.94; $p < 0.001$), with a borderline non-significant trend from 1999 to 2014 (APC: 0.73%; 95% CI: -0.01 to 1.48; $p = 0.053$) and a significant increase during 2014–2024 (APC: 4.87%; 95% CI: 3.85 to 5.90; $p < 0.001$).

ARIMA projections indicate continued increases in AAMRs across all regions through 2040. In the Northeast, rates are projected to reach 7.01 (95% CI: 5.44 to 8.59) by 2030 and 8.15 (95% CI: 5.59 to 10.72) by 2040, corresponding to a forecasted AAPC of 1.58%. In the Midwest, AAMRs are expected to increase to 9.41 (95% CI: 7.73 to 11.09) by 2030 and 10.98 (95% CI: 8.25 to 13.71) by 2040 (forecast AAPC: 1.52%). The South is projected to experience the steepest increase, reaching 8.49 (95% CI: 6.34 to 10.64) by 2030 and 10.83 (95% CI: 4.53 to 17.12) by 2040, with a forecasted AAPC of 2.63%. In the West, AAMRs are predicted to rise to 8.52 (95% CI: 6.66 to 10.39) by 2030 and 9.83 (95% CI: 6.78 to 12.88) by 2040, reflecting a forecasted AAPC of 1.49%.

Overall, while all regions demonstrate sustained increases in AAMRs, the South shows the most pronounced future growth, whereas the Northeast, Midwest, and West exhibit continued but relatively slower increases compared to historical trends (**Figure 6, Supplementary Table 3 and 8**)

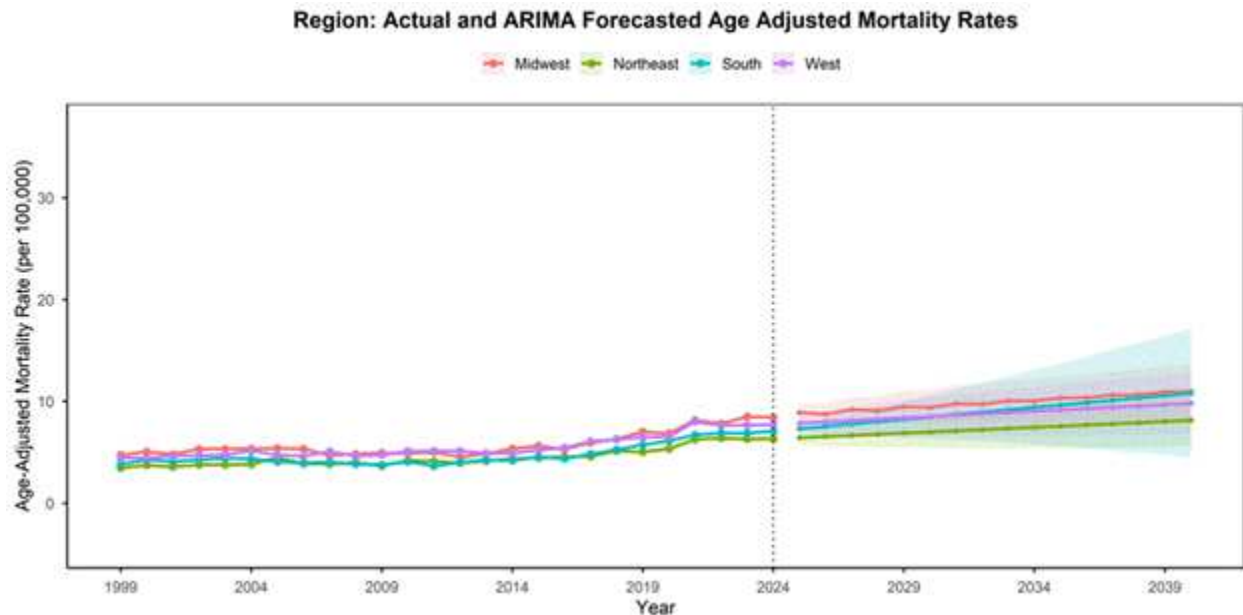


Figure 6. Census region–stratified age-adjusted mortality rates (AAMRs) for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years, 1999–2024, with ARIMA-based projections through 2040.

