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Original Article

Long-Term Mortality Trends in Atrial Fibrillation and Renal Disease in the United States, 1999–2023: A Retrospective Analysis

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ABSTRACT

Background: The coexistence of atrial fibrillation (AF) and renal disease is a significant contributor to mortality and morbidity. However, comprehensive national mortality trends for AF among older adults with renal disease, including demographic and geographic variations, remain largely unexamined.
Methods: We performed a retrospective analysis of U.S. adult deaths (≥65 years) from 1999 to 2023 using the CDC WONDER Multiple Cause of Death database. Deaths were included when AF and kidney disease appeared in any mention field of the death certificate, regardless of the underlying cause of death. We calculated crude and age-adjusted mortality rates (CMR, AAMR) per 100,000 population, and temporal trends were assessed using Joinpoint regression to estimate annual percent change (APC) and average annual percent change (AAPC).
Results: A total of 372,652 deaths were attributed to both AF and renal disease in older adults. The national AAMR increased more than threefold, from 16.67 in 1999 to 54.45 per 100,000 in 2023 (AAPC: 5.10; $p < 0.001$). Men had higher absolute mortality, but women experienced a slightly steeper increase in AAMR. Non-Hispanic White individuals had the highest absolute mortality, while all racial/ethnic groups showed significant increases. The South reported the most deaths, the Northeast had the highest AAMR, and non-metropolitan areas consistently showed higher AAMR than metropolitan areas. Most deaths occurred in medical facilities (54.55
Conclusions: Mortality from AF and renal disease has substantially risen over the past 25 years, with marked disparities by sex, race/ethnicity, geography, and urbanization.

1. Introduction

Renal disease and atrial fibrillation (AF) significantly contribute to a major health burden, as their coexistence is one of the most significant causes of mortality and morbidity [1, 2]. Renal disease, which includes acute kidney injury (AKI), chronic kidney disease (CKD), renal insufficiency, and other unspecified renal disorders, poses a substantial health strain. The incidence of newly diagnosed AKI has increased from 80 to 242 cases per 1,000 patient years between 2007 and 2022 [3]. AKI alone represents a growing clinical challenge, and CKD affects over 35.5 million U.S. adults (≈ 14% of the adult population) as of 2023 [4]. Meanwhile, in 2021, AF was recorded on 232,030 death certificates and was the primary cause of death in 28,037 cases [5]. Therefore, AF and renal diseases have a high prevalence, especially in older adults [1].

Renal disease and AF have a bidirectional relationship. Patients with renal diseases are susceptible to developing AF due to fluid retention [6]. Also, these patients are further predisposed to AF by structural heart alterations, such as left atrial enlargement and fibrosis, and by electrolyte imbalances, such as elevated potassium or calcium levels, which can interfere with normal myocardial conduction and cause arrhythmias [7]. These are proposed mechanisms rather than mechanisms proven by mortality data. Because our

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analysis is based on death certificate data, the biological pathway linking renal disease and AF cannot be directly adjudicated. However, the onset of AF in patients with renal disease deteriorates renal outcomes through progressive organ damage, renal hypoperfusion, and thromboembolic events. This vicious cycle, in which each illness makes the others worse, results in a faster rate of clinical deterioration and an earlier death.

There are disparities in renal disease burden and AF-related mortality among U.S. racial/ethnic groups and by geography. For example, non-Hispanic (NH) Black adults bear a higher CKD burden relative to NH White adults [8, 9]. Because our study examines mortality mentions in the national death certificate database, rather than diagnosis or disease-detection rates, we focus on disparities in mortality rather than differential AF detection.

Long-term national trends in both AF and renal disease-related mortality among adults remain inadequately described. Most available evidence is limited to hospital-based cohorts or selected populations, and it lacks a comprehensive examination of demographic, geographic, and temporal variations across the United States. Our study aims to close this gap by using the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause-of-Death database to assess trends in AF and renal disease mortality among patients 65 or older in the United States between 1999 and 2023.

2. Methods

2.1. Study Design and Population

We conducted a retrospective analysis using death-certificate data from the CDC WONDER Multiple Cause of Death database for U.S. adults aged ≥ 65 years from 1999 to 2023. Deaths were included when AF (ICD-10 I48) and renal disease (ICD-10 N17, N18, N19, N28.9) appeared in any-mention (multiple-cause) fields of the death certificate, regardless of the underlying cause of death. These ICD-10 codes have been previously used to identify AF and renal disease in administrative databases [10, 11]. The primary kidney-disease definition included N17, N18, N19, and N28.9 to capture acute and chronic renal conditions, as well as unspecified renal disorders, commonly recorded on death certificates. Older adults were defined as individuals aged 65 years or older at the time of death, consistent with prior studies [12]. Similar investigations using the Multiple Cause-of-Death public-use files have been published previously [10, 13]. Institutional review board approval was not required for this study, as it used de-identified public-use data provided by the government and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting [14].

2.2. Data Abstraction

Data on population size and demographics, including sex, age, race, region, and state, were extracted. Place of Death was categorized into medical facilities, hospice, home, and nursing home/long-term care facilities. Racial and ethnic categories were classified as NH White, NH Black or African American, Hispanic or Latino, NH American Indian or Alaskan Native, and NH Asian or Pacific Islander. The National Center for Health Statistics Urban-Rural Classification Scheme was used to classify the population by urban (population ≥ 50,000) and rural (population < 50,000) counties, per the 2013 U.S. Census classification. [15] Regions were stratified into Northeast, Midwest, South, and West according to the U.S. Census Bureau definitions [16].

2.3. Data Quality and Completeness

Preliminary data exploration revealed substantial suppression of mortality counts in certain demographic strata, driven by small cell sizes (<10 deaths), potentially contributing to instability in rate estimates for these subgroups. CDC WONDER applies suppression to protect confidentiality; therefore, suppressed values were excluded from subgroup-specific analyses and included only in aggregated analyses where suppression was automatically resolved, and no imputation was performed. To maintain consistency across the study period, we used NCHS bridged-race population estimates for both mortality numerators and denominators, with age-adjusted mortality rates calculated using census-based and post-censal estimates standardized to the 2000 U.S. standard population. Deaths with unknown or missing demographic characteristics were included in overall analyses but excluded from subgroup-specific estimates (e.g., race- and sex-stratified analyses), following CDC WONDER reporting conventions.

2.4. Statistical Analysis

Crude and age-adjusted mortality rates (CMRs and AAMRs) with 95% CIs per 100,000 U.S. residents aged 65 years and older were extracted by year, sex, race/ethnicity, and state from 1999 to 2023, and urban-rural status was calculated for 1999-2020. The 2000 U.S. standard population was used to maintain consistency with CDC WONDER default settings and facilitate comparison with other published mortality studies [17]. Urban–rural analyses were limited to 1999–2020; 2021–2023 urban–rural rates were not available. CMR was determined by dividing the number of AF and renal disease patients by the corresponding U.S. population of that year. To quantify national annual trends in AF and renal disease-related mortality, the Joinpoint Regression Program (Joinpoint V 5.4.0, National Cancer Institute) was used to determine the annual percent change (APC) with 95% CI in AAMR. This method allows identification of significant changes in AAMR over time by fitting log-linear regression models where temporal variation occurred. Statistical significance was assessed using Monte Carlo permutation tests. The Average Annual Percent Change (AAPC) was calculated to summarize the overall trend across the entire study period. Results are presented with 95% CI, with $p < 0.05$ deemed statistically significant.

3. Results

3.1. Overall Mortality Trends

Throughout the study period, from 1999 to 2023, a total of 372,652 deaths occurred in which both AF and renal disease were co-mentioned on the death certificate. Place-of-death data were available for 372,646 cases. The majority of deaths occurred in medical facilities (54.55%), followed by nursing homes/long-term care facilities (20.30%), decedent's residence (17.09%), and hospice settings (4.93%). A small proportion (0.14%) of deaths occurred in unspecified locations, while the remaining (2.99%) occurred in other locations **(Supplemental Tables 1, 2)**.

The AAMR showed a significant increase overall, from 16.67 (95% CI: 16.23-17.10) in 1999 to 54.45 (95% CI: 53.82-55.08) in 2023, with an AAPC of 5.10 (95% CI: 4.51 to 6.30; $p < 0.001$). From 1999-2012, AAMR exhibited a significant increases, from 16.67 to 44.07 (APC: 5.88; 95% CI: 4.49 to 10.32; $p = 0.002$), which was followed by a subsequent non-significant decline to 32.1 in 2015 (APC: -8.43; 95% CI: -13.17 to 1.80; $p = 0.13$), and then a significant increase to 54.45 in 2023 (APC: 9.35; 95% CI: 7.01 to 16.08; $p = 0.002$) **(Supplemental Tables 3, 4)** and **(Figure 1)**.

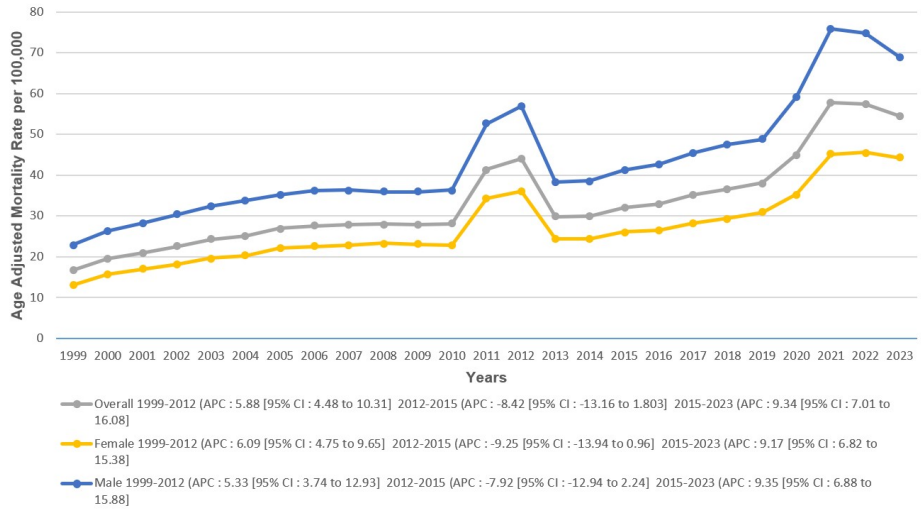

Figure 1: Overall and Sex-Stratified Atrial Fibrillation and Renal Disease-Related AAMRs per 100,000 in Adults in the United States, 1999-2023.

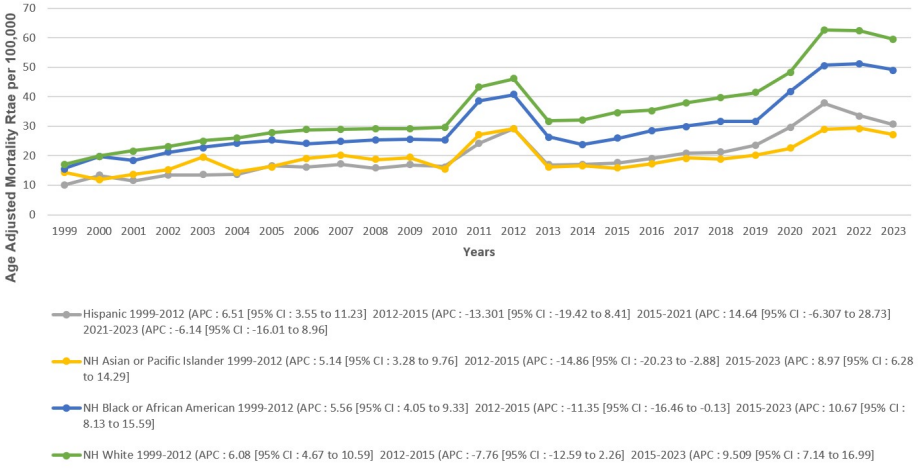

Figure 2: Atrial Fibrillation and Renal Disease-Related AAMRs per 100,000 Stratified by Race in Adults in the United States 1999-2023.

3.2. Gender Trends

Overall, men (deaths: 188,630, AAMR: 43.21) showed higher mortality rates than women (deaths: 184,022, AAMR: 26.85). However, women exhibited a greater AAPC of 5.04 (95% CI: 4.49 to 6.15; $p < 0.001$) than men, with an AAPC of 4.88 (95% CI: 4.22 to 6.19; $p < 0.001$). In 1999, the AAMR for men was 23.01 (95% CI: 22.14-23.88) compared to 13.16 (95% CI: 12.69-13.64) in women. These values increased to 68.92 (95% CI: 67.80–70.04) and 44.24 (95% CI: 43.50–44.99) by the year 2023.

AAMR for women showed a marked increase, from 13.16 in 1999 to 36.0 in 2012 (APC: 6.10; 95% CI: 4.75 to 9.66; $p = 0.004$), followed by a non-significant decline to 26.1 in 2015 (APC: -9.25; 95% CI: -13.94 to 0.96; $p = 0.08$), and then a significant increase to 44.24 in 2023 (APC: 9.17; 95% CI: 6.83 to 15.38; $p = 0.001$). In men, AAMR saw a sharp yet significant increase from 23.01 in 1999 to 56.9 in 2012 (APC: 5.33; 95% CI: 3.75 to 12.93; $p = 0.003$), followed by a steady yet non-significant drop to 41.22 in 2015 (APC: -7.93; 95% CI: -12.95 to 2.24; $p = 0.18$), and a significant surge to 68.92 in 2023 (APC: 9.35; 95% CI: 6.88 to 15.88; $p = 0.007$) **(Supplemental Tables 1-4)** and **(Figure 1)**.

3.3. Racial Trends

NH White individuals accounted for the highest number of deaths (319,700), followed by NH Black/African American individuals (27,666), Hispanic/Latino (15,744), and NH Asian/Pacific Islander (8,134). Consequently, NH White individuals demonstrated the greatest overall AAMR of 35.30, followed by NH Black/African American individuals (29.72), Hispanic/Latino individuals (19.83), and NH Asian/Pacific Islander individuals (19.49).

All races observed a significant increase in AAMR between 1999 and 2023; 17.12 to 59.63 (AAPC: 5.35; 95% CI: 4.77 to 6.57; $p < 0.001$) among NH White individuals, 15.71 to 49.1 (AAPC: 4.93; 95% CI: 4.30 to 6.09; $p < 0.001$) among NH Black/African American individuals, 10.05 to 30.53 (AAPC: 4.63; 95% CI: 3.76 to 6.21; $p < 0.001$) among Hispanic/Latino individuals, and 14.31 to 27.18 (AAPC: 3.63; 95% CI: 2.88 to 5.16; $p < 0.001$) among NH Asian/Pacific Islander individuals.

In brief, NH Asian/Pacific Islander individuals experienced a significant increase in AAMR from 14.31 in 1999 to 29.24 in 2012 (APC: 5.14; 95% CI: 3.28 to 9.76; $p = 0.004$), followed by a significant reduction to 15.72 in 2015 (APC: -14.86; 95% CI: -20.24

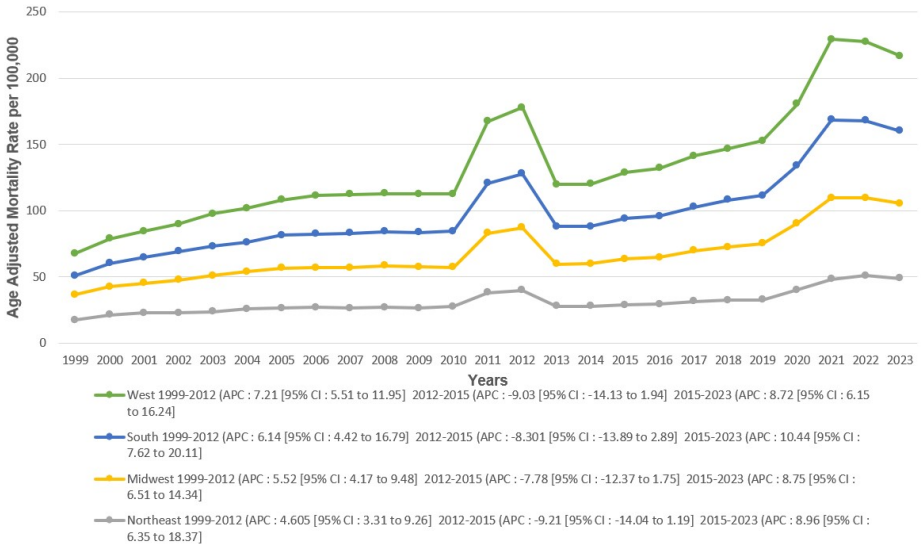

Figure 3: Atrial Fibrillation and Renal Disease-Related AAMRs per 100,000 Stratified by Census Region in Adults in the United States 1999-2023.

to -2.88; p = 0.008), and a sharp upward trend to 27.18 in 2023 (APC: 8.98; 95% CI: 6.29 to 14.29; p = 0.001). NH Black/African American individuals demonstrated a significant surge in AAMR throughout the study period, initially from 15.71 in 1999 to 40.61 in 2012 (APC: 5.56; 95% CI: 4.05 to 9.34; p < 0.001), followed by a significant decline, reaching 25.92 in 2015 (APC: -11.35; 95% CI: -16.46 to -0.14; p = 0.04), and a sharp yet significant rise to 49.10 in 2023 (APC: 10.68; 95% CI: 8.14 to 15.59; p = 0.004).

Hispanic/Latino individuals saw an initial significant incline in AAMR from 10.05 in 1999 to 29.28 in 2012 (APC: 6.52; 95% CI: 3.56 to 11.23; p = 0.02), followed by a non-significant drop to 17.58 in 2015 (APC: -13.30; 95% CI: -19.42 to 8.41; p = 0.07), a non-significant increase to 37.8 (APC: 14.64; 95% CI: -6.31 to 28.73; p = 0.06), and a non-significant decline to 30.53 in 2023 (APC: -6.15; 95% CI: -16.01 to 8.96; p = 0.37). NH White individuals experienced a significant rise from 17.12 in 1999 to 46.05 in 2012 (APC: 6.08; 95% CI: 4.68 to 10.60; p = 0.003), a non-significant decline to 34.81 in 2015 (APC: -7.77; 95% CI: -12.59 to 2.27; p = 0.17), and a significant surge in AAMR, reaching 59.63 in 2023 (APC: 9.51; 95% CI: 7.14 to 16.99; p = 0.003) **(Supplemental Tables 1, 3, 5)** and **(Figure 2)**.

3.4. Regional Trends

The Southern region reported the highest number of deaths (128,801), followed by the Midwest (90,671), the West (83,902), and the Northeast (69,278). Overall, AAMRs were highest in the Northeast (40.00), followed by the Midwest (35.89), the West (34.75), and the South (31.58). All regions demonstrated an overall increase in AAMR between 1999 and 2023. In the Northeast, AAMR increased from 17.61 to 48.97 (AAPC: 4.18; 95% CI: 3.61 to 5.38; p < 0.0001), while the Midwest saw a rise from 19.09 to 55.54 (AAPC: 4.81; 95% CI: 4.25 to 5.89; p < 0.001). The South saw an increase from 14.27 to 54.68 (AAPC: 5.61; 95% CI: 4.94 to 7.31; p < 0.001) over the same period. The West experienced an increase from 16.79 to 56.47 (AAPC: 5.52; 95% CI: 4.86 to 6.91; p < 0.001).

AAMR in the Northeast saw an initial, significant incline, from 17.61 in 1999 to 39.99 in 2012 (APC: 4.61; 95% CI: 3.31 to 9.26; p = 003), followed by a non-significant drop to 28.82 in 2015 (APC: -9.22; 95% CI: -14.05 to 1.19; p = 0.10), and a significant surge, reaching 48.97 in 2023 (APC: 8.96; 95% CI: 6.36 to 18.37; p = 0.005). In the Midwest, AAMR rose sharply and significantly from 19.09 in 1999 to 47.09 in 2012 (APC: 5.52; 95% CI: 4.17 to 9.49; p = 0.002), followed by a non-significant decline to 34.63 in 2015 (APC: -7.78; 95% CI: -12.38 to 1.75; p = 0.14), and a significant rise to 55.54 in 2023 (APC: 8.76; 95% CI: 6.51 to 14.34; p = 0.002).

In the Southern region, AAMR rose significantly from 14.27 in 1999 to 40.9 in 2012 (APC: 6.14; 95% CI: 4.43 to 16.79; p = 0.005), followed by a non-significant drop, reaching 30.71 in 2015 (APC: -8.30; 95% CI: -13.89 to 2.90; p = 0.22), and a significant surge to 54.68 in 2023 (APC: 10.45; 95% CI: 7.63 to 20.12; p = 0.009). The Western region experienced a marked increase in AAMR from 16.79 in 1999 to 49.70 in 2012 (APC: 7.21; 95% CI: 5.51 to 11.96; p = 0.006), followed by a non-significant reduction to 34.49 in 2015 (APC: -9.03; 95% CI: -14.14 to 1.95; p = 0.13), and a significant rise to 56.47 in 2023 (APC: 8.72; 95% CI: 6.16 to 16.24; p = 0.002) **(Supplemental Tables 3, 6)** and **(Figure 3)**.

3.5. Stratified by Urbanization

Between 1999 and 2020, metropolitan areas accounted for more deaths (226,486) than non-metropolitan areas (58,353). From 1999 to 2020, both metropolitan and non-metropolitan areas showed an increase in AAMR. AAMR in metropolitan areas rose from 16.35 to 42.89 (AAPC: 4.14; 95% CI: 3.48 to 5.19; p < 0.001), compared to non-metropolitan areas, which increased from 17.95 to 55.66 (AAPC: 4.73; 95% CI: 4.01 to 5.92; p < 0.001). The overall AAMR remained higher in non-metropolitan areas (34.51) relative to metropolitan areas (29.05).

Segmented trend analysis (1999-2020) showed that metropolitan regions experienced a significant increase in AAMR from 16.35 in 1999 to 43.11 in 2012 (APC: 5.86; 95% CI: 4.43 to 8.42; p = 0.010), followed by a non-significant decrease to 30.99 in 2015 (APC: -8.22; 95% CI: -12.49 to 0.33; p = 0.05), and a significant rise to 42.89 in 2020 (APC: 7.66; 95% CI: 3.80 to 17.51; p = 0.001). In non-metropolitan areas, AAMR rose significantly from 17.95 in 1999 to 48.68 in 2012 (APC: 5.98; 95% CI: 4.67 to 9.08; p = 0.012), followed by a non-significant drop to 37.34 in 2015 (APC: -7.61; 95% CI: -12.12 to 1.53; p = 0.09), and a significant surge,

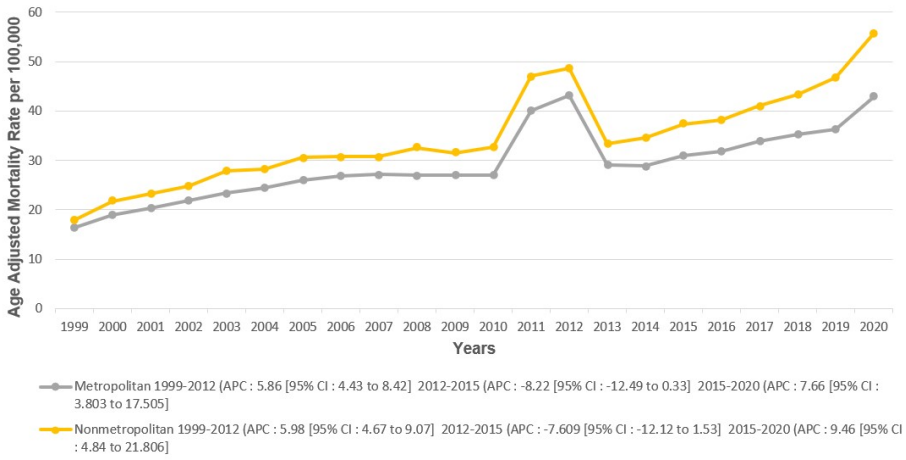

Figure 4: Atrial Fibrillation and Renal Disease-Related AAMRs per 100,000 Stratified by Urban-Rural Status in Adults in the United States 1999-2023.

reaching 55.66 in 2020 (APC: 9.46; 95% CI: 4.85 to 21.81; $p < 0.001$) **(Supplemental Tables 3, 7)** and **(Figure 4)**.

4. Discussion

This 25-year nationwide study has shown a dramatic increase in mortality with the co-occurrence of AF and renal disease mentioned on the death certificate in the United States. The AAMR increased by more than 3 times over the 25 years of this study. Overall, males had higher AAMR than females; however, females showed a steeper increase in AAMR over the same period. There were race-related patterns in mortality, with mortality being highest for NH Whites, yet steeply increasing AAMR trends were noted among Black, Hispanic, and Asian individuals as well. Increases in AAMR were highest in the Northeast, while more deaths occurred in the South. Non-metropolitan areas had higher AAMR than metropolitan areas for the entire period. Most of the deaths occurred in medical facilities; hospice had the lowest proportion of deaths. Across all subgroups, a recurring pattern of a sharp rise until 2012, followed by a temporary dip and a subsequent surge post-2015, was consistently observed, underscoring a growing and disproportionate mortality burden in this dual-disease population.

A sex-stratified analysis reveals a paradoxical yet well-established phenomenon: men have higher AAMRs, but the increase in AAMR is steeper in women. In the literature, it is recognized that AF in women has historically been underdiagnosed, and it tends to have a higher stroke risk, more symptomatic burden, and potentially delayed rhythm control therapy [18–21]. This may help contextualize the observed steeper rise in mortality among women, suggesting potential gaps in recognition and management of AF in this subgroup that warrant further study. The present findings parallel reports that suggest a diagnostic gap in AF and renal disease care, especially for CKD, based on gender. There was a notable difference in the timing of the mortality peak: women had an earlier peak (1999 - 2012) than men (1999 - 2012), suggesting earlier progression or poorer health-seeking behavior [22, 23]. The second phase of acceleration (2015 -2023) aligns with national principal trends of diminishing gains in cardiovascular mortality, particularly affecting women with comorbidities [24].

Racial differences in AAMR were observed, with NH White people having the highest AF-associated renal mortality consistently over time, followed by NH Black and Hispanic people. Nonetheless, the steepest increases in AAMR were observed across all races, especially among NH Black and Hispanic people in the 2015 or later timeframe. These patterns may reflect broader structural and healthcare disparities that influence disease recognition, documentation, and outcomes, though mechanistic explanations remain speculative and untested in this dataset [25, 26]. AF has been historically underreported in Black individuals because of diagnostic bias and lower AF awareness. Still, new, larger population-based cohort studies demonstrate an increasing presentation with worse outcomes in Black renal disease cohorts [26–28]. Additionally, the variation in Hispanic and Asian/Pacific Islander AAMRs—evidenced by a collateral rise, decline, and resurgence—likely signifies instability within the health system.

Geographically, the Southern U.S. reported the most deaths, while the Northeast had the highest AAMR. The Northeast's higher AAMR may reflect underlying demographic age structure, regional differences in healthcare utilization, or variation in death certificate reporting practices. Meanwhile, the trends in the Midwest and the West were more intermediate. Interestingly, all regions showed a decline in 2012–2015, followed by a pickup that most likely coincides with national shifts in ICD coding practice and evolving renal disease management guidelines. The sharp AAMR increase in the West may also reflect regional variation in ICD-10 coding accuracy, cardiology workforce availability, or adoption of state-level quality initiatives that influence disease documentation [29–31].

As shown, although the absolute deaths occurred in metropolitan regions, AAMRs were significantly higher in non-metropolitan regions. It is important to note that urbanization data in CDC WONDER is available only through 2020; thus, urban–rural comparisons do not extend into the post-pandemic era. Fewer specialists, delayed presentation of conditions, and a greater burden of comorbidities among rural populations may explain some of the differences [32–34]. While telehealth expansion during COVID-19 was intended to reduce rural care disparities, our data extend only through 2020 and do not capture pandemic-era implementation or its effects on AF care delivery. Therefore, any telehealth-related inferences must be interpreted with caution [35]. Interpretation of mortality trends after 2019 should be approached cautiously, given the potential influence of COVID-era disruptions in death certification and coding practices. During 2020–2021, competing mortality risks,

strained healthcare access, and changes in cause-of-death attribution may have impacted the observed data. Additionally, shifts in ICD-10 coding guidance and COVID comorbidity reporting could artifactually influence the attribution of AF or renal disease.

The place-of-death analyses demonstrated that over half of the renal deaths attributed to AF were in medical facilities and fewer at home, or through hospice, which may reflect limited access to palliative care pathways. However, under-recording of hospice enrollment and selection effects in documentation likely contribute as well [36, 37]. However, low hospice utilization may also reflect structural and clinical constraints beyond access barriers. Prognostication in AF with CKD is often uncertain, complicating eligibility for hospice, which requires a six-month life expectancy. Medicare regulations discourage concurrent dialysis and hospice care, limiting enrollment for ESRD patients who choose to continue dialysis. Additionally, many patients receive palliative care in nursing homes without a formal hospice designation. Thus, the low hospice proportion may partly reflect systemic limitations in eligibility and care models. Past research shows that patients with AF and CKD frequently miss out on hospice referrals because they are often too complicated based on medication and unplanned rehospitalization needs [38, 39]. This highlights the need for early discussions at the end-of-life, particularly as slowing, progressive kidney disease is common in older adults who are also experiencing overall declining functional status.

4.1. Strengths and Limitations

This analysis used 25 years of nationally representative mortality data, providing a complete, stratified, geographically contextualized understanding of AF-related renal mortality, unlike previous studies that have either explored CKD or AF in isolation. This dual-disease perspective, including all the renal diseases along with AF, has unearthed rich, real-world mortality patterns across gender, race, region, and urbanization. The level of detail from the joinpoint regression has yielded valuable insights into inflection points that would be obscured in linear analyses. In addition, this research fills important epidemiologic gaps by reporting underrecognized disparities in minority and rural populations with renal diseases and CVD, highlighting how systemic inequities may intersect with disease-specific risk.

As a retrospective review of the data available from CDC WONDER, this research is limited to the inherent limitations of death certificate reporting, the potential for misclassifying individuals based on their death records, and the absence of patient-level clinical detail (e.g., disease trajectory, type of AF (paroxysmal vs permanent), and treatment variables (e.g., dialysis, anticoagulation). The research design cannot establish causation due to its ecological and retrospective nature, nor can it account for competing risks from other cardiovascular comorbidities. Urbanization data was only available until 2020, and race/ethnicity classification may lack granularity to account for multiracial populations. In addition, the study protocol did not examine intermediate outcomes, such as hospitalization or arrhythmia burden, that might enable a richer mechanistic understanding of the renal disease's implications for mortality in CVD populations. The study protocol was vulnerable to the ecological fallacy, and results cannot substitute longitudinal cohort or randomized trial data. Still, these findings represent an exciting first step towards further prospective study and targeted interventions.

Another limitation is the inability to differentiate between AKI, CKD, and ESRD using the ICD-10 codes, which introduces heterogeneity within the renal population. Changes in dialysis practices—such as expanded access, revised initiation thresholds, increased use of home and peritoneal dialysis, and conservative kidney management—have evolved significantly over 25 years and may confound temporal trends in mortality. These shifting practices may influence both disease trajectory and how renal disease is recorded on death certificates, affecting the interpretation of AF-related mortality patterns.

Additional limitations include the inability to differentiate between the underlying cause and any-mention coding of AF and renal disease, which could influence the interpretation of mortality attribution. Race and ethnicity data on death certificates are subject to misclassification, especially among Hispanic, Asian, and multiracial individuals. The ICD-10 code N28.9, included in this study, is a non-specific renal diagnostic code and may lack clinical precision. The dataset relies on bridged-race methodology, which may obscure within-group heterogeneity. Importantly, treatment-related variables such as anticoagulation use, dialysis modality, or rhythm control strategies are unmeasured, and COVID-era deaths may not be directly comparable due to shifts in coding and care patterns during the pandemic.

4.2. Clinical implications and future directions

The steady rise in mortality due to AF and renal disease suggests the need for a unified care model that addresses the seamless transition of patient care from nephrologists to cardiologists, that addresses early diagnosis, anticoagulation appropriateness, and rhythm control focused on symptoms [40, 41]. Palliative care integration for late-stage renal disease with AF should also be prioritized to align end-of-life care and access to hospice better, and patients should be fast-tracked to guidelines that recognize the complexities of AF across all renal disease populations, particularly when considering bleeding risks and the burden of any underlying arrhythmia [42, 43]. Future research should explore the impact of emerging therapies—such as non-vitamin K antagonist oral anticoagulants in CKD or catheter ablation strategies in ESRD—on outcomes in this high-risk population, as these treatments could modify risk but are not captured in mortality data [44]. Finally, qualitative research exploring barriers to hospice access and to shared decision-making in patients with AF and renal disease is needed to improve health equity [45, 46].

4.3. Secular Trends in Detection and Documentation

When interpreting the observed rise in AF mortality, it is important to consider secular changes in diagnostic and documentation practices throughout the study period. After the shift to ICD-10 coding around 1999, there were numerous Centers for Medicare & Medicaid Services (CMS) initiatives in the 2011-2012 time frame aimed at increasing chronic comorbidity capture for reimbursement and risk adjustment, and some of the changes observed during this period may be due to those efforts [47]. Detection of AF also significantly improved during the study period due to the introduction of electronic health record (EHR)- triggered alerts and alerts from implantable cardiac monitors, point-of-care ECGs, and consumer-use wearables. These innovations led to improved detection sensitivity, and detection rather than increased incidence may have contributed to the perceived increase in morbidity and severity [48]. CKD detection and staging also changed during the study window due to standardized CKD staging (KDIGO 2002 and 2012 updates) and earlier detection, increasing the likelihood that renal disease would be identified as a contributing cause on death

certificates [49]. Lastly, a national effort to improve death certificate completion and education of physicians regarding completing the death certificate and documenting "coexisting conditions" such as AF and CKD, may have improved the identification of these conditions as being present at the time of death. Overall, these secular changes in practice indicate that some of the rise in atrial fibrillation-associated renal mortality in the United States may be due to improvements in identification and documentation rather than to increased biological or epidemiological factors.

5. Conclusions

Using a 25-year national dataset, we have demonstrated a concerning rise in AF and renal disease mortality in elderly individuals, with notable disparities based on sex, race, geography, and urbanization. The persistence of adverse mortality trends underscores a growing epidemiological burden among older adults with coexisting AF and renal disease. These findings call for targeted, prospective studies, particularly those linked to clinical registries, to better understand treatment patterns, disease trajectories, and opportunities for equitable intervention in this high-risk population.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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None.

Authors Contribution

MFH and AAI contributed to conceptualization, writing-original draft, and writing-review & editing. MRS, AG, and MH contributed to formal analysis and writing-original draft. MRF contributed to data curation and writing-original draft. MT contributed to formal analysis. KP contributed to data extraction and data curation. NH, MS, and ES contributed to writing-original draft. AA and MFA contributed to writing-review & editing. AA contributed to writing-review & editing. AMA and RA contributed to writing-review & editing, validation, and supervision.

Data Availability

The data that support the findings of this study are openly available in CDC-WONDER at https://wonder.cdc.gov/. The data supporting the findings of this study were obtained from the CDC WONDER online database (Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research). Further inquiries can be directed to the corresponding author.