Stratified by State:

State-level analysis showed substantial variation in AAMRs. The highest rates were observed in Oregon (8.39 per 100,000), Vermont (8.00), Minnesota (7.66), South Dakota (7.54), and North Dakota (7.41). In contrast, the lowest rates were reported in Nevada (2.17), Arizona (3.11), New York (3.14), and Georgia (3.17).

Most states had intermediate rates (4–6 per 100,000), including California (4.87), Texas (4.94), and Florida (3.64). Overall, higher rates were generally observed in northern and Midwestern

states, whereas lower rates clustered in parts of the South and Northeast (Figure 7, Supplementary Table 5)

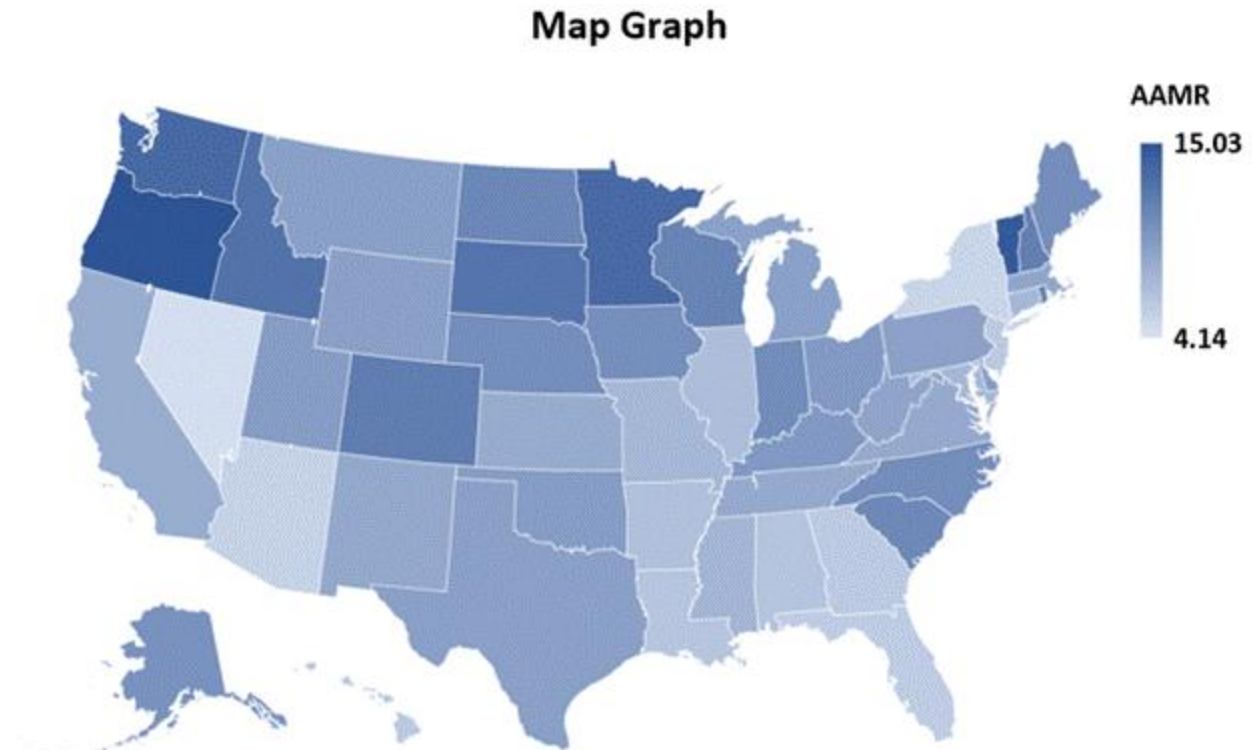


Figure 7. Geographic distribution of state-level age-adjusted mortality rates (AAMRs) for mortality involving both heart failure and interstitial lung disease among U.S. adults aged ≥ 55 years in the United States, 1999–2024.