References

1. Chen TH, Chu YC, Ou SM, Tarng DC. Associations of atrial fibrillation with renal function decline in patients with chronic kidney disease. Heart. 2022;108(6):438-44. [PMID: 34193464, https://doi.org/10.1136/heartjnl-2021-319297].
2. Lau YC, Proietti M, Guiducci E, Blann AD, Lip GYH. Atrial Fibrillation and Thromboembolism in Patients With Chronic Kidney Disease. J Am Coll Cardiol. 2016;68(13):1452-64. [PMID: 27659468, https://doi.org/10.1016/j.jacc.2016.06.057].
3. Centers for Disease Control and Prevention. CDC Surveillance System: Trends in Incidence Rate of Acute Kidney Injury by Diagnosis Code;.
4. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2023; 2024.
5. Centers for Disease Control and Prevention. About atrial fibrillation; 2024.
6. Kiuchi MG. Atrial fibrillation and chronic kidney disease: A bad combination. Kidney Res Clin Pract. 2018;37(2):103-5. [PMID: 29971204, PMCID: PMC6027811, https://doi.org/10.23876/j.krcp.2018.37.2.103].
7. Thomas L, Abhayaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and Clinical Significance. JACC Cardiovasc Imaging. 2017;10(1):65-77. [PMID: 28057220, https://doi.org/10.1016/j.jcmg.2016.11.003].
8. Chu CD, Powe NR, McCulloch CE, Crews DC, Han Y, Bragg-Gresham JL, et al. Trends in Chronic Kidney Disease Care in the US by Race and Ethnicity, 2012-2019. JAMA Netw Open. 2021;4(9):e2127014. [PMID: 34570204, PMCID: PMC8477264, https://doi.org/10.1001/jamanetworkopen.2021.27014].
9. Miller CE, Vasan RS. The southern rural health and mortality penalty: A review of regional health inequities in the United States. Soc Sci Med. 2021;268:113443. [PMID: 33137680, PMCID: PMC7755690, https://doi.org/10.1016/j.socscimed.2020.113443].
10. Ahmad O, Farooqi HA, Ahmed I, Jamil A, Nabi R, Ullah I, et al. Temporal Trends in Mortality Related to Stroke and Atrial Fibrillation in the United States: A 21-Year Retrospective Analysis of CDC-WONDER Database. Clin Cardiol. 2024;47(12):e70058. [PMID: 39679968, PMCID: PMC11648035, https://doi.org/10.1002/clc.70058].
11. Faheem MSB, Masood MB, Rehman A, Cheema S, Mughal H, Ahmed F, et al. Mortality trends of renal diseases due to hypertension in adults: an analysis of gender, race, place of death, and geographical disparities in the United States from 1999 to 2020. Int Urol Nephrol. 2025;57(9):2995-3008. [PMID: 40183882, https://doi.org/10.1007/s11255-025-04493-3].
12. Hemida MF, Ibrahim AA, Goel A, Hussein M, Patel K, Sarfraz MR, et al. Twenty-Five Years of Angina–Related Mortality in Elderly Adults Aged 65 Years: A Retrospective Cohort Study Using Real-World Data from the USA. ASIDE Internal Medicine. 2025;2(3):33-42. [https://doi.org/10.71079/aside.Im.110925248].
13. Hemida MF, Ibrahim AA, Shahriar Z, Khalid M, Zeeshan N, Qaisi W, et al. Mortality trends in multiple sclerosis and cardiovascular disease in adults in the United States: A 25-year mortality perspective. Mult Scler Relat Disord. 2025;105:106861. [PMID: 41308235, https://doi.org/10.1016/j.msard.2025.106861].
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. [PMID: 18313558, https://doi.org/10.1016/j.jclinepi.2007.11.008].
15. Aggarwal R, Chiu N, Loccoh EC, Kazi DS, Yeh RW, Wadhera RK. Rural-Urban Disparities: Diabetes, Hypertension, Heart Disease, and Stroke Mortality Among Black and White Adults, 1999-2018. J Am Coll Cardiol. 2021;77(11):1480-1. [PMID: 33736831, PMCID: PMC8210746, https://doi.org/10.1016/j.jacc.2021.01.032].
16. Ingram DD, Franco SJ. 2013 NCHS Urban-Rural Classification Scheme for Counties. Vital Health Stat 2. 2014;(166):1-73. [PMID: 24776070].

17. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. Natl Vital Stat Rep. 1998;47(3):1-16, 20. [PMID: 9796247].
18. Ko D, Rahman F, Martins MA, Hylek EM, Ellinor PT, Schnabel RB, et al. Atrial fibrillation in women: treatment. Nat Rev Cardiol. 2017;14(2):113-24. [PMID: 27786235, PMCID: PMC5520636, https://doi.org/10.1038/nrcardio.2016.171].
19. Passman RS. Sex, Symptoms, and Atrial Fibrillation. JAMA Cardiol. 2016;1(3):292-3. [PMID: 27438107, https://doi.org/10.1001/jamacardio.2016.0545].
20. Prabakaran S, Gongora Nieto MC, Lundberg G. Atrial Fibrillation in Women: Risks and Management. J Womens Health (Larchmt). 2018;27(1):107-14. [PMID: 29028452, https://doi.org/10.1089/jwh.2016.6282].
21. Volgman AS, Benjamin EJ, Curtis AB, Fang MC, Lindley KJ, Naccarelli GV, et al. Women and atrial fibrillation. J Cardiovasc Electrophysiol. 2021;32(10):2793-807. [PMID: 33332669, PMCID: PMC8281363, https://doi.org/10.1111/jce.14838].
22. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Rev Nephrol. 2018;14(3):151-64. [PMID: 29355169, https://doi.org/10.1038/nrneph.2017.181].
23. Swartling O, Yang Y, Clase CM, Fu EL, Hecking M, Hodlmoser S, et al. Sex Differences in the Recognition, Monitoring, and Management of CKD in Health Care: An Observational Cohort Study. J Am Soc Nephrol. 2022;33(10):1903-14. [PMID: 35906075, PMCID: PMC9528319, https://doi.org/10.1681/ASN.2022030373].
24. Lindley KJ. Call for Action to Address Increasing Maternal Cardiovascular Mortality in the United States: Strategies for Improving Maternal Cardiovascular Care. Circulation. 2022;145(7):502-4. [PMID: 35157515, https://doi.org/10.1161/CIRCULATIONAHA.122.058772].
25. Jackson Ii LR, Friedman DJ, Francis DM, Maccioni S, Thomas VC, Coplan P, et al. Race and Ethnic and Sex Differences in Rhythm Control Treatment of Incident Atrial Fibrillation. Clinicoecon Outcomes Res. 2023;15:387-95. [PMID: 37273820, PMCID: PMC10237629, https://doi.org/10.2147/CEOR.S402344].
26. Nanda A, Kabra R. Racial Differences in Atrial Fibrillation Epidemiology, Management, and Outcomes. Curr Treat Options Cardiovasc Med. 2019;21(12):85. [PMID: 31820122, https://doi.org/10.1007/s11936-019-0793-5].
27. Ayinde H, Markson F, Ogbenna UK, Jackson n L. Addressing racial differences in the management of atrial fibrillation: Focus on black patients. J Natl Med Assoc. 2024;116(5):490-8. [PMID: 38114334, https://doi.org/10.1016/j.jnma.2023.11.007].
28. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol. 2011;4(1):26-32. [PMID: 21076159, PMCID: PMC3049935, https://doi.org/10.1161/CIRCEP.110.957100].
29. Deering TF, Reiffel JA, Solomon AJ, Tamirisa KP. Chapter 1: The Evolving Atrial Fibrillation Landscape: Importance of Early Diagnosis and Treatment. Am J Cardiol. 2023;205 Suppl 1:S4-6. [PMID: 37777297, https://doi.org/10.1016/j.amjcard.2023.08.027].
30. Lip GY, Kakar P, Watson T. Atrial fibrillation–the growing epidemic. Heart. 2007;93(5):542-3. [PMID: 17435064, PMCID: PMC1955544, https://doi.org/10.1136/hrt.2006.110791].
31. Otto CM. Heartbeat: Healthcare approaches to reducing adverse outcomes in patients with atrial fibrillation. Heart. 2017;103(24):1925-7. [PMID: 29180520, https://doi.org/10.1136/heartjnl-2017-312538].
32. Brod C, Groth N, Rudeck M, Artang R, Rioux M, Benziger C. Oral anticoagulation use in non-valvular atrial fibrillation patients in rural setting. Am J Med Open. 2023;9:100026. [PMID: 39035056, PMCID: PMC11256238, https://doi.org/10.1016/j.ajmo.2022.100026].
33. Deguchi I, Osada T, Arai N, Takahashi S. Differences in oral anticoagulant prescriptions between specialists and non-specialists in patients with cardioembolic stroke caused by non-valvular atrial fibrillation. Heart Vessels. 2022;37(5):867-74. [PMID: 34797401, https://doi.org/10.1007/s00380-021-01984-y].
34. Norby FL, Lutsey PL, Shippee ND, Chen LY, Henning-Smith C, Alonso A, et al. Direct Oral Anticoagulants and Warfarin for Atrial Fibrillation Treatment: Rural and Urban Trends in Medicare Beneficiaries. Am J Cardiovasc Drugs. 2022;22(2):207-17. [PMID: 34633646, PMCID: PMC9833644, https://doi.org/10.1007/s40256-021-00502-9].
35. Bin Abdul Baten R, Zohora FT, Siddiqui MUH. Disparities in telehealth utilization between US rural and urban areas during the COVID-19 pandemic. J Rural Health. 2025;41(1):e12910. [PMID: 39722428, https://doi.org/10.1111/jrh.12910].
36. Brown EA. Epidemiology of renal palliative care. J Palliat Med. 2007;10(6):1248-52. [PMID: 18095800, https://doi.org/10.1089/jpm.2007.0033].
37. Holley JL. Palliative care in end-stage renal disease: focus on advance care planning, hospice referral, and bereavement. Semin Dial. 2005;18(2):154-6. [PMID: 15771661, https://doi.org/10.1111/j.1525-139X.2005.18208.x].
38. Sturgill D, Bear A. Unique palliative care needs of patients with advanced chronic kidney disease - the scope of the problem and several solutions. Clin Med (Lond). 2019;19(1):26-9. [PMID: 30651241, PMCID: PMC6399628, https://doi.org/10.7861/clinmedicine.19-1-26].
39. Tapoi L, Ureche C, Sascau R, Badarau S, Covic A. Atrial fibrillation and chronic kidney disease conundrum: an update. J Nephrol. 2019;32(6):909-17. [PMID: 31321745, https://doi.org/10.1007/s40620-019-00630-1].
40. Law MM, Wong MCG, Morton JB. Atrial Fibrillation: More Than a Subclinical Problem in Patients on Hemodialysis. Kidney International Reports. 2022;7(2):141-3. [https://doi.org/10.1016/j.ekir.2021.11.023].
41. Mark PB, Vecchio LD, Valdivielso JM, Malyszko J. Same rhythm, different song-approaches to atrial fibrillation management by cardiologists and nephrologists. Clin Kidney J. 2021;14(1):9-13. [PMID: 33564401, PMCID: PMC7857826, https://doi.org/10.1093/ckj/sfaa146].
42. Khanna S, Khanna U. Palliative Care in Advanced Kidney Disease: The Approach for a Nephrologist. Indian Journal of Kidney Diseases. 2024;3(3):74-7. [https://doi.org/10.4103/ijkd.ijkd_15_24].
43. Lam DY, Scherer JS, Brown M, Grubbs V, Schell JO. A Conceptual Framework of Palliative Care across the Continuum of Advanced Kidney Disease. Clin J Am Soc Nephrol. 2019;14(4):635-41. [PMID: 30728167, PMCID: PMC6450347, https://doi.org/10.2215/CJN.09330818].
44. Kee YK, Jeon HJ, Oh J, Yoo TH, Kang D, lee J, et al. 2022. [https://doi.org/10.21203/rs.3.rs-1706182/v1].
45. O'Riordan J, Noble H, Kane PM, Smyth A. Advance care plan barriers in older patients with end-stage renal disease: a qualitative nephrologist interview study. BMJ Support Palliat Care. 2020;10(4):e39. [PMID: 31239255, https://doi.org/10.1136/bmjspcare-2018-001759].
46. Shi Y, Li W, Duan F, Pu S, Peng H, Ha M, et al. Factors promoting shared decision-making in renal replacement therapy for patients with end-stage kidney disease: systematic review and qualitative meta-synthesis. Int Urol Nephrol. 2022;54(3):553-74. [PMID: 34159522, PMCID: PMC8831292, https://doi.org/10.1007/s11255-021-02913-8].
47. Jain V, Rao B, Quintero E, Shah AD, Merchant FM, El-Chami MF, et al. Trends and Disparities in Atrial Fibrillation and Stroke Related Mortality in the United States from 1999 to 2020. Pacing Clin Electrophysiol. 2025;48(2):280-3. [PMID: 39603815, https://doi.org/10.1111/pace.15111].
48. Santala OE, Lipponen JA, Jantti H, Rissanen TT, Tarvainen MP, Valiaho ES, et al. Novel Technologies in the Detection of Atrial Fibrillation: Review of Literature and Comparison of Different Novel Technologies for Screening of Atrial Fibrillation. Cardiol Rev. 2024;32(5):440-7. [PMID: 36946975, PMCID: PMC11296284, https://doi.org/10.1097/CRD.0000000000000526].
49. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11. [PMID: 35529086, PMCID: PMC9073222, https://doi.org/10.1016/j.kisu.2021.11.003].

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Original Article

Mortality Trends and Disparities in Hypertensive Heart and Renal Disease: A 25-Year Analysis (1999–2023) Using the CDC WONDER Database

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ABSTRACT

Background: Hypertensive heart and renal disease remain major contributors to mortality in the United States. Tracking long-term mortality patterns is essential for identifying high-risk populations and guiding public health strategies.
Methods: We conducted a nationwide ecological time-trend analysis using CDC WONDER underlying cause-of-death data for Hypertensive Heart and Renal Disease (ICD-10 I13) from 1999–2023. Age-adjusted mortality rates (AAMR) for all ages were examined by sex, race/ethnicity, census region, and urbanization level. Temporal changes were assessed using joinpoint regression with annual percent change (APC) and average annual percent change (AAPC).
Results: AAMR increased from 1.2 (95% CI: 1.2–1.3) per 100,000 in 1999 to 4.2 (95% CI: 4.2–4.3) in 2023. After relative stability in the early years, a marked rise began around 2011, with the South and Midwest showing the steepest increases. From 2013–2023, the AAPC was not statistically significant for females (AAPC = 6.26%; p = 0.1678) but was significant for males (AAPC = 10.67%; p = 0.000117). Males(with AAMR of 4.7 vs 3.9 in females in 2023), older adults, and Black individuals consistently exhibited the highest mortality, while American Indian or Alaska Native groups experienced the most rapid recent increases. A modest decline from 2021–2023 was observed; potential explanations include shifts in healthcare access, reporting, or coding practices.
Conclusions: Rising mortality from hypertensive heart and renal disease from 1999 to 2023 highlights persistent demographic and geographic disparities requiring targeted interventions. Keywords: Hypertensive heart disease; Renal disease; Mortality trends; Age-adjusted mortality; Health disparities

1. Introduction

Hypertension, with a high prevalence of exposure, is the strongest risk factor for cardiovascular disease (CVD), which is the leading cause of mortality and morbidity in the United States [1, 2]. Hypertension is defined as systolic blood pressure greater than 130 mm of Hg and diastolic blood pressure greater than 80 mm of Hg [3]. According to an analysis, the prevalence of hypertension was nearly 48% in the US during August 2021-August 2023. It remains above the target goal of Healthy People 2030, raising health concerns [4, 5]. Based on several cohort studies, this epidemic is a significant risk factor for several conditions like atrial fibrillation, cerebrovascular diseases, heart failure, coronary heart disease, aortic syndromes ,chronic kidney disease, and dementia [1].

Hypertension mediated organ damage (HMOD) like hypertensive heart and renal disease is more common among people with long standing or severe hypertension but asymptomatic population or people with less severe hypertension also suffer from these complications [6, 7].

While delving deep into the pathophysiological mechanism behind these complications, it is found that left ventricular hypertrophy is the earliest manifestation of hypertensive heart disease and it progresses to other complications like heart failure and end stage renal disease (ESRD) [8, 1].Similarly, hypertension also damages the renal microvasculature directly due to high pressure transmission resulting in fibrosis and hypertensive renal disease [9].

Based on our analysis of the Centres For Disease Control and Prevention Wide-Ranging OnLine Data for Epidemiological Research (CDC WONDER) database, the mortality rates in the US due to combined hypertensive heart and renal disease have increased in the last two decades with the age-adjusted mortality rates (AAMR) of 4.2 (95% CI 4.2 to 4.3) per 100,000 population in 2023 with 17,623 deaths due hypertensive heart and renal disease [10]. Several studies have shown higher mortality rates in men and younger adults due to hypertensive heart disease and in African

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Americans and populations in the West and metropolitan areas of the US due to hypertensive renal disease [11, 12]. These trends in mortality rates warrant further research into several contributing factors. Therefore, this study aims to examine nationwide trends and disparities in ICD-10–coded mortality due to hypertensive heart and renal disease (I13) in the United States from 1999 to 2023, with specific focus on variations by gender, race, age group, and geographic region. This analysis of variations and temporal trends is valuable for the development of effective hypertensive heart and renal disease management strategies.

2. Methods

2.1. Study setting and population

In this nationwide ecological time-trend analysis, an in-depth search was conducted on Hypertensive Heart and Renal Disease in the US population from 1999 to 2023 and death certificate based data were retrieved from CDC WONDER underlying cause of death for all ages. The study used the diagnostic codes from the 10th version of the International Classification of Diseases and Related Health Problems (ICD-10) including I13 for "Hypertensive Heart and Renal Disease". This data set has been used by previous studies for mortality analysis of cardiovascular diseases and their complications. Information from death certificates from all 50 states and the District of Columbia is used in this collection [10]. This study used deidentified data from government-issued public use data set, therefore, this research did not necessitate an approval from local institutional review board. It follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting.

2.2. Data Abstraction

This data set included year, population size, demographic characteristics, urban-rural classification, geographical segmentation, and location of death, including hospitals, nursing homes, long-term care facilities, households, and hospices. The demographics included age, race, and gender. Race (any ethnicity) was classified as White, Black or African American, American Indian or Alaskan Native, and Asian or Pacific Islander. Hispanic individuals of any race were analyzed as a separate group. This collection was retrieved from CDC WONDER. [10]. The population was assessed in urban and rural counties per the 2013 U.S. census classification in accordance with the National Center for Health Statistics Urban-Rural Classification Scheme to all study years (1999–2023) to ensure consistency in county categorization and comparability across the full analysis period [13]. According to the United States Census Bureau, geographical categories included West, Northeast, South, and Midwest [14]. Mortality rates were analyzed using two age groups, <65 years and ≥65 years, to reflect the markedly higher concentration of cardiovascular and renal risk in older adults. For clearer temporal assessment, year-interval groupings were organized into 5-year blocks (e.g., 1999–2003, 2004–2008). Place-of-death and urbanization analyses were restricted to 1999–2020, reflecting the last year for which these variables were available in the CDC WONDER database.

2.3. Statistical Analysis

We used crude death rates and AAMRs per 100,000 from 1999 to 2023 from CDC WONDER to examine the trend. These rates were further divided into groups based on gender, year, age, race, and State. 95% confidence intervals (CI) were included. We obtained AAMR directly from CDC WONDER (2000 U.S. standard population) [15]. Crude mortality rates were calculated by dividing the number of deaths caused by Hypertensive Heart and Renal Disease by the corresponding US population of that year. Annual Percent Change (APC) with 95% confidence intervals was calculated using the Joinpoint Regression Program (Joinpoint V 5.3.0.0, National Cancer Institute) [16]. A log-linear, weighted model was used to identify statistically significant changes in mortality trends. Using two-tailed testing, APC estimates were considered increasing or decreasing when the slope differed significantly from zero, with a p-value < 0.05 denoting statistical significance. The final model allowed up to three joinpoints. Missing or unknown values were excluded for analysis of cohorts.

3. Results

The AAMR due to hypertensive heart and renal disease has increased from 1.2 (95% CI=1.2 to 1.3) in 1999 to 4.2 (95% CI = 4.2 to 4.3) in 2023 with a total number of 148,337 deaths from 1999 to 2023. From 1999 to 2011, it remained relatively stable; however an increasing trend in AAMR was noted during the next 12 years, with a relatively sharp increase from 2017 to 2020. The South and Midwest experienced the sharpest increases in mortality rates, particularly in the last decade. Males showed a statistically significant upward trend in mortality rates, while the increase for females was less consistent and not statistically significant. Significant increases were observed across Hispanic ethnicity, and among races including White, Black, and Asian populations in recent years, with particularly rapid increases in the American Indian or Alaska Native population from 2014 to 2023.