Stratified by Place of Death:

Across the combined study periods, most deaths occurred in medical facilities, particularly inpatient settings ($n = 42,538$), followed by deaths at home ($n = 28,679$) and in nursing home/long-term care facilities ($n = 17,183$). Smaller proportions were observed in hospice facilities ($n =$

5,444), outpatient or emergency settings ($n = 3,625$), and other locations ($n = 3,570$), while relatively few deaths were recorded as dead on arrival ($n = 218$) or with unknown place of death (Figure 8, Supplementary Table 6)

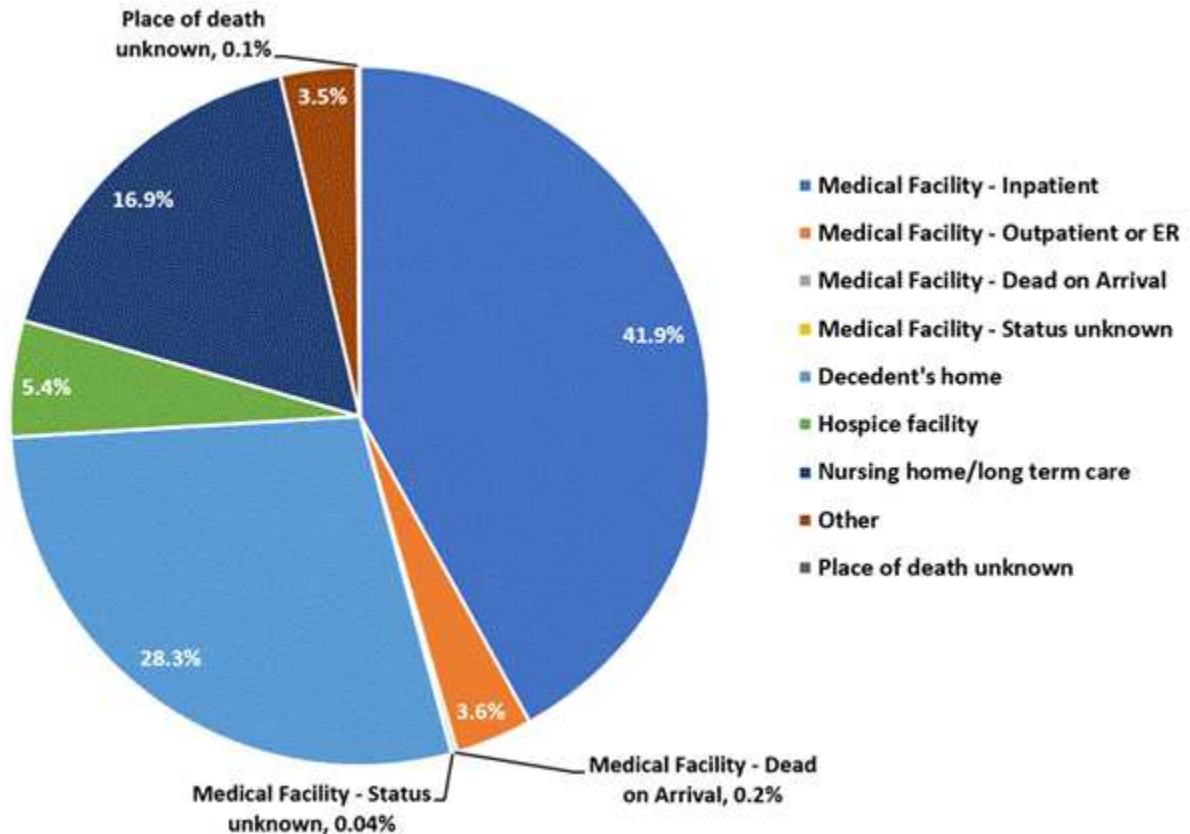
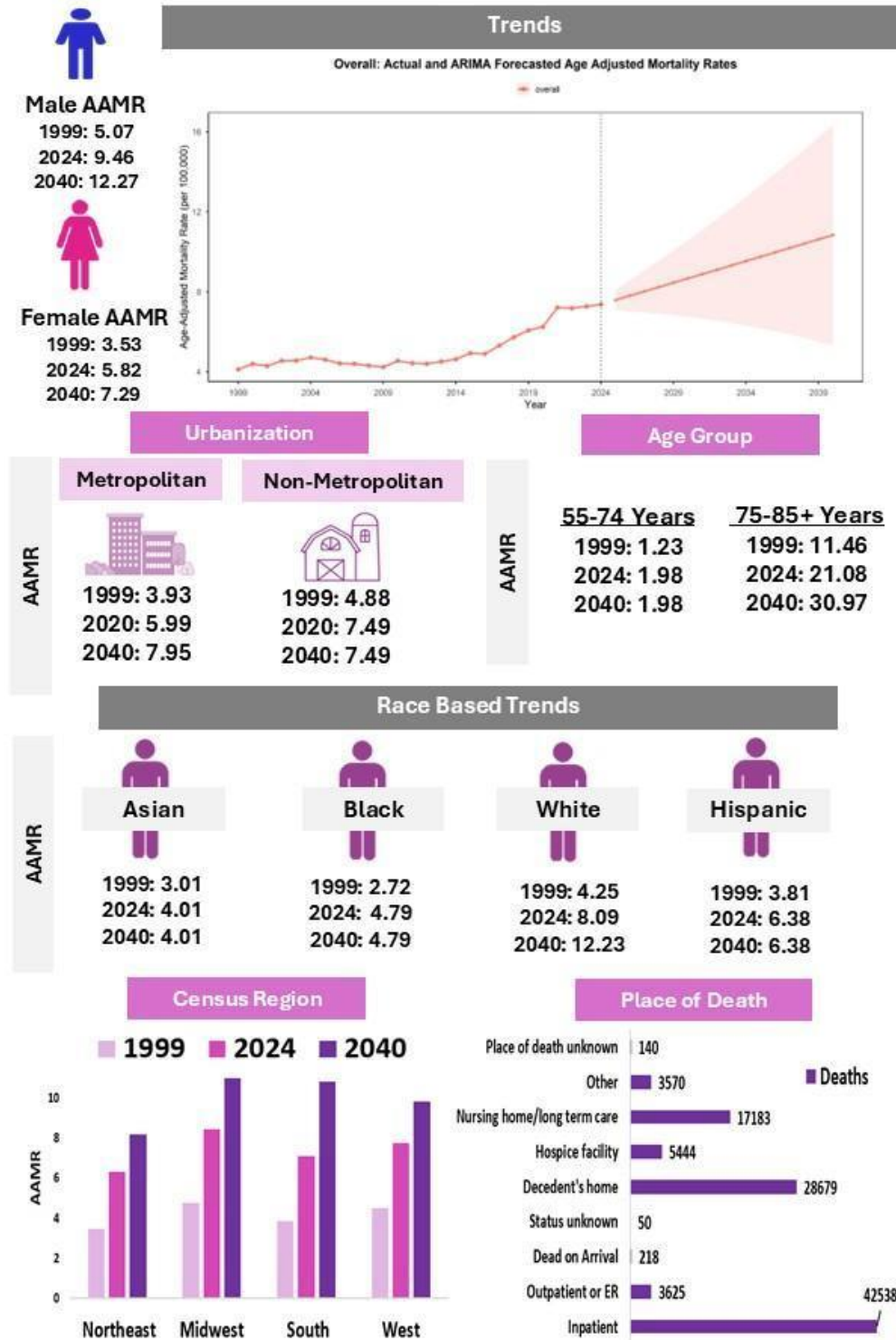