3.1. Gender stratification

From 1999 to 2023, men had consistently higher mortality rates as compared to women as shown in **(Figure 1)**. For females, the rate began at 1.1 in 1999, reaching 3.9 by 2023 as given in **Supplementary Table S1**. Their AAMR increased significantly from 2013 to 2021 (APC = 24.9, 95% CI = 17.95 to 32.25, $p < 0.001$) and then there was a period of decline from 2021 to 2023 (APC = -44.34, 95% CI = -65.8 to -9.4, $p = 0.03$) as shown in **Supplementary Table S2**. Despite a statistically significant incline in AAMR from 2013 to 2021, the trend for overall AAPC from 2013 to 2023 was not statistically significant for females (AAPC = 6.26%, 95% CI = -2.52 to 15.83, $p = 0.17$) as shown in **(Figure 2)**.

For males, the mortality rate started higher, at 1.4 in 1999, reaching to 4.7 in 2023 as shown in **Supplementary Table S1**. Their AAMR increased significantly from 2011 to 2021

(APC = 23.36, 95% CI = 17.64 to 29.37, p < 0.001) and then there was a period of decline from 2021 to 2023 (APC = -35.72, 95% CI = -51.79 to -14.29, p = 0.01) as shown in **Supplementary Table S2**. This trend of increasing mortality was statistically significant for males from 2011 to 2023 (AAPC = 10.67%, 95%CI = 5.1 to 16.5, p < 0.001) as shown in **(Figure 3)**.

3.2. Racial stratification

The racial trends for hypertensive heart and renal disease, shown in **(Figure 4)**, demonstrate the highest mortality rates for Black individuals with their APC shown in **Supplementary Table S3**. For American Indian or Alaska Native, a notable increase in mortality was observed from 2014 to 2021, with an APC of 22.22 (95% CI = 13.81 to 23.26) and APC of 6.93 from 2021 to 2023. Overall, AAPC from 2014 to 2023 was 18.44 (95% CI = 13.81 to 23.26, p < 0.001).

For Black individuals, from 1999 to 2010, there was a decrease in mortality rates (APC = -3.46, 95% CI = -4.78 to -2.1, p < 0.001). However, from 2010 to 2015, APC shifted to 3.2 (95% CI= -4.11 to 11.08, p = 0.38) and from 2015 to 2023, it shifted to 10.43 (95% CI = 8.7 to 12.18) reflecting a positive trend and a significant increase in mortality for this group. Overall, the trend of increased mortality from 1999 to 2023 was statistically significant (AAPC = 2.38, 95% CI = 0.74 to 4.05, p = 0.01).

For Asian or Pacific Islander, a negative APC of -3.48 (95% CI = -5.51 to -1.40, p < 0.001) was observed from 1999 to 2010, followed by an increase in mortality from 2010 to 2023, where the APC reached 6.92 (95% CI = 5.71 to 8.14, p < 0.001). Overall, the trend of increased mortality from 1999 to 2023 was statistically significant (AAPC = 2.02, 95% CI = 0.92 to 3.13, p < 0.001)

For White individuals, the mortality trend showed a decline from 1999 to 2009 (APC = -1.79, 95% CI = -3.08 to -0.47, p = 0.01), followed by a significant increase after 2009. From 2009 to 2015, the APC was 7.19 (95% CI = 3.46 to 11.04, p < 0.001) and from 2015 to 2021, the APC surged to 20.52(95% CI= 18.57 to 22.50), showing a major upward trend with a very significant p < 0.001. This continued into 2023, with an APC of 10.55 (95% CI = 6.71 to 14.51, p < 0.001), confirming that mortality rates for Whites have been increasing rapidly in recent years. Overall, the trend of increased mortality from 1999 to 2023 was statistically significant (AAPC = 6.7, 95% CI = 5.58 to 7.83, p < 0.001)

When stratified based on ethnicity, Hispanics had the APC from 1999 to 2010 was -2.67 (95% CI = -4.75 to -0.54, p = 0.02), suggesting a decrease in mortality during that period. However, from 2010 to 2020, the APC increased to 9.42 (95% CI = 7.60 to 11.25, p < 0.001) indicating a recent upward trend in mortality for this group. Overall, the trend of increased mortality from 1999 to 2020 was statistically significant (AAPC = 2.9, 95% CI = 1.6 to 4.2, p < 0.001)

Table 1: Number of deaths according to the place of death.

Place of Death	Number of Deaths
Decedent's home	32,813
Nursing home/long-term care	25,208
Medical facility–Inpatient	24,593
Medical facility–Outpatient or ER	7,985
Other	4,771
Hospice facility	4,473
Medical facility–Dead on arrival	626
Place of death unknown	180
Medical facility–Status unknown	56

3.3. Mortality trends by census regions

The AAMR show significant regional variation over the years from 1999 to 2023 as shown in **(Figure 5)**and **Supplementary Table S4**. In the Northeast, the AAMR started at 0.9 in 1999 and saw an increase, reaching 2.4 by 2023. This represents a steady upward trend over the 25 years. In the Midwest, the rate began at 1.1 in 1999, with fluctuations until 2020, when it spiked to 3.1. By 2023, the rate had increased to 4.6, reflecting a strong upward trajectory, particularly in the last decade. The South experienced a similar pattern, starting at 1.5 in 1999. The rate remained relatively stable at 1.2 throughout much of the early 2000s but began rising significantly from 2015 onwards, reaching 5.5 by 2023. This indicates a sharp increase in mortality rates, especially in the last 8 years. In the West, the AAMR began at 1.3 in 1999 and saw less fluctuation compared to the other regions. The rate gradually increased to 3.4 by 2023, with steady growth over the years.

3.4. Urbanization trends

From 1999 to 2020, mortality rates for hypertensive heart and renal diseases generally increased across various levels of urbanization as shown in **Supplementary Table S5**. In large central metropolitan areas, the rate increased to 2.9 in 2020 from 1.4 in 1999. Similarly, large fringe metropolitan areas saw a rise from 1.0 to 2.4 over the same period. Medium metro areas experienced a steady increase, climbing from 1.3 to 3.5, while small metro areas moved from 1.1 to 3.1. Similarly, rural areas such as micropolitan and noncore regions experienced increases, with micropolitan areas rising from 1.2 to 3.3 and noncore regions moving from 1.1 to 3.1. These trends, shown in **(Figure 6)**, highlight that while mortality rates have been rising across all areas.

3.5. Place of Death

Analyzing the number of deaths from 1999 to 2020, shown in **(Table 1)**, the maximum number of deaths took place in the decedent's home followed by nursing homes, inpatient facilities, and outpatient settings. Other places of death, such as hospice facilities settings accounted for a smaller proportion of total deaths. These figures reflect simple distributions and do not indicate rates or relative risk.

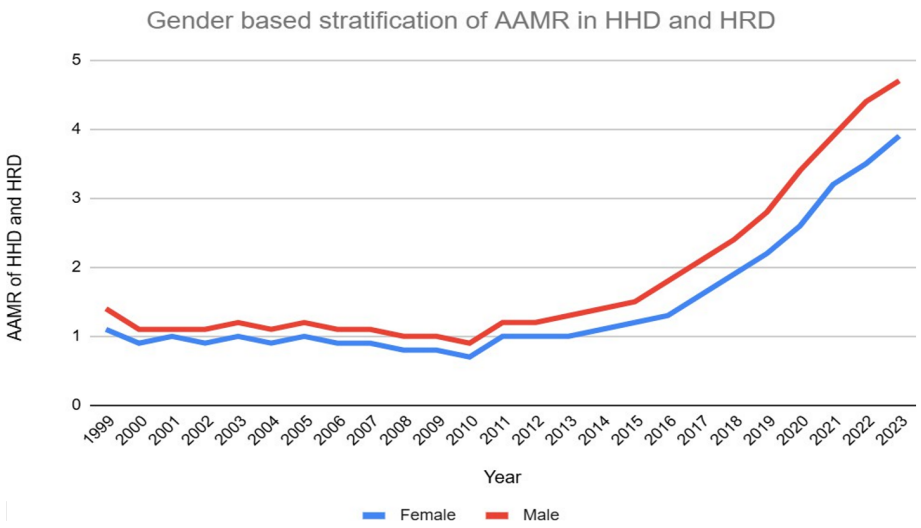

Figure 1: Gender based stratification of AAMR of hypertensive heart and renal disease.

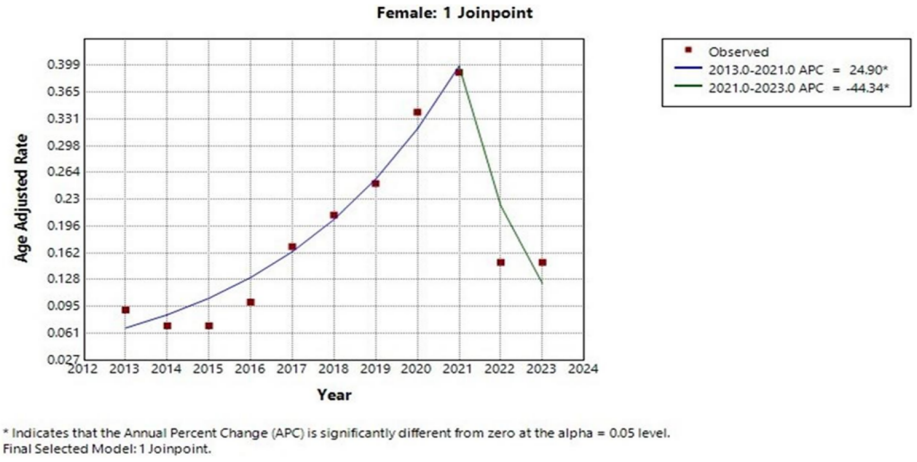

Figure 2: Annual percentage change (APCs) in hypertensive heart and renal disease related mortality in females.

3.6. Age-based stratification

The number of deaths was consistently higher in the population above 65 years of age. The age adjusted death rate from 1999 to 2003 in this population was 7.0, which was followed by a decline to 6.8, from 2004 to 2008. After 2008, there was an increase, with a very prominent increase after 2014 reaching a rate of 23.9. For people below 65 years of age, the death rate due to hypertensive heart and renal disease remained relatively stable, reaching 0.5 during 2018 to 2023. The overall trend, shown in **(Table 2)**, clearly shows that as people age, the risk of death from these conditions increases substantially.

3.7. Mortality stratified by geographic region

The state-wise trends reveal considerable variation across the United States. Some states like Oklahoma, and Mississippi show notably higher age-adjusted rates, reaching as high as 24.4 and 8.1 in 2023, indicating a more pronounced issue with hypertension-related deaths. Meanwhile, states like Wyoming and Montana report the lowest rates, with an average AAMR (extracted from CDC WONDER) of 0.6 from 1999 to 2020. Other states such as California, Florida, and Michigan, fall in the middle, reflecting more moderate trends in the age-adjusted rates. Overall, while some states face greater challenges in managing hypertensive diseases, there is a general spread, with urbanized regions showing a broad but stable incidence, and rural or less urbanized regions tending to have higher mortality rates from these conditions.

4. Discussion

Our study has demonstrated an overall increase in mortality rate from hypertensive heart and renal disease from 1999 to 2023 across all races, genders, census regions and urbanization groups. Males had a consistently higher mortality rate as compared to females. Among different races, Blacks or African Americans had the highest mortality rates with the rapid increase in mortality rates of American Indians

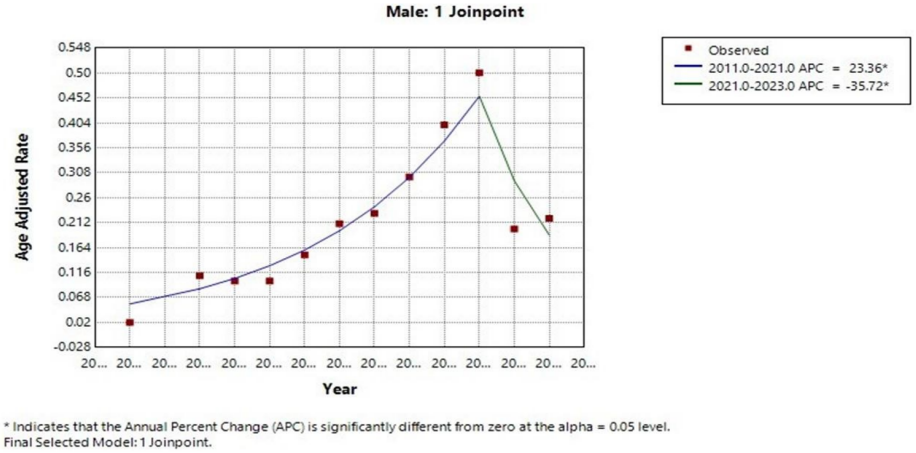

Figure 3: Annual percentage change (APCs) in hypertensive heart and renal disease related mortality in males.

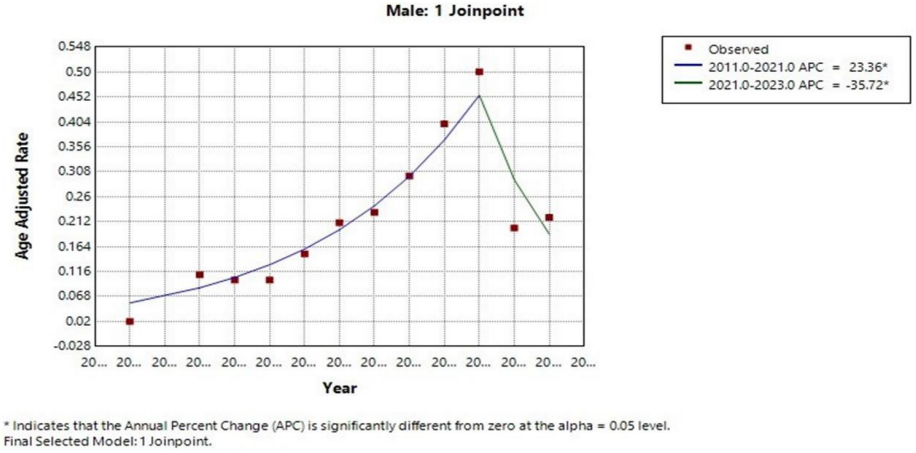

Figure 4: Annual Percentage change (APCs) in hypertensive heart and renal disease related mortality in different races.

or Alaska Natives. Similarly, older adults had higher mortality rates as compared to younger individuals due to Hypertensive Heart and Renal Disease. Chronic elevation of blood pressure produces structural and functional changes in the heart and coronary arteries resulting in left ventricular hypertrophy, ultimately leading to heart failure and conduction abnormalities. Hypertensive heart disease is a constellation of these abnormalities [17]. Similarly chronic elevation of blood pressure also damages the blood vessels in kidneys and leads to glomerular hypertrophy which precedes glomerulosclerosis [18]. These conditions can coexist in people suffering from hypertension. Moreover, one condition can worsen the other . For example, CKD can also lead to heart failure and cardiac fibrosis in histology. Additionally, cardiovascular morbidity and mortality are inversely associated with kidney function [19, 20].

Our study has demonstrated higher mortality rates in males as compared to females. It is consistent with the trends seen in other studies for hypertensive heart and renal disease. Raja et al. concluded that Men had higher AAMRs from hypertensive heart disease than women during 1999 to 2020 (overall AAMR men: 23.1; 95% CI: 23.0-23.1; women: 16.4; 95% CI: 16.3-16.4) [12]. It is also consistent with findings of another study that older men had higher mortality rates from hypertensive heart disease as compared to older women [21]. Similarly, males had higher mortality rates due to hypertension-related ESRD [22]. Men appear more susceptible to hypertensive kidney disease and renal function decline than women, as shown in a Chinese cohort. Women, by contrast, demonstrate relative protection from renal and cardiovascular consequences. However, these mechanistic insights derive from non-U.S. populations and may not fully explain the mortality patterns in our nationwide analysis. They should thus be considered plausible explanations rather than definitive causes [23, 24, 25].

Analysis of racial disparities reveals that African Americans are more likely to have both hypertensive heart disease and renal disease. This can be explained by the fact that the incidence of hypertension in this population is higher than in others. Some other factors, like tobacco use and incidence of diabetes, also support this finding in African Americans [26, 12]. Some other studies have also supported higher in-hospital mortality rates of non-Hispanic Blacks as compared

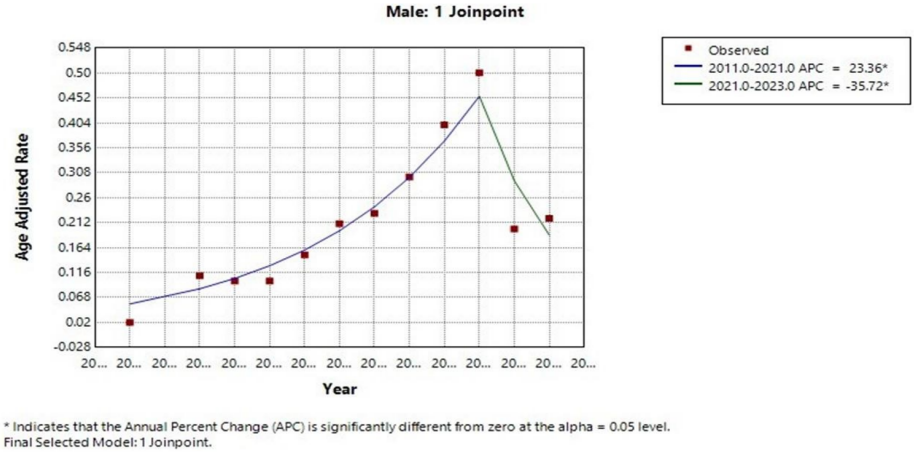

Figure 5: AAMR stratified by Census region in hypertensive heart and renal disease related mortality.