Figure 8. Distribution of place of death among decedents with mortality involving both heart failure and interstitial lung disease in the United States, 1999–2024.

Figure 9. Central Illustration

Central Illustration : “Temporal Trends and Projections in Mortality from Heart Failure and Interstitial Lung Disease in the United States, 1999–2040: A CDC WONDER Analysis”.



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367 **DISCUSSION**

368 The convergence of heart failure (HF) and interstitial lung disease (ILD) within the same patient
369 represents a pathophysiological alliance whose joint mortality consequences have received limited
370 systematic characterization at the population level. The present analysis, spanning more than two
371 decades of national mortality data, documents a sustained and accelerating upward trajectory in
372 AAMR among adults aged 55 years and older with coexisting HF and ILD in the United States,
373 rising from 4.12 to 7.37 per 100,000 between 1999 and 2024. This trajectory is not an artifact of
374 aging demographics alone; it reflects two mutually amplifying disease processes operating through
375 shared fibrotic, hemodynamic, and inflammatory pathways within a healthcare system that has
376 historically managed these conditions in isolation from one another [20,21]. No prior population-
377 based study has characterized the full temporal, demographic, and geographic scope of this co-
378 mortality burden across a multi-decade window, and the findings carry direct implications for
379 clinical management, public health strategy, and resource allocation for one of the most
380 underrecognized high-risk populations in American medicine.

381

382 The multi-phase upward trajectory observed across the study period reflects mechanisms deeply
383 and bidirectionally embedded in the pathophysiology of both conditions. ILD initiates chronic
384 hypoxia and progressive pulmonary fibrosis that elevates pulmonary vascular resistance, driving
385 pulmonary hypertension and right ventricular failure [22]. The right ventricle, ill-designed for
386 sustained pressure overload, undergoes progressive decompensation substantially accelerated
387 when the pulmonary vascular bed is simultaneously destroyed by fibrotic disease [23]. Conversely,
388 left-sided HF generates pulmonary venous congestion and elevated capillary wedge pressure,

creating an interstitial edematous milieu that impairs gas exchange and may independently promote fibrotic remodeling through chronically elevated hydrostatic forces and inflammatory signaling [24]. These bidirectional mechanisms share common molecular substrates, including transforming growth factor-beta signaling, extracellular matrix dysregulation, and renin-angiotensin-aldosterone system activation, all of which promote fibrosis simultaneously in the myocardium and pulmonary interstitium [25,26]. Identification of shared extracellular matrix receptor interactions and focal adhesion signaling as common pathogenic denominators for both conditions at the genetic level reinforces the biological coherence of the co-mortality burden documented here [27].

The most striking feature of the overall trend is the pronounced acceleration between 2016 and 2021, coinciding with progressive aging of large birth cohorts into the highest-risk age stratum, and sustained epidemiological consequences of cigarette exposure. The increasing trend between these years can also be due to the impact of the COVID-19 pandemic on cardiopulmonary mortality, as COVID-19 produced documented excess HF-related mortality of approximately 13 to 26 percent above projected baseline rates, especially pronounced among males, older adults, and rural residents populations constituting the highest-risk subgroups in this analysis [28]. The ARIMA-projected trajectory estimated at 8.67 per 100,000 by 2030 and 10.84 by 2040, though subject to uncertainty in the outer forecast years, provides no reassurance that the underlying epidemiological forces driving this burden have been contained.

The substantially higher AAMR among males throughout the study period reflects the sexual dimorphism in both HF epidemiology and ILD phenotypic distribution. Men are disproportionately predisposed to systolic heart failure due to a higher lifetime prevalence of

coronary artery disease and myocardial infarction, conditions that directly compromise contractile function and propagate left-heart congestion [29], while idiopathic pulmonary fibrosis (IPF), the most prevalent and most lethal form of progressive ILD, occurs predominantly in older males with histories of cigarette exposure [21]. The compounding of these two phenotypes creates a particularly hostile cardiopulmonary environment in which right ventricular failure from fibrotic lung disease and left ventricular dysfunction from ischemic cardiomyopathy coexist, each worsening the other through ventricular interdependence [24].

The persistent near-equivalent rate of increase across both sexes warrants specific attention. Women with HF are more frequently affected by heart failure with preserved ejection fraction phenotype, whose pulmonary hemodynamic consequences may impose an independent ILD-promoting burden through chronically elevated pulmonary venous pressures [25,29]. Sex disparities in cardiovascular medicine are well-documented: women are systematically underdiagnosed, undertreated, and underrepresented in clinical trials defining the evidence base for both HF and ILD management [30]. The sustained rise in female co-mortality signals that sex-specific biological vulnerabilities and structural barriers to diagnosis are converging to produce a trajectory neither improving nor diverging from the male trajectory in a clinically meaningful way, demanding sex-disaggregated research and equitable trial representation [30].

White populations carried the highest absolute rates throughout the study period, consistent with the greater prevalence and incidence of IPF in White Americans, driven partly by differences in genetic susceptibility, occupational exposure histories, and smoking patterns [31]. The steepest recent increase among Black or African American populations from 2013 to 2024 parallels documented national trends in which Black individuals bear disproportionately high age-adjusted HF mortality rates, driven by higher hypertension prevalence, earlier HF onset, and structural

inequities in access to guideline-directed medical therapy and advanced HF interventions [32]. The convergence of elevated HF burden with documented underdiagnosis of ILD among Black patients, attributable partly to limited access to specialist evaluation and high-resolution CT imaging, creates conditions in which both diseases progress further before recognition, translating into higher population-level mortality [31].