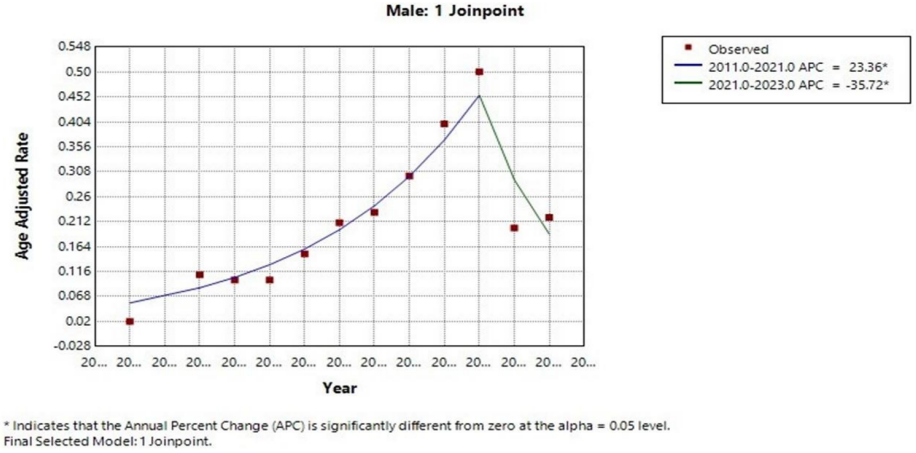

Figure 6: AAMR stratification based on urbanization for hypertensive heart and renal disease.

to their White counterparts due to poor control of hypertension. It is attributable to lack of access to primary care providers, compromised quality of care, and lesser insurance coverage [27, 28].

Another important trend observed in our study is the decline in AAMR for females (APC = −44.34, 95% CI = −65.8 to −9.4, p = 0.03) and males (APC = −35.72, 95% CI = −51.79 to −14.29, p = 0.01) from 2021 to 2023. A similar pattern has been documented for mortality due to diabetes and hypertension, with AAMR decreasing from 96.86 in 2021 to 84.58 in 2023, corresponding to an APC of −8.96 (95% CI: −14.42 to −2.002; p = 0.02) in females and −7.93 (95% CI: −12.80 to −1.89; p = 0.02) in males [29]. In addition, a study by Waqas et al. reported that following the pandemic, overall hypertension-related death rates fell 4.0%, from 258.2 (2020–2021) to 247.9 (95% CI: 247.5–248.3) in the post-pandemic period [30].

The observed decline may be related to several factors, including changes in coding practices, competing mortality from COVID-19, and improved access to healthcare as services resumed after the pandemic. COVID-19 also likely altered the way hypertension-related conditions were recorded on death certificates, but the accuracy of these designations has not been systematically investigated [31]. Moreover, although CDC's updated excess-death estimation method improves stability during and after the pandemic, mortality estimates for the most recent years remain uncertain due to prolonged COVID-19–related disruptions [32].

Inadequate control of blood pressure remains an important driver of mortality related to hypertension. NHANES III Linked Mortality Study demonstrates that both untreated and treated-but-uncontrolled hypertensive adults face significantly higher risks of all-cause and CVD-specific death as compared to those with controlled hypertension who do not show excess mortality risk [33]. This highlights the need for interventions to ensure proper blood pressure control, especially in high-risk groups.

The 2017 ACC/AHA guidelines tightened the threshold and lowered the recommended goal to <130/80 mmHg for most patients; mortality trends from 2018 to 2023 did not show

Table 2: Age-based stratification of death due to hypertensive heart and renal disease.

Time Period	No. of deaths (≥65 years)	Age-adjusted mortality (≥65 years)	No. of deaths (<65 years)	Age-adjusted mortality (<65 years)
1999–2003	12,236	7.0	2,705	0.2
2004–2008	12,088	6.3	2,907	0.2
2009–2013	13,949	6.5	3,330	0.2
2014–2018	26,148	10.8	4,760	0.3
2019–2023	62,441	23.9	7,770	0.5

≥, greater than or equal to; age-adjusted mortality, deaths per 100,000 population.

any decrease in deaths due to hypertensive heart and renal disease. Looking at the mortality trends, it does not appear that the guideline change has had a measurable impact on them so far, and more years of data will likely be required to determine whether a meaningful impact emerges over time [34].

Our findings highlight the urgent need for targeted interventions to eliminate gender-based and racial disparities in rising mortality rates due to hypertension-related heart and renal disease. Some studies have highlighted the causes of these disparities and suggested solutions [35, 36, 30]. However, data is limited, and future research should focus more on exploring the underlying causes of sex, racial, and regional disparities and ways to eliminate these disparities. Additionally, prospective studies should be conducted to determine the long-term impact of changes in post-pandemic access to health care delivery.

Future work should explore the potential positive impact of hypertension-related awareness, anti-hypertensive treatment, and control on mortality rates [37]. Integration of social determinants of health can help identify vulnerable groups and target interventions to them [37]. By addressing these research gaps, evidence-based policies can be constituted to target groups affected by hypertension-related heart disease and renal disease.

This nationwide study, using CDC WONDER data, analyzes age-adjusted mortality trends for hypertensive heart and renal disease (I13) but has some limitations. The analysis is subject to cause-of-death misclassification due to the use of death certificate data, which may affect mortality estimates. In addition, by focusing solely on ICD-10 I13, which shows hypertensive heart and renal disease, the analysis may underestimate the broader burden of isolated hypertensive heart or renal disease. Moreover, using the 2013 urban–rural scheme across all years may misclassify counties that changed over time, which should be considered when interpreting long-term trends. Additionally, mortality data for 2022–2023 were provisional and obtained from the most recent CDC WONDER release, and trends in these final years may change as data are updated and finalized. The short duration of certain trend segments, including those overlapping the COVID-19 period, may contribute to instability in APC estimates, which represents an inherent limitation of annual mortality data. In this study, a small proportion of records contained missing demographic or geographic information, which represents an additional limitation of the subgroup analyses. This analysis lacks individual-level data on risk factors such as blood pressure control, medication use, socioeconomic status, and comorbidities, which limits the ability to adjust for underlying clinical and social determinants of mortality.

5. Conclusions

From 1999 to 2023, mortality due to hypertensive heart and renal disease has risen significantly across the United States, increasing from an AAMR of 1.2 to 4.2. Misclassification and the absence of individual-level clinical or socioeconomic data may influence the observed trends, but the early years showed relative stability, and since the early 2010s, a sustained upward trend has emerged, particularly in the South and Midwest regions, among males, and among African Americans. It highlights persistent health disparities and the need for targeted interventions to improve hypertension management. Future research must prioritize identifying and eliminating disparities in hypertension-related mortality through targeted interventions and integrating social determinants into evidence-based policies.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding Source

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Acknowledgments

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Institutional Review Board (IRB)

This study used publicly available, de-identified CDC data and did not require IRB approval.

Large Language Model

No AI or large-language model tools were used in the writing, editing, or preparation of this manuscript.

Authors Contribution

Conceptualization was performed by AJ, FR, Methodology was carried out by AJ, FR, Data curation involved AJ, FR,

AM, HR, Formal analysis was conducted by AJ, FR, Writing of the original draft was completed by AJ, FR, BN, MA, Writing review and editing were undertaken by AJ, FR, BN, MA, Supervision was provided by JM

Data Availability

All data used in this study are publicly available from the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database.

References

1. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension. 2020;75(2):285-92. [PMID: 31865786, PMCID: PMC10243231, https://doi.org/10.1161/HYPERTENSIONAHA.119.14240].
2. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38-360. [PMID: 26673558, https://doi.org/10.1161/CIR.0000000000000350].
3. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334-57. [PMID: 32370572, https://doi.org/10.1161/HYPERTENSIONAHA.120.15026].
4. Fryar CD, Kit B, Carroll MD, Afful J. Hypertension prevalence, awareness, treatment, and control among adults age 18 and older: United States, August 2021-August 2023. CDC; 2024.
5. United States Department of Health and Human Services. Healthy People 2030: Reduce the proportion of adults with high blood pressure. health.gov; 2025.
6. Cuspidi C, Ambrosioni E, Mancia G, Pessina AC, Trimarco B, Zanchetti A, et al. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: the Assessment of Prognostic Risk Observational Survey. J Hypertens. 2002;20(7):1307-14. [PMID: 12131527, https://doi.org/10.1097/00004872-200207000-00017].
7. Cuspidi C, Valerio C, Negri F, Sala C, Masaidi M, Giudici V, et al. Prevalence and correlates of multiple organ damage in referred treated hypertensives: data from the ETODH study. J Hum Hypertens. 2008;22(11):801-3. [PMID: 18528408, https://doi.org/10.1038/jhh.2008.56].
8. Dumitrescu M, Constantin A, Nemecz AM, Dragan E, Popov LD, Tanko G. Hypertension induces compensatory left ventricular hypertrophy by a mechanism involving gap junction lateralization and overexpression of CD36, PKC and MMP-2. Rom J Morphol Embryol. 2021;62(3):713-21. [PMID: 35263399, PMCID: PMC9019672, https://doi.org/10.47162/RJME.62.3.08].
9. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension. 2004;44(5):595-601. [PMID: 15452024, https://doi.org/10.1161/01.HYP.0000145180.38707.84].
10. Centers for Disease Control and Prevention. CDC WONDER;.
11. Abughazaleh S, Tarawneh M, Nawaiseh AMA, Obeidat O, Qadadeh Z, Pondicherry-Harish RC. Trends in Hypertensive Heart Disease Associated Mortality in the United States: A Population-Based Time-Trend Analysis Using the Global Burden of Diseases Database, 1990-2019. Journal of the American College of Cardiology. 2024;83(13). [https://doi.org/10.1016/s0735-1097(24)03861-0].
12. Raja A, Raja S, Amin SB, Salman M, Azeem B, Kumar L. Temporal trends in hypertension related end stage renal disease mortality rates: an analysis of gender, race/ethnicity, and geographic disparities in the United States. Front Nephrol. 2023;3:1339312. [PMID: 38288382, PMCID: PMC10823365, https://doi.org/10.3389/fneph.2023.1339312].
13. Aggarwal R, Chiu N, Loccoh EC, Kazi DS, Yeh RW, Wadhera RK. Rural-Urban Disparities: Diabetes, Hypertension, Heart Disease, and Stroke Mortality Among Black and White Adults, 1999-2018. J Am Coll Cardiol. 2021;77(11):1480-1. [PMID: 33736831, PMCID: PMC8210746, https://doi.org/10.1016/j.jacc.2021.01.032].
14. Centers for Disease Control and Prevention, National Center for Health Statistics. NCHS urban-rural classification scheme for counties; 2024.
15. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard; 1998.
16. National Cancer Institute. Joinpoint Regression Program;.
17. Tackling G, Borhade MB. In: Hypertensive heart disease. Treasure Island (FL): StatPearls Publishing; 2025.
18. Hughson MD, Puelles VG, Hoy WE, Douglas-Denton RN, Mott SA, Bertram JF. Hypertension, glomerular hypertrophy and nephrosclerosis: the effect of race. Nephrol Dial Transplant. 2014;29(7):1399-409. [PMID: 24327566, PMCID: PMC4071048, https://doi.org/10.1093/ndt/gft480].
19. Law JP, Pickup L, Pavlovic D, Townend JN, Ferro CJ. Hypertension and cardiomyopathy associated with chronic kidney disease: epidemiology, pathogenesis and treatment considerations. J Hum Hypertens. 2023;37(1):1-19. [PMID: 36138105, PMCID: PMC9831930, https://doi.org/10.1038/s41371-022-00751-4].
20. Zannad F, Rossignol P. Cardiorenal Syndrome Revisited. Circulation. 2018;138(9):929-44. [PMID: 30354446, https://doi.org/10.1161/CIRCULATIONAHA.117.028814].
21. Arshad MS, Tharwani ZH, Deepak FNU, Abdullah A, Kumar R, Bhimani RK, et al. Trends in hypertensive heart disease-related mortality among older adults in the USA: a retrospective analysis from CDC WONDER between 1999 and 2020. Egypt Heart J. 2025;77(1):27. [PMID: 40035900, PMCID: PMC11880464, https://doi.org/10.1186/s43044-025-00622-6].
22. Ayyan M, Amir S, Zahid A, Naveed A, Umer M, Siddique MU, et al. Abstract 4147016: Trends in Hypertension-related End-Stage Renal Disease (ESRD) across the United States from 1999-2022: An Analysis of Age, Gender, and Ethnic Disparities. Circulation. 2024;150(Suppl_1). [https://doi.org/10.1161/circ.150.suppl_1.4147016].
23. Baiardi G, Macova M, Armando I, Ando H, Tyurmin D, Saavedra JM. Estrogen upregulates renal angiotensin II AT1 and AT2 receptors in the rat. Regul Pept. 2005;124(1-3):7-17. [PMID: 15544836, https://doi.org/10.1016/j.regpep.2004.06.021].
24. Gillis EE, Sullivan JC. Sex Differences in Hypertension: Recent Advances. Hypertension. 2016;68(6):1322-7. [PMID: 27777357, PMCID: PMC5159215, https://doi.org/10.1161/HYPERTENSIONAHA.116.06602].
25. Wang Q, Xie D, Xu X, Qin X, Tang G, Wang B, et al. Blood pressure and renal function decline: a 7-year prospective cohort study in middle-aged rural Chinese men and women. J Hypertens. 2015;33(1):136-43. [PMID: 25255396, https://doi.org/10.1097/HJH.0000000000000360].
26. Lea JP. Racial Disparities in Hypertensive Cardiovascular Disease and Chronic Kidney Disease. The FASEB Journal. 2010;24(S1). [https://doi.org/10.1096/fasebj.24.1_supplement.409.1].
27. Noah GU, Omohoro MU, Magacha HM, Fuko CD, Ezike T. Racial Disparities in Hypertension-Related Hospital Mortality Among Adults in the United States. Cureus. 2025;17(3):e81043. [PMID: 40264630, PMCID: PMC12014224, https://doi.org/10.7759/cureus.81043].
28. Williams DR, Mohammed SA. Racism and Health I: Pathways and Scientific Evidence. Am Behav Sci. 2013;57(8). [PMID: 24347666, PMCID: PMC3863357, https://doi.org/10.1177/0002764213487340].
29. Hashmi S, Safdar I, Kazmi MH, Zulfiqar E, Shahzad M, Hurjkaliani S, et al. Rising Mortality Related to Diabetes Mellitus and Hypertension: Trends and Disparities in the United States (1999-2023). Clin Cardiol. 2025;48(4):e70132. [PMID: 40237249, PMCID: PMC12000922, https://doi.org/10.1002/clc.70132].
30. Waqas SA, Hurjkaliani S, Salim H, Collins P, Ahmed R. Post-COVID shifts and disparities in hypertension-related mortality in the United States. Ann Epidemiol. 2025;107:20-3. [PMID: 40412631, https://doi.org/10.1016/j.annepidem.2025.05.010].

31. Vaughan AS, Coronado F, Casper M, Loustalot F, Wright JS. County-Level Trends in Hypertension-Related Cardiovascular Disease Mortality-United States, 2000 to 2019. J Am Heart Assoc. 2022;11(7):e024785. [PMID: 35301870, PMCID: PMC9075476, https://doi.org/10.1161/JAHA.121.024785].
32. Centers for Disease Control and Prevention. Excess Deaths Associated with COVID-19. CDC; 2022.
33. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. Sci Rep. 2018;8(1):9418. [PMID: 29925884, PMCID: PMC6010458, https://doi.org/10.1038/s41598-018-27377-2].
34. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, et al. Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e116-35. [PMID: 29133355, https://doi.org/10.1161/HYP.0000000000000067].
35. Ferdinand KC, Nasser SA. Racial/ethnic disparities in prevalence and care of patients with type 2 diabetes mellitus. Curr Med Res Opin. 2015;31(5):913-23. [PMID: 25772230, https://doi.org/10.1185/03007995.2015.1029894].
36. Jafar TH, Hatcher J, Poulter N, Islam M, Hashmi S, Qadri Z, et al. Community-based interventions to promote blood pressure control in a developing country: a cluster randomized trial. Ann Intern Med. 2009;151(9):593-601. [PMID: 19884620, https://doi.org/10.7326/0003-4819-151-9-200911030-00004].
37. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134(6):441-50. [PMID: 27502908, PMCID: PMC4979614, https://doi.org/10.1161/CIRCULATIONAHA.115.018912].

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Original Article

Cardiac Arrest and Cardiomyopathy Related Mortality in the United States, 1999-2025: Trends and Disparities

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ABSTRACT

Background: Cardiac arrest and cardiomyopathy are major contributors to cardiovascular mortality and sudden death. However, long-term national mortality trends and demographic disparities remain unclear. This study aimed to evaluate U.S. mortality trends from 1999 to 2025 and assess differences by sex, race/ethnicity, and age.

Methods: We conducted a cross-sectional analysis of U.S. mortality data from 1999–2025 using the CDC WONDER Multiple Cause-of-Death database. Deaths among adults aged ≥ 25years were identified using ICD-10 codes I42 (cardiomyopathy) and I46 (cardiac arrest), including cases where these codes appeared as underlying or contributing causes of death. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated. Temporal trends were assessed using Joinpoint regression and expressed as average annual percent change (AAPC), stratified by sex, race/ethnicity, and three age groups (25–44, 45–64, and ≥ 65years).

Results: Between 1999 and 2025, 237,958 deaths from cardiac arrest and cardiomyopathy occurred among U.S. adults ≥ 25 years. Overall, AAMR declined from 6.33 to 2.41 (AAPC −3.83; 95% CI: −4.18 to −3.57). Males had higher mortality than females (AAMR 5.82 vs 2.71) with declines from 9.13 to 3.28 and 4.36 to 1.62, respectively. Non-Hispanic (NH) Black individuals had the highest AAMR (7.42), followed by Hispanics (4.62). Mortality was highest among those aged ≥ 65 years (CMR 14.74), declining from 23.88 to 7.88 between 1999 and 2025.

Conclusion: Mortality from cardiac arrest and cardiomyopathy declined significantly from 1999–2025. However, substantial disparities persisted, with higher mortality among males, NH Black individuals, and adults ≥ 65 years, highlighting ongoing inequities in cardiovascular outcomes.

1. Introduction

Cardiac arrest and cardiomyopathy represent major contributors to cardiovascular morbidity and mortality worldwide and remain a significant public health concern in the United States [1]. Sudden cardiac arrest alone affects more than 350,000 individuals annually in the United States, with survival rates remaining low despite advances in resuscitation and emergency care. Approximately 90% of out-of-hospital cardiac arrest events are fatal, underscoring the persistent burden of this condition on the healthcare system and population health [1–3]. Cardiomyopathies, including hypertrophic, dilated, restrictive, and arrhythmogenic forms, are important underlying causes of heart failure, malignant arrhythmias, and sudden cardiac death. Hypertrophic cardiomyopathy, one of the most common inherited cardiac disorders, affects roughly 1 in 500 individuals, while dilated cardiomyopathy remains a leading cause of heart transplantation and advanced heart failure [4–6].

Cardiomyopathies contribute substantially to cardiac arrest and cardiovascular mortality through structural and electrical remodeling of the myocardium, which predisposes patients to ventricular arrhythmias and progressive cardiac dysfunction. Epidemiological

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studies have demonstrated that cardiomyopathy-related deaths continue to impose a considerable burden in the United States, with thousands of deaths reported annually. For instance, analyses of national mortality data identified over 168,000 deaths attributed to dilated cardiomyopathy between 1999 and 2020 [7]. Furthermore, cardiomyopathy-related mortality frequently exhibits demographic and geographic disparities, with higher mortality rates reported among males, older adults, and certain racial and ethnic populations [7].

Temporal analyses of cardiac arrest mortality in the United States suggest complex patterns over the past two decades. While some studies report an initial decline in age-adjusted mortality rates during the early 2000s, more recent years have shown stagnation or even reversal of these improvements, potentially related to the growing burden of cardiovascular risk factors, aging populations, and disparities in access to advanced cardiovascular care [8, 9]. Additionally, cardiac arrest associated with conditions such as heart failure and metabolic disturbances has demonstrated increasing mortality trends since approximately 2011 in national datasets [8]. The recent Lancet Commission to Reduce the Global Burden of Sudden Cardiac Death emphasized that sudden cardiac death remains a major global health challenge with survival rates from sudden cardiac arrest below 10% in most regions worldwide, calling for urgent multidisciplinary strategies to improve prevention, risk stratification, and systems of care [10].

Despite the clinical significance of these conditions, limited studies have comprehensively examined the combined national mortality trends and demographic disparities associated with both cardiac arrest and cardiomyopathy over extended time periods. Understanding these patterns is essential for identifying vulnerable populations, informing prevention strategies, and guiding healthcare policy. Therefore, the present study aims to evaluate long-term trends and disparities in mortality from cardiac arrest and cardiomyopathy in the United States from 1999 to 2025 using national mortality data.

2. Methods

2.1. Study Design and Population

We conducted a retrospective population-based study using the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause-of-Death database. We analyzed national death certificate data for adults aged ≥25 years from 1999 through 2025 to evaluate mortality associated with cardiomyopathy and cardiac arrest in the United States. This age cutoff has been used to define adults in prior cardiovascular research [11, 12], and restricting the analysis to ≥25 years improves the robustness and stability of mortality estimates. Deaths were identified using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes I42 (cardiomyopathy) and I46 (cardiac arrest). The CDC WONDER query was structured to extract record-level mortality data from the Multiple Cause-of-Death files, including deaths in which I42 and/or I46 appeared anywhere on the death certificate, whether as the underlying cause of death or as contributing causes. Each decedent was counted once in the analysis, consistent with CDC WONDER's person-level mortality reporting structure. The query parameters included: years 1999 – 2025; age ≥25 years; stratification by sex, race/ethnicity, age group, and place of death; and grouping by ICD-10 codes I42 and I46. Age-adjusted mortality rates were calculated using the standard CDC WONDER methodology. Institutional review board approval was not required because this study used publicly available, de-identified government data. The study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [13].

2.2. Data Abstraction

Data for population size and demographics, such as sex and race, were extracted. The place of death was categorized into medical facilities, hospice, home, and nursing home/long-term care facilities. Racial and ethnic categories were classified as non-Hispanic (NH) white, NH Black or African American, Hispanic or Latino, NH American Indian or Alaska Native, and NH Asian or Pacific Islander. Age groups were divided into 3 groups: (25 – 44, 45 – 64, and ≥ 65 years). In accordance with CDC WONDER data-use policies, cells with fewer than 10 deaths are suppressed by the database. Suppressed cells were excluded from subgroup-specific analyses, and no imputation was performed.

2.3. Statistical Analysis

Age-adjusted mortality rates (AAMRs) and crude mortality rates (CMRs) per 100,000 population from 1999–2025, by year, sex, and race, with 95% CIs, were calculated, using the 2000 U.S. population as the standard [14]. CMRs were determined by dividing the number of cardiac arrest and cardiomyopathy-related mortalities among adults by the corresponding U.S. population of that year. The Joinpoint Regression Program (Joinpoint V 5.4.0.0, National Cancer Institute) was used to determine the average annual percent change (AAPC) and the annual percent change (APC). Joinpoint regression, a segmented regression technique, was used to identify points of trend change (join points) by fitting log-linear models and using permutation tests to select the optimal number of join points, thereby ensuring model fit. This method allows identification of significant changes in AAMR over time by fitting log-linear regression models where temporal variation occurred. APCs were considered increasing or decreasing if the slope describing the change in mortality was significantly different from zero using a two-tailed t-test. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Overall Trends

Between 1999 and 2025, cardiac arrest and cardiomyopathy accounted for a total of 237,958 deaths among adults aged 25 years and older in the United States. Most of the deaths occurred in medical facilities as inpatients (47.10%), followed by decedent's home (24.10%) and nursing home or long-term care settings (10.85%), outpatient or emergency room settings (12.73%), hospice facilities (1.05%), medical facilities – dead on arrival (0.85%), other locations (2.83%), medical facilities – status unknown (0.11%), and for 0.38% of cases, the place of death was not specified **(Supplementary Table 1)**.

The overall AAMR declined substantially from 6.33 per 100,000 in 1999 to 2.41 in 2025, with an AAPC of -3.83 (95% CI: -4.18 to -3.57; $p < 0.001$). The mean AAMR was 4.04 (95% CI: 3.96 to 4.13). From 1999 to 2006, mortality decreased sharply from 6.33 to 4.53 (-4.87; 95% CI: -7.26 to -3.87, $p < 0.001$), followed by a continued but more gradual decline from 4.53 in 2006 to 2.95 in 2022 (-2.69; 95% CI: -2.98 to -1.19; $p < 0.022$). A further significant decline was observed from 2.95 in 2022 to 2.41 in 2025 (-7.37; 95% CI: -12.55 to -4.15; $p < 0.001$) **(Figure 1)** and **(Supplementary Table 2)**.

3.2. Sex-Stratified Trends

Throughout the study period, a total of 146,218 deaths were recorded among males and 91,740 among females. Males exhibited higher

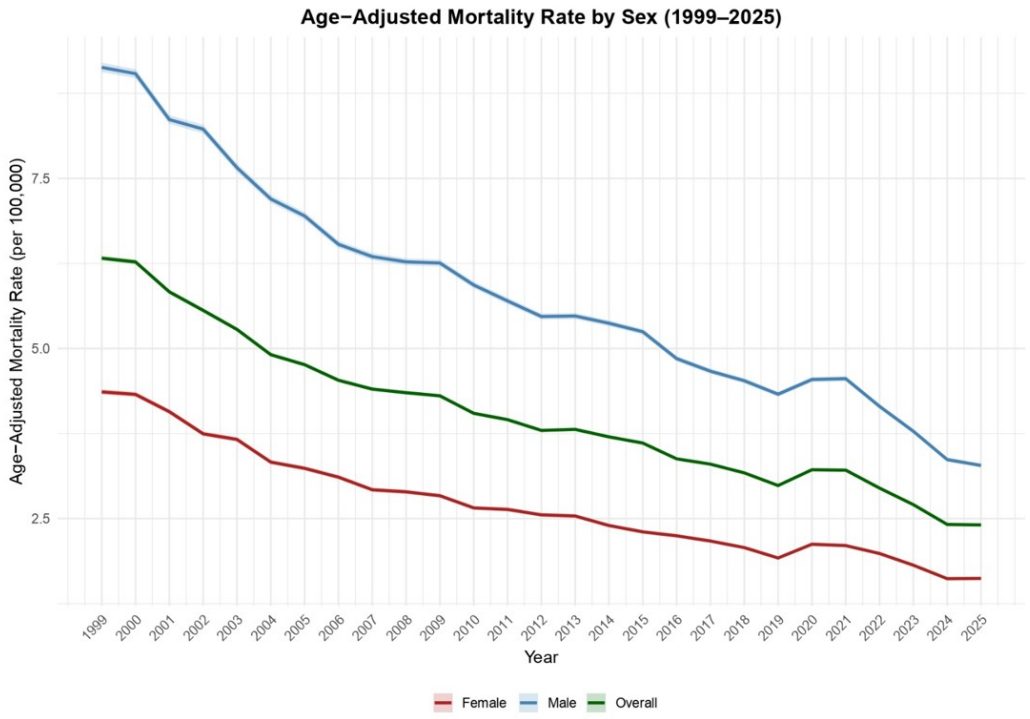

Figure 1: Trends in age-adjusted mortality rates (AAMR) for cardiac arrest and cardiomyopathy in U.S. adults aged ≥25 years from 1999 to 2025, overall and stratified by sex.

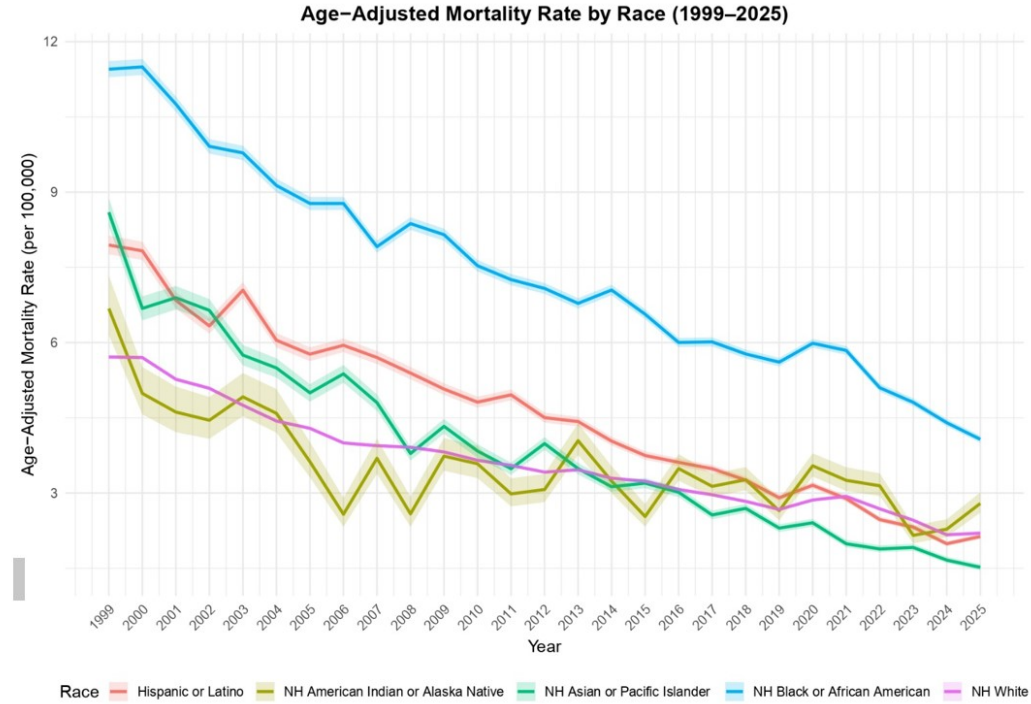

Figure 2: Race- and ethnicity-specific trends in age-adjusted mortality rates (AAMR) for cardiac arrest and cardiomyopathy among U.S. adults aged ≥25 years from 1999 to 2025.

mortality, with an AAMR of 5.82 (95% CI: 5.67 to 5.98) compared with 2.71 (95% CI: 2.62 to 2.81) in females. On average, males experienced a greater decline in mortality than females [Males: AAPC: -4.04 (95% CI: -4.23 to -3.89; $p < 0.001$); Females: AAPC: -3.93 (95% CI: -4.24 to -3.74; $p < 0.001$)].

Among males, the AAMR declined from 9.13 in 1999 to 3.28 in 2025. Joinpoint regression revealed four segments: a marked decrease from 9.13 in 1999 to 6.53 in 2006 (-4.83; 95% CI: -6.40 to -4.09; $p < 0.001$), continued decline from 6.53 in 2006 to 5.25 in 2015 (-2.64; 95% CI: -3.18 to -0.47; $p < 0.019$), a further reduction from 5.25

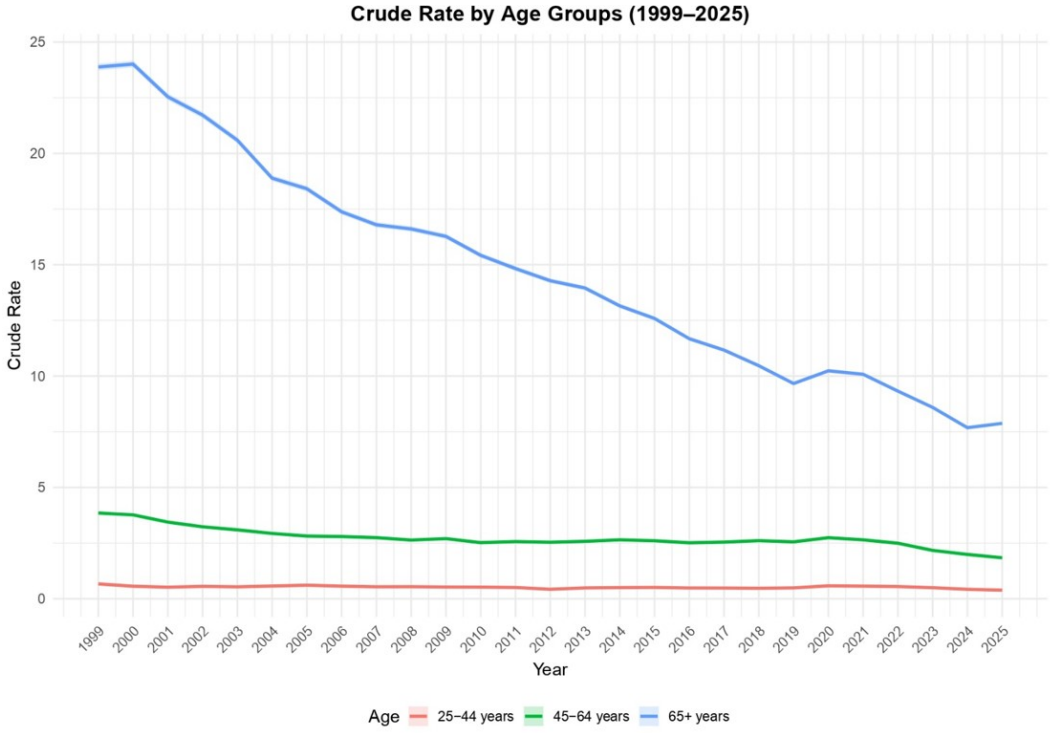

Figure 3: Age-specific trends in crude mortality rates (CMR) for cardiac arrest and cardiomyopathy among U.S. adults aged ≥25 years from 1999 to 2025.

in 2015 to 4.53 in 2018 (-5.07; 95% CI: -6.52 to -3.35; $p < 0.001$), a slight non-significant increase from 4.53 in 2018 to 4.56 in 2021 (0.62; 95% CI: -1.69 to 2.13; $p < 0.547$), and again a significant decline from 4.56 in 2021 to 3.28 in 2025 (-8.31; 95% CI: -10.11 to -7.27; $p < 0.001$).

Among females, mortality decreased from 4.36 in 1999 to 1.62 in 2025. Significant decline was observed from 4.36 in 1999 to 3.24 in 2005 (-5.37; 95% CI: -8.18 to -4.30; $p < 0.001$) and from 3.24 in 2005 to 2.07 in 2018 (-3.30; 95% CI: -4.34 to -2.76; $p < 0.001$). A slight non-significant rise was noticed from 2.07 in 2018 and 2.10 in 2021 (0.19; 95% CI: -2.70 to 1.65; $p < 0.786$), followed by a significant decline from 2.10 in 2021 to 1.62 in 2025 (-6.79; 95% CI: -10.33 to -5.15; $p < 0.001$) **(Figure 1)** and **(Supplementary Table 2)**.

3.3. Race/Ethnicity Trends

Across racial/ethnic groups, the highest overall AAMR was observed among NH Black or African Americans (7.42; 95% CI: 7.05 to 7.79), followed by Hispanics (4.62; 95% CI: 4.27 to 4.97), NH Asian or Pacific Islanders (3.94; 95% CI: 3.50 to 4.39), NH Whites (3.64; 95% CI: 3.56 to 3.73), and NH American Indian or Alaska Natives (3.54; 95% CI: 2.63 to 4.67). Distinct trends were observed among these groups [NH American Indian or Alaska Natives: AAPC: -2.92 (95% CI: -3.92 to -1.59; $p < 0.001$); NH Asian or Pacific Islanders: AAPC: -5.74 (95% CI: -6.14 to -5.35; $p < 0.001$); NH Blacks: AAPC: -3.90 (95% CI: -4.31 to -3.67; $p < 0.001$); NH Whites: AAPC: -3.83 (95% CI: -4.18 to -3.54; $p < 0.001$); Hispanics: AAPC: -5.22(95% CI: -5.76 to -4.78; $p < 0.001$)].

Among NH American Indian or Alaska Natives, mortality declined steeply from 6.68 in 1999 to 2.58 in 2006 (-7.26; 95% CI: -22.68 to -2.27; $p < 0.011$), with a non-significant change from 2.58 in 2006 to 2.79 in 2025 (-1.27; 95% CI: -2.69 to 5.69; $p < 0.352$). NH Asian or Pacific Islanders experienced a consistent and significant decline from 8.60 in 1999 to 1.52 in 2025 (-5.74; 95% CI: -6.14 to -5.35; $p < 0.001$). For NH Blacks, mortality decreased significantly from 11.45 in 1999 to 5.77 in 2018 (-3.49; 95% CI: -4.90 to -3.18; $p < 0.024$), showed a non-significant plateau with an AAMR of 5.77 in 2018 and 5.84 in 2021 (0.24; 95% CI: -3.17 to 1.97; $p < 0.7$), and declined markedly from 5.84 in 2021 to 4.07 in 2025 (-8.72; 95% CI: -13.88 to -6.62; $p < 0.001$). Among NH Whites, significant decreases were observed from 5.71 in 1999 to 4.00 in 2006 (-5.10; 95% CI: -7.15 to -4.08; $p < 0.001$), from 4.00 in 2006 to 2.68 in 2022 (-2.63; 95% CI: -2.94 to -0.97; $p < 0.025$), and from 2.68 in 2022 to 2.20 in 2025 (-7.15; 95% CI: -12.48 to -3.66; $p < 0.001$). Hispanics experienced a significant decline from 7.95 in 1999 to 3.16 in 2020 (-4.47; 95% CI: -4.79 to -3.81; $p < 0.015$), followed by a continued significant reduction from 3.16 in 2020 to 2.13 in 2025 (-8.30; 95% CI: -15.31 to -5.69; $p < 0.001$) **(Figure 2)** and **(Supplementary Table 3)**.