The more recent acceleration among Hispanic or Latino and Asian or Pacific Islander populations may reflect increasing penetration of smoking-related and aging-related cardiopulmonary disease as risk factor prevalence evolves. Rising rates of hypertension, diabetes, and metabolic syndrome in these groups, combined with accelerating demographic aging, create a foundation for co-morbid HF-ILD mortality likely to grow substantially without targeted preventive and diagnostic intervention [33]. Forecasted plateaus for these populations through 2040 should be interpreted with caution, given wide confidence intervals and the sensitivity of projections to future access-to-care interventions.

The dramatic concentration of mortality in the 75 to 85 year age stratum, with rates more than tenfold those among adults aged 55 to 74 years, captures the compounding interaction between aging biology, accumulated fibrotic burden, and diminished physiological reserve. Aging is now recognized as the single most powerful predisposing biological process for both IPF and systolic HF, operating through accelerated biological aging of both alveolar epithelial and myocardial cell populations [34]. IPF typically presents in the seventh decade or later with incidence increasing exponentially with age, closely mirroring the age-associated rise in HF prevalence [21].

The projected continued increase in older adult mortality is estimated at 24.86 per 100,000 by 2030 and 30.97 by 2040 in the 75–85 year age group, with projections carrying widening uncertainty at longer time horizons occurring against an American population aging at an historically

unprecedented rate. HF prevalence is projected to affect 8.7 million Americans by 2030 and more than 11 million by 2050, the majority in this oldest age stratum [33]. The intersection of these demographic forces with the mortality consequences of coexisting ILD makes this growing burden not merely a historical observation but a prospective public health emergency requiring immediate investment in cardiopulmonary comorbidity screening for older adults [20,21].

Consistently higher mortality in non-metropolitan compared with metropolitan populations represents one of the most consequential structural inequities in these findings. Rural Americans carry a disproportionate burden of risk factors underlying both HF and ILD, including higher smoking rates, greater occupational exposure to pulmonary fibrogenic agents, including mineral dust and agricultural particulates, and substantially higher prevalence of uncontrolled hypertension and ischemic heart disease, all compounded by documented barriers to cardiology and pulmonary specialist care [35,36]. Patients with ILD in rural areas present to specialty centers with more advanced disease, reflecting delayed diagnosis and absence of antifibrotic therapy during the early, most treatment-responsive phase [35,36]. Older adults with decompensated HF presenting to rural hospitals experience significantly higher 30- and 90-day mortality than those managed in urban facilities, even after adjustment for clinical comorbidities, reflecting structural deficits in procedural capacity and specialist availability [35].

Geographic variation across U.S. Census regions, with the South projected to experience the steepest future increase in co-mortality rates and the Midwest sustaining the highest absolute burden, reflects the intersection of regional cardiovascular risk factor profiles, healthcare access infrastructure, and historical pulmonary exposure patterns [37]. The South's combination of high cardiovascular risk factor prevalence, tobacco use, economic disadvantage, limited insurance coverage, and concentration of high-burden HF and ILD populations creates conditions for the

most pronounced future growth in co-mortality, consistent with the region's documented position as the highest-burden area for cardiovascular mortality nationally [35,37]. State-level variation reflects a complex interplay of population age structure, occupational exposure histories, specialist density, and regional patterns of guideline-directed therapy receipt [36,37].

The predominance of inpatient medical facilities as the setting of death reflects the acute decompensation and progressive hypoxemic respiratory failure that characterize the terminal trajectory of coexisting HF and ILD conditions that individually and collectively tend to culminate in acute exacerbations requiring intensive medical intervention [23]. National trends document a gradual shift toward greater home and hospice-based HF death over time, with proportions occurring in hospice facilities rising significantly between 2003 and 2017 [38]. The substantial proportion of co-mortality occurring at home, however, may reflect a heterogeneous mix of planned home-based palliative care and unplanned terminal events with limited specialist involvement, a distinction with profound implications for end-of-life care quality that death certificate data alone cannot resolve, and one warranting dedicated investigation in this combined cardiopulmonary population [38,39].

Nursing home and long-term care facility deaths delineate a population in whom advanced cardiopulmonary disease has eroded functional independence to the point of institutional dependency, often without antifibrotic or advanced HF therapy, given barriers to specialist engagement in that setting [39]. Antifibrotic therapies nintedanib and pirfenidone have demonstrated meaningful slowing of forced vital capacity decline and improvement in transplant-free survival in real-world IPF populations, benefits systematically unavailable to patients managed entirely within nursing facilities or outside specialist networks [40,41].

Limitations:

Several limitations warrant acknowledgment. Firstly, death certificate-based surveillance is subject to systematic misclassification and underascertainment of coexisting conditions; ILD requires specialist evaluation for accurate coding, while HF may be underreported when another condition dominates [20,21]. Additionally, the requirement that both diagnoses appear concurrently on the same certificate introduces ascertainment bias, most pronounced in non-metropolitan areas, racial and ethnic minority populations, and older adults with limited specialist access [31,35]. Urbanization classifications spanning 1999–2020 reflect county-level designations that may not capture within-county heterogeneity or temporal reclassification, potentially misrepresenting rural-urban gradients. ICD-10 coding limitations further constrain diagnostic specificity, precluding granular etiologic differentiation between clinically distinct ILD and HF subcategories. Lastly, mortality data for American Indian or Alaska Native populations were subject to data suppression due to small cell counts, limiting estimates for this group and representing a critical surveillance gap.

This study leverages a nationally representative mortality dataset spanning over two decades, enabling robust temporal and geographic trend analyses across diverse demographic strata. The large sample size supports stable subgroup estimates, while standardized death certificate coding ensures consistency across states and years, facilitating valid national comparisons.

The ecological study design and absence of individual-level data preclude adjustment for critical confounders, including tobacco exposure history, body mass index, comorbid pulmonary hypertension, ejection fraction phenotype, antifibrotic therapy receipt, and socioeconomic determinants of healthcare access. Causal inference from population-level trends to individual-level mechanisms is not warranted, and all interpretations are contextualized as consistent with prior mechanistic and epidemiological literature rather than as proof of mechanism [25,26,27]. The

inability to distinguish ILD subtypes on the death certificate, in particular IPF from other fibrotic and inflammatory ILD phenotypes with different natural histories and therapeutic responsiveness, and the absence of data on disease severity, time from diagnosis to death, or the specific sequence of clinical deterioration represent further limitations [21]. Additionally, the ARIMA model used for time-series forecasting relies on assumptions of linearity and stationarity, which may limit its ability to capture nonlinear or abrupt shifts in mortality trends; projections derived from this model should therefore be interpreted with caution [42].

Conclusion:

From 1999 to 2024, mortality associated with coexisting HF and ILD among adults aged 55 years and older demonstrated a sustained upward trajectory that accelerated between 2016 and 2021, with projections indicating a continued rise through 2040. These deaths reflect the convergence of two mutually reinforcing diseases sharing fibrotic pathways, hemodynamic consequences, and common risk determinants. Disparities across sex, age, race and ethnicity, urbanization, and geography reveal a burden concentrated in populations with the greatest barriers to specialist care. These findings underscore the urgent need for integrated cardiac and pulmonary co-management, equity-focused expansion of antifibrotic and HF therapies into underserved communities, and improved documentation standards to fully capture the true burden of cardiopulmonary co-mortality.

Declarations:

- **Ethics approval and consent to participate:** This study utilized publicly available de-identified data from the CDC WONDER database and did not require institutional review board approval or informed consent.

- **Consent for publication:** Not applicable.
- **Availability of data and materials:** The datasets analyzed during the current study are publicly available in the CDC WONDER Multiple Cause-of-Death database at <https://wonder.cdc.gov/>
- **Competing interests:** The authors declare that they have no competing interests.
- **Funding:** No funding was received for this study.
- **Authors' contributions:** Conceptualization, Gaaitri Lohano; methodology, Gaaitri Lohano; Govinda Lohano; software and statistical analysis, Gaaitri Lohano; Hamza Sajid; validation, Gaaitri Lohano and Govinda Lohano; formal analysis, Gaaitri Lohano and Hamza Sajid; investigation, Gaaitri Lohano; data curation, Gaaitri Lohano and Fizzah Ikram ul Haq; writing—original draft preparation, Bhawan Kumar; Govinda Lohano; Muhammad Vazaym; Muhammad Jawad; Maryam Waqar; writing—review and editing, Bhawan Kumar, Arsalan Ahmed, Anid Hassan, Sakshi Chawla, Krish Patel, and Govinda Lohano; visualization, Fizzah Ikram ul Haq; supervision, Gaaitri Lohano; project administration, Gaaitri Lohano. All authors have read and agreed to the published version of the manuscript.
- **Acknowledgements:** Not applicable.

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