3.4. Age-Specific Trends

Age-specific CMRs demonstrated marked disparities across the study period. Adults aged 65+ years had the highest mortality (14.74; 95% CI: 14.38 to 15.10), followed by those aged 45-64 years (2.72; 95% CI: 2.61 to 2.84) and 25-44 years (0.52; 95% CI: 0.47 to 0.57). On average, 65+ years age group experienced greater decline in mortality over the study period, followed by 45-64 years age group and 25-44 years age group [65+ years: AAPC: -4.21 (95% CI: -4.39 to -4.03; $p < 0.001$); 45-64 years: AAPC: -2.86 (95% CI: -3.06 to -2.69; $p < 0.001$); 25-44 years: AAPC: -1.64 (95% CI: -2.20 to -1.28; $p < 0.001$)].

Among adults aged 25-44 years, CMR decreased from 0.67 in 1999 to 0.39 in 2025. Joinpoint analysis showed a modest decline from 0.67 in 1999 to 0.47 in 2018 (-1.30; 95% CI: -2.08 to -0.86; $p < 0.001$), a significant slight increase from 0.47 in 2018 to 0.57 in 2021 (8.49; 95% CI: 1.52 to 11.83; $p < 0.006$), and a significant decrease from 0.57 in 2021 to 0.39 in 2025 (-10.12; 95% CI: -16.29 to -6.65; $p < 0.001$).

Among adults aged 45-64 years, mortality decreased from 3.85 in 1999 to 1.84 in 2025. Significant reductions were observed from 3.85 in 1999 to 2.93 in 2004 (-5.63; 95% CI: -7.91 to -4.56; $p < 0.001$) and from 2.93 in 2004 to 2.52 in 2010 (-2.21; 95% CI: -3.65 to -0.62; $p < 0.011$). Mortality rates remained relatively stable from 2.52 in 2010 to 2.65 in 2021 (0.34; 95% CI: -0.04 to 1.22; $p < 0.066$), followed by a significant decline from 2.65 in 2021 to 1.84 in 2025 (-8.81; 95% CI: -10.25 to -7.10; $p < 0.001$).

Among adults aged ≥65 years, CMR declined markedly from 23.88 in 1999 to 7.88 in 2025, with a sustained, statistically significant reduction of -4.21 (95% CI: -4.39 to -4.03; $p < 0.001$), with no joinpoints identified **(Figure 3)** and **(Supplementary Table 4)**.

4. Discussion

In this nationwide analysis of mortality trends from cardiac arrest and cardiomyopathy among U.S. adults aged ≥25 years between 1999 and 2025, several important findings emerged. Overall mortality declined substantially during the study period, with age-adjusted mortality decreasing from 6.33 to 2.41 per 100,000. Males consistently demonstrated higher mortality rates than females, although both sexes experienced significant reductions over time. Significant racial disparities were observed, with NH Black individuals experiencing the highest mortality rates despite overall improvements across all racial and ethnic groups. Mortality increased markedly with age, with adults aged ≥65 years having the greatest burden of death. While mortality declined across most subgroups, temporary plateaus or slight increases occurred in some populations during the late 2010s and early 2020s.

The substantial decline in mortality observed in this study parallels improvements in cardiovascular care, emergency response systems, and resuscitation science over the past 27 years. Several population-based studies have reported improved survival following cardiac arrest due to enhanced emergency medical services (EMS), increased public awareness of cardiopulmonary resuscitation (CPR), and expanded availability of automated external defibrillators (AEDs). For example, analysis from the CARES registry demonstrated significant improvements in survival following out-of-hospital cardiac arrest in the United States between 2005 and 2012 [15]. Similarly, national analyses have documented improvements in survival from cardiac arrest in recent years, reflecting advances in resuscitation protocols and post-resuscitation care [16]. Improvements in in-hospital cardiac arrest outcomes have also been reported, with increasing survival rates observed over time in national registries [17].

Cardiomyopathies are important underlying causes of ventricular arrhythmias and sudden cardiac death. Inherited and acquired cardiomyopathies, including hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic cardiomyopathy, are frequently implicated in cardiac arrest events [18]. Hypertrophic cardiomyopathy affects approximately 1 in 500 individuals and represents one of the most common genetic cardiovascular diseases associated with sudden cardiac death [19]. Dilated cardiomyopathy is another major cause of sudden cardiac death and advanced heart failure worldwide [20]. Risk stratification strategies, including the use of implantable cardioverter-defibrillators (ICDs), have significantly reduced sudden death risk in patients with cardiomyopathies [21]. Genetic screening and improved diagnostic imaging have also enhanced early identification of high-risk individuals with inherited cardiomyopathies [22].

Our findings demonstrate consistently higher mortality among males compared with females. This observation is consistent with prior studies showing that sudden cardiac death occurs more frequently in men [23]. Biological factors such as hormonal influences, electrophysiological differences, and variations in cardiac ion channel expression may contribute to sex-specific susceptibility to malignant arrhythmias [24]. Additionally, men generally have a higher prevalence of structural heart disease and ischemic heart disease, which increases the risk of ventricular arrhythmias and sudden cardiac death [25]. Nevertheless, improvements in cardiovascular care have led to declining mortality rates among both sexes over time.

Our study identified substantial racial disparities in cardiac arrest and cardiomyopathy-related mortality, with NH Black individuals experiencing the highest mortality rates. Previous research has demonstrated that Black populations in the United States experience higher rates of sudden cardiac death and cardiovascular mortality [26]. Multiple factors likely contribute to these disparities, including higher prevalence of hypertension, heart failure, and cardiomyopathy in Black populations [26, 27]. Differences in socioeconomic status, healthcare access, and structural determinants of health also contribute to disparities in cardiovascular outcomes [27, 28]. Importantly, several studies have demonstrated that Black individuals experiencing out-of-hospital cardiac arrest are less likely to receive bystander CPR, which significantly influences survival outcomes [29].

Age was strongly associated with mortality in our analysis, with adults aged ≥65 years demonstrating the highest death rates. Aging is associated with structural and electrophysiological changes in the myocardium that increase susceptibility to arrhythmias and sudden cardiac death [30]. Older adults also have a higher prevalence of heart failure and cardiomyopathy, which further increases the risk of cardiac arrest [31]. Comorbidities and frailty may also contribute to poorer outcomes following cardiac arrest among elderly individuals [31, 32]. Despite these challenges, improvements in cardiovascular care have led to declining mortality rates, even among older adults.

Furthermore, analysis of place-of-death data revealed that a substantial proportion of deaths occurred at home or in out-of-hospital settings. This pattern may reflect gaps in early recognition of cardiac events, delays in emergency response, limited access to timely medical care, or missed opportunities for bystander intervention. Higher home-based mortality underscores the importance of targeted community education, widespread CPR training, rapid EMS dispatch, and improved access to preventive care for high-risk populations.

4.1. Future Directions

Future directions for research on cardiac arrest and cardiomyopathy-related mortality in the United States should focus on integrating granular clinical data, including comorbidities, treatment modalities, and genetic profiles, to better elucidate mechanisms underlying observed disparities. Prospective studies evaluating the impact of early detection strategies, personalized risk stratification, and targeted interventions such as widespread use of implantable cardioverter-defibrillators and community-based CPR training are warranted. Additionally, research should examine the influence of socioeconomic factors, healthcare access, and regional variations to develop equitable prevention and management strategies that further reduce mortality across high-risk populations.

4.2. Strengths

This study has several notable strengths. First, it utilized a large nationwide mortality database spanning more than two decades, enabling comprehensive evaluation of long-term epidemiological trends. Second, the use of age-adjusted mortality rates allowed accurate comparisons across demographic groups and time periods.

Third, detailed stratification by sex, race/ethnicity, and age provided important insights into demographic disparities in cardiac arrest and cardiomyopathy-related mortality. Finally, the application of joinpoint regression allowed identification of temporal changes in mortality patterns and potential shifts in epidemiologic trends.

4.3. Limitations

Several limitations should be considered when interpreting these findings. First, this analysis relied on death certificate data from the CDC WONDER database, which may be subject to misclassification or inaccuracies in cause-of-death reporting. Variability in death-certificate completion and differences by certifier type (e.g., physician vs. medical examiner/coroner) could further affect accuracy. Second, the database lacks detailed clinical information, including comorbidities, disease severity, and treatment modalities, which limits the ability to explore mechanisms underlying observed mortality trends. Third, the data do not distinguish between out-of-hospital and in-hospital cardiac arrest events and may reflect differences in access to care, emergency response, and missed opportunities for intervention. Fourth, socioeconomic variables and healthcare access indicators were unavailable, preventing further investigation into factors contributing to the observed disparities. Additionally, in accordance with CDC WONDER data-use policies, cells with fewer than 10 deaths are suppressed and were excluded from subgroup analyses; this suppression may introduce bias in smaller demographic strata and could slightly underestimate mortality rates in certain subgroups, as well as affect trend estimates in less populous groups. Finally, as an observational analysis of ecological mortality data, causal or individual-level inferences cannot be drawn, and temporal or coding changes over the study period may have influenced trends.

5. Conclusion

Mortality related to cardiac arrest and cardiomyopathy in the United States declined substantially between 1999 and 2025. Despite these improvements, significant disparities persist across sex, race, and age groups. Males and NH Black individuals continue to experience disproportionately higher mortality rates, and older adults remain the most affected population. Continued efforts to improve early identification and management of cardiomyopathies, expand access to high-quality emergency cardiovascular care, and address structural health disparities are essential to further reduce mortality and improve outcomes.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Institutional Review Board (IRB)

Institutional Review Board approval was not required for this study because it used publicly available, de-identified data.

Large Language Model

No large language model tools were used in the preparation of this manuscript.

Author Contributions

MA and MFH conceived the study and designed the research framework. AE, MS, AAI, MRF, and RM were responsible for data extraction, formal analysis, and drafting the initial manuscript. BH, MZ, AI, KOA, WB, HAM, EA, and MMAM contributed to data analysis, literature review, and critical revisions of the manuscript for intellectual content. IU and MFH provided overall supervision, project administration, and final approval of the published version. All authors have read and agreed to the published version of the manuscript and are accountable for the integrity of the work.

Data Availability

The data that support the findings of this study are openly available in CDC-WONDER at https://wonder.cdc.gov/. The data supporting the findings of this study were obtained from the CDC WONDER online database (Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research). Further inquiries can be directed to the corresponding author.

References

1. Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, et al. 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2025;151(8):e41-e660. [PMID: 39866113, PMCID: PMC12256702, https://doi.org/10.1161/CIR.0000000000001303].
2. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. 2023;147(8):e93-e621. [PMID: 36695182, PMCID: PMC12135016, https://doi.org/10.1161/CIR.0000000000001123].
3. Tseng ZH, Nakasuka K. Out-of-Hospital Cardiac Arrest in Apparently Healthy, Young Adults. JAMA. 2025;333(11):981-96. [PMID: 39976933, PMCID: PMC12107904, https://doi.org/10.1001/jama.2024.27916].
4. H B, MH A, P R, et al. Hypertrophic Cardiomyopathy [Internet]; 2026. Updated 2024 Jun 7. In: StatPearls. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK430788.
5. Massera D, Sherrid MV, Maron MS, Rowin EJ, Maron BJ. How common is hypertrophic cardiomyopathy... really?: Disease prevalence revisited 27 years after CARDIA. Int J Cardiol. 2023;382:64-7. [PMID: 37028711, https://doi.org/10.1016/j.ijcard.2023.04.005].
6. Monda E, Limongelli G, Pelliccia F. Hypertrophic Cardiomyopathy-Current Challenges and Future Perspectives. J Clin Med. 2023;12(18). [PMID: 37763033, PMCID: PMC10531662, https://doi.org/10.3390/jcm12186093].
7. Javaid SS, Ashraf SU, Khan A, Irfan M, Alamgir MU, Ahmed Jilanee SD, et al. Demographic and regional mortality trends in dilated cardiomyopathy in the United States; 1999-2020. SAGE Open Med. 2025;13:20503121251329806. [PMID: 40143927, PMCID: PMC11938866, https://doi.org/10.1177/20503121251329806].
8. Gonuguntla K, Chobufo MD, Shaik A, Roma N, Penmetsa M, Thyagaturu H, et al. Temporal Trends in Race and Sex Differences in Cardiac Arrest Mortality in the USA, 1999-2020. J Cardiol. 2025;85(2):63-8. [PMID: 39154781, https://doi.org/10.1016/j.jjcc.2024.08.006].
9. Jain V, Rao B, Knijnik L, Shah AD, Lloyd MS, El-Chami MF, et al. Rising burden of cardiac arrest- and heart failure-related mortality in the United States from 1999 to 2020. Heart Rhythm O2. 2024;5(4):254-5. [PMID: 38690139, PMCID: PMC11056454, https://doi.org/10.1016/j.hroo.2024.03.001].

10. Marijon E, Narayanan K, Smith K, Barra S, Basso C, Blom MT, et al. The Lancet Commission to reduce the global burden of sudden cardiac death: a call for multidisciplinary action. Lancet. 2023;402(10405):883-936. [PMID: 37647926, https://doi.org/10.1016/S0140-6736(23)00875-9].
11. Hemida MF, Ibrahim AA, Shahriar Z, Khalid M, Zeeshan N, Qaisi W, et al. Mortality trends in multiple sclerosis and cardiovascular disease in adults in the United States: A 25-year mortality perspective. Mult Scler Relat Disord. 2026;105:106861. [PMID: 41308235, https://doi.org/10.1016/j.msard.2025.106861].
12. Hemida MF, Ibrahim AA, Zeeshan N, Faisal MR, Patel K, Hussein M, et al. Trends and disparities in aortic dissection mortality in the united states: a retrospective analysis. BMC Cardiovasc Disord. 2026;26(1):66. [PMID: 41572202, PMCID: PMC12825201, https://doi.org/10.1186/s12872-025-05446-5].
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. [PMID: 18313558, https://doi.org/10.1016/j.jclinepi.2007.11.008].
14. Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. Natl Vital Stat Rep. 1998;47(3):1-16, 20. [PMID: 9796247].
15. Chan PS, McNally B, Tang F, Kellermann A, Group CS. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation. 2014;130(21):1876-82. [PMID: 25399396, PMCID: PMC4276415, https://doi.org/10.1161/CIRCULATIONAHA.114.009711].
16. Odom E, Nakajima Y, Vellano K, Al-Araji R, Coleman King S, Zhang Z, et al. Trends in EMS-attended out-of-hospital cardiac arrest survival, United States 2015-2019. Resuscitation. 2022;179:88-93. [PMID: 35944819, https://doi.org/10.1016/j.resuscitation.2022.08.003].
17. Holmberg MJ, Wiberg S, Ross CE, Kleinman M, Hoeyer-Nielsen AK, Donnino MW, et al. Trends in Survival After Pediatric In-Hospital Cardiac Arrest in the United States. Circulation. 2019;140(17):1398-408. [PMID: 31542952, PMCID: PMC6803102, https://doi.org/10.1161/CIRCULATIONAHA.119.041667].
18. Polovina M, Tschope C, Rosano G, Metra M, Crea F, Mullens W, et al. Incidence, risk assessment and prevention of sudden cardiac death in cardiomyopathies. Eur J Heart Fail. 2023;25(12):2144-63. [PMID: 37905371, https://doi.org/10.1002/ejhf.3076].
19. Stroumpoulis KI, Pantazopoulos IN, Xanthos TT. Hypertrophic cardiomyopathy and sudden cardiac death. World J Cardiol. 2010;2(9):289-98. [PMID: 21160605, PMCID: PMC2998829, https://doi.org/10.4330/wjc.v2.i9.289].
20. H M, VS Y, M S. Dilated Cardiomyopathy [Internet]; 2026. Updated 2023 Apr 7. In: StatPearls. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK441911/.
21. Ruscio E, Scacciavillani R, Gurgoglione FL, Pinnacchio G, Bencardino G, Perna F, et al. Risk Stratification and Optimal Use of Implantable Cardioverter-Defibrillator Therapy in Primary Prevention of Sudden Cardiac Death in Genetic Cardiomyopathies, with Assessment of the Role of Genetic Variants in Guiding Therapeutic Decisions. Biomedicines. 2025;13(11). [PMID: 41301721, PMCID: PMC12650546, https://doi.org/10.3390/biomedicines13112626].
22. Aiyer S, Kalutskaya E, Agdamag AC, Tang WHW. Genetic Evaluation and Screening in Cardiomyopathies: Opportunities and Challenges for Personalized Medicine. J Pers Med. 2023;13(6). [PMID: 37373876, PMCID: PMC10302702, https://doi.org/10.3390/jpm13060887].
23. Butters A, Arnott C, Sweeting J, Winkel BG, Semsarian C, Ingles J. Sex Disparities in Sudden Cardiac Death. Circ Arrhythm Electrophysiol. 2021;14(8):e009834. [PMID: 34397259, https://doi.org/10.1161/CIRCEP.121.009834].
24. Zaman S, Deshmukh T, Aslam A, Martin C, Kovoor P. Sex Differences in Electrophysiology, Ventricular Tachyarrhythmia, Cardiac Arrest and Sudden Cardiac Death Following Acute Myocardial Infarction. Heart Lung Circ. 2020;29(7):1025-31. [PMID: 31558356, https://doi.org/10.1016/j.hlc.2019.07.017].
25. Skjelbred T, Rajan D, Svane J, Lynge TH, Tfelt-Hansen J. Sex differences in sudden cardiac death in a nationwide study of 54 028 deaths. Heart. 2022;108(13):1012-8. [PMID: 35277455, https://doi.org/10.1136/heartjnl-2021-320300].
26. Zhao D, Post WS, Blasco-Colmenares E, Cheng A, Zhang Y, Deo R, et al. Racial Differences in Sudden Cardiac Death. Circulation. 2019;139(14):1688-97. [PMID: 30712378, PMCID: PMC6443438, https://doi.org/10.1161/CIRCULATIONAHA.118.036553].
27. Abrahamowicz AA, Ebinger J, Whelton SP, Commodore-Mensah Y, Yang E. Racial and Ethnic Disparities in Hypertension: Barriers and Opportunities to Improve Blood Pressure Control. Curr Cardiol Rep. 2023;25(1):17-27. [PMID: 36622491, PMCID: PMC9838393, https://doi.org/10.1007/s11886-022-01826-x].
28. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation. 2018;137(20):2166-78. [PMID: 29760227, PMCID: PMC5958918, https://doi.org/10.1161/CIRCULATIONAHA.117.029652].
29. Garcia RA, Spertus JA, Girotra S, Nallamothu BK, Kennedy KF, McNally BF, et al. Racial and Ethnic Differences in Bystander CPR for Witnessed Cardiac Arrest. N Engl J Med. 2022;387(17):1569-78. [PMID: 36300973, PMCID: PMC9760357, https://doi.org/10.1056/NEJMoa2200798].
30. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res. 2012;110(8):1097-108. [PMID: 22499900, PMCID: PMC3366686, https://doi.org/10.1161/CIRCRESAHA.111.246876].
31. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin. 2012;8(1):143-64. [PMID: 22108734, PMCID: PMC3223374, https://doi.org/10.1016/j.hfc.2011.08.011].
32. Hamlyn J, Lowry C, Jackson TA, Welch C. Outcomes in adults living with frailty receiving cardiopulmonary resuscitation: A systematic review and meta-analysis. Resusc Plus. 2022;11:100266. [PMID: 35812717, PMCID: PMC9256816, https://doi.org/10.1016/j.resplu.2022.100266].

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Case Report

Hypoxemia After Inferior Atrial Septal Defect Repair Due to Iatrogenic Diversion of Inferior Vena Cava to Left Atrium: A Case Report

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ABSTRACT

Iatrogenic diversion of the inferior vena cava (IVC) into the left atrium (LA) is a rare but serious complication of surgical atrial septal defect (ASD) repair, particularly in inferior or low-lying defects. When echocardiography is inconclusive, cross-sectional imaging can be critical for diagnosis. A 17-year-old girl with a history of surgical closure of a low-lying ASD at 15 years of age presented with exertional dyspnea and mild oxygen desaturation of 90%-94%. Transthoracic echocardiography showed an intact atrial septal patch. Still, it could not clearly demonstrate the relationship of the inferior vena cava to the right atrium or assess the inferior margin of the repair. Contrast-enhanced CT angiography demonstrated direct drainage of the IVC into the LA with exclusion of the IVC orifice from the right atrium by the atrial septal patch, confirming iatrogenic diversion of the IVC. The patient was referred for surgical re-exploration and corrective re-repair. However, the details of the revision surgery are not available. Iatrogenic diversion of the IVC should be suspected in postoperative ASD patients presenting with unexplained desaturation when echocardiography is inconclusive. CT angiography provides definitive delineation of caval drainage and patch anatomy, enabling accurate diagnosis. This case also underscores the importance of careful intraoperative identification of the inferior rim and confirmation of IVC drainage during repair of low-lying ASDs to prevent this complication.

1. Introduction

Surgical closure of atrial septal defect (ASD) is a commonly performed and generally safe procedure. Rarely, iatrogenic diversion of the inferior vena cava (IVC) into the left atrium (LA) may occur, particularly when the defect involves the inferior portion of the atrial septum near the inferior vena cava (IVC) orifice, particularly in inferiorly located secundum ASDs with a deficient inferior rim or in IVC-type sinus venosus defects [1, 2]. Although this complication was more frequent in the pre – cardiopulmonary bypass era due to limited visualisation and misidentification of the inferior septal margin – often confusing the Eustachian valve for the true rim – it continues to be reported in contemporary practice [3].

We report a case of delayed adolescent presentation of iatrogenic diversion of the IVC into the LA following repair of an inferior ASD, in which transthoracic echocardiography (TTE) was inconclusive and contrast-enhanced CT angiography provided a definitive anatomical diagnosis. This case highlights an important diagnostic pitfall and emphasizes the role of cross-sectional imaging in evaluating unexplained hypoxemia following repair of an inferior ASD.

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2. Case Presentation

A 17-year-old girl presented with intermittent exertional dyspnea for two years. At 15 years of age, she had undergone surgical closure of a low-lying (inferior) ASD at another institution. Operative records described a secundum/low-ostium ASD extending toward the IVC, closed with a pericardial patch. No documentation of intraoperative transesophageal echocardiography (TEE) assessing caval drainage was available.

On examination, oxygen saturation on room air ranged from 90% to 94%. There was no history of cyanosis, clubbing, stroke, or paradoxical embolism. Growth and development were appropriate for the age. Cardiac examination revealed normal heart sounds without murmurs, and there were no signs of heart failure.

Routine laboratory investigations showed a hemoglobin level of 13.8 g/dL, without evidence of significant polycythemia. Electrocardiography demonstrated a normal sinus rhythm. Chest radiography showed clear lung fields, a normal cardiothoracic ratio, and no pulmonary vascular abnormality. TTE revealed an intact atrial septal patch, normal chamber dimensions, no demonstrable atrial-level shunt, and normal right-sided pressures. Visualization of the IVC – RA junction was suboptimal due to limited acoustic windows.

Given persistent hypoxemia and the history of prior inferior ASD repair, CT angiography was performed to evaluate postoperative atrial anatomy and caval connections. CT demonstrated IVC is coursing posteriorly and draining directly into the LA. The atrial septal patch excluded the IVC orifice from the RA, effectively diverting systemic venous return into the LA. Pulmonary venous drainage was normal, and no additional vascular anomalies were identified. These findings were diagnostic of iatrogenic diversion of the IVC to the LA, resulting in a right-to-left shunt following surgical

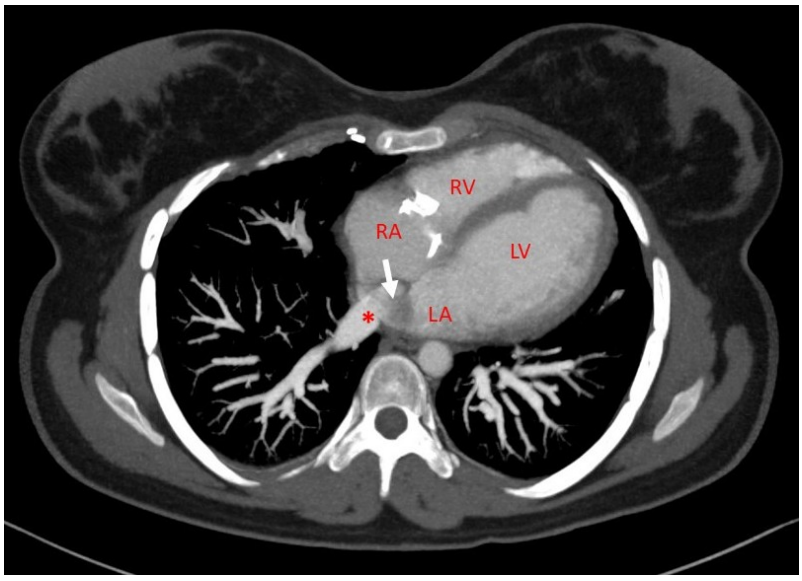

Figure 1: CT Angiography Axial MPR (Multiplanar Reformation) image- IVC (white arrow) seen opening into left atrium close to opening of right inferior pulmonary vein (red star). (abbreviation: RA- right atrium, LA- left atrium, RV- right ventricle, LV- left ventricle).

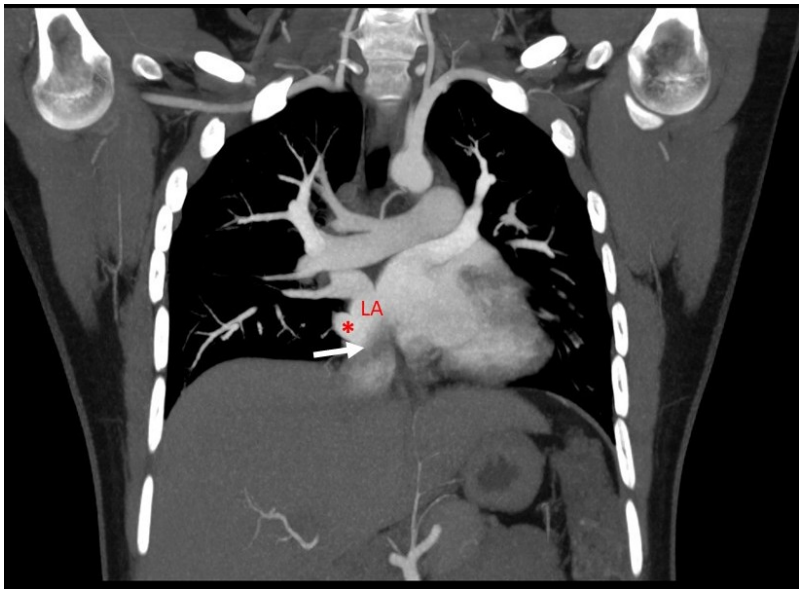

Figure 2: CT Angiography Coronal MPR image- IVC (white arrow) seen opening into left atrium (LA) close to opening of right inferior pulmonary vein (red star).

ASD closure **(Figure 1-4)**. Arterial blood gas analysis, contrast echocardiography, and formal exercise-induced desaturation testing were not performed prior to cross-sectional imaging.

The patient was referred for surgical re-exploration to allow direct visualization and definitive correction of the defect. Surgical re-vision was preferred over transcatheter intervention because the abnormality involved postoperative anatomical distortion requiring patch repositioning/baffle reconstruction, which cannot be reliably addressed with catheter-based techniques.

Also, while awaiting definitive surgical correction, the patient was counselled regarding the risk of paradoxical embolic events resulting from systemic venous admixture into the left atrium. Preventive measures included avoidance of strenuous exertion and dehydration, careful aspiration of air during intravenous access, using air filters when feasible, and close clinical monitoring for neurological or cardiopulmonary symptoms. The patient was maintained under regular follow-up until surgical re-exploration was undertaken.

3. Discussion

Iatrogenic diversion of the IVC, although rare in the contemporary surgical era, sporadic cases continue to be reported. The mechanism usually involves misidentification of the inferior rim of the defect, particularly in inferiorly located secundum ASDs or IVC-type sinus venosus defects, where a prominent Eustachian valve may be mistaken for the true septal margin [1, 2]. Clinical presentation is variable, ranging from early postoperative cyanosis to delayed manifestations such as exertional dyspnea, hypoxemia, or paradoxical embolism years later [3–5].

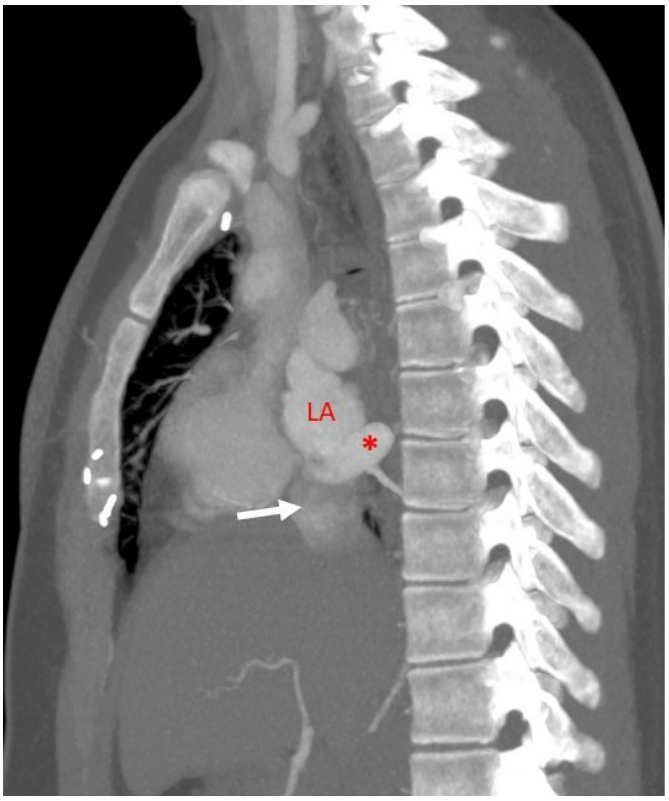

Figure 3: CT Angiography Sagittal MPR image- IVC (white arrow) seen opening into left atrium (LA) close to opening of right inferior pulmonary vein (red star).

Echocardiography is the first-line imaging modality, but may be limited in assessing the IVC – RA junction. In such cases, CT angiography provides definitive, non-invasive delineation of venous anatomy and is invaluable for diagnosis and surgical planning [2, 5]. Prevention of this complication relies on meticulous intraoperative assessment in patients with inferior or low-lying atrial septal defects. Particular attention should be paid to identifying the true inferior margin of the defect and distinguishing it from the Eustachian valve, which may otherwise be mistakenly incorporated into the patch. Before completing patch closure, the surgeon should confirm that the inferior vena cava orifice remains unobstructed and drains freely into the right atrium. In addition, intraoperative transesophageal echocardiography or direct inspection after patch placement can help verify appropriate caval drainage before separation from cardiopulmonary bypass, thereby minimizing the risk of inadvertent IVC diversion [2, 3].

(Table 1) summarizes the published Reports of Iatrogenic Diversion of IVC to the Left atrium following ASD closure compared with the present case. Previously reported cases span both pediatric and adult populations, with presentations ranging from immediate postoperative cyanosis to delayed manifestations years after ASD repair [1–5]. The present case adds to the literature by emphasizing the technical challenges of repairing low-lying inferior ASDs and the need for intraoperative verification of the true inferior margin and appropriate caval drainage before weaning from cardiopulmonary bypass.

A practical diagnostic approach may be considered in postoperative patients presenting with unexplained desaturation following repair of an inferior or low-lying atrial septal defect. Initial evaluation typically includes TTE; however, visualization of the inferior vena cava – right atrial junction and postoperative atrial septal anatomy may be limited. Targeted visualization using TEE may be performed, providing superior, close-up acoustic windows to inspect the interatrial septum, evaluate the integrity of the surgical patch or closure device, and examine the proximal pulmonary veins. Further, physiologic confirmation may be obtained with an echocardiographic study using agitated saline (bubble), which may demonstrate shunting. Also, definitive anatomical evaluation can be performed with cross-sectional imaging, such as CT angiography or cardiac MRI, to delineate the IVC pathway, patch/baffle position, and atrial connections, thereby confirming inadvertent diversion and guiding surgical correction. Cardiac MRI is preferred when flow quantification, shunt physiology (Qp/Qs), and ventricular functional assessment are required in addition to anatomical evaluation. Catheter angiography is reserved for cases where hemodynamic assessment, confirmation of shunt physiology, or potential transcatheter intervention is required, or when noninvasive imaging findings remain inconclusive [6]. A diagnostic algorithm in a postoperative ASD patient with unexplained hypoxemia, cyanosis, or desaturation is suggested in the flowchart **(Figure 5)**.

Despite the clear anatomical diversion of the inferior vena cava into the left atrium, the patient demonstrated only mild resting desaturation. Similar variable or delayed desaturation in IVC-to-LA diversion has been reported earlier [1, 3]. This may be explained by physiologic factors such as preferential streaming of oxygenated pulmonary venous blood toward the left ventricular inflow and partial mixing within the atrium, which can limit systemic desaturation at rest. In addition, the inferior vena cava contributes a smaller proportion of total venous return compared with the superior vena cava under resting conditions [7]. However, during exertion,

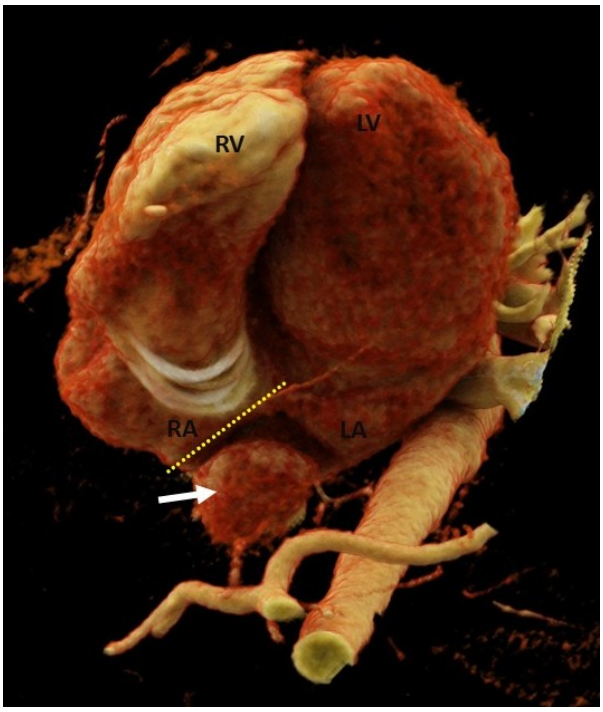

Figure 4: CT Angiography Cinematic VRT (Volume Rendering Technique) reconstruction demonstrating the relationship between the surgical patch (yellow dotted line) and the redirected IVC pathway (white arrow) into the left atrium. (abbreviation: RA- right atrium, LA- left atrium, RV- right ventricle, LV- left ventricle).

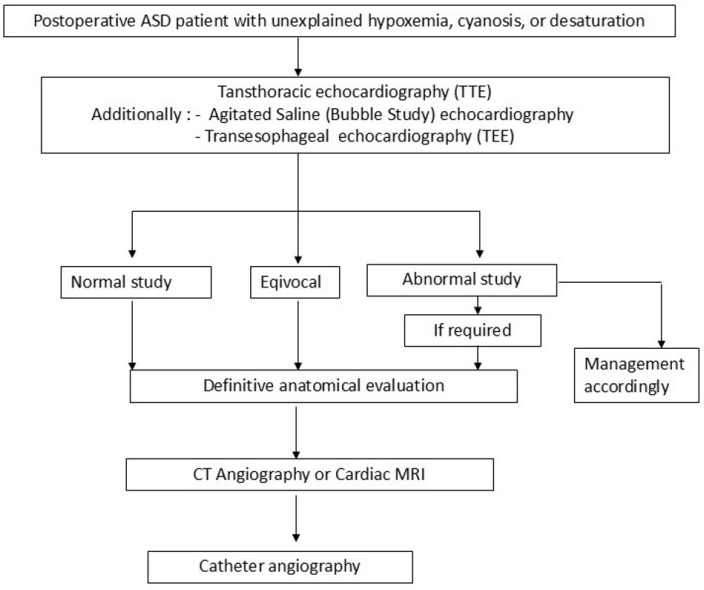

Figure 5: Flowchart: Diagnostic algorithm in Postoperative ASD patient

increased venous return from the lower body may augment right-to-left shunting, thereby explaining the patient's predominant exertional dyspnea and desaturation [8].

This report has certain limitations. The exact intraoperative mechanism of the diversion cannot be confirmed because original intraoperative imaging and transesophageal echocardiography documentation from the index surgery were not available, and the interpretation relies on the available operative notes together with postoperative CT findings. Therefore, the proposed mechanism – misidentification of the inferior rim of the defect or the Eustachian valve during patch closure – should be considered the most likely explanation. Another limitation of the case report is that the details of the revision surgery are not available.

4. Conclusion

Iatrogenic diversion of the IVC to the left atrium is a rare but important complication following surgical closure of ASD. Clinical suspicion should be particularly high in patients with a history

Table 1: Published Reports of Iatrogenic Diversion of Inferior Vena Cava (IVC) to the Left Atrium Following ASD Closure Compared with the Present Case (1-5)

S No	Study	Age	Patient / Lesion Type	Timing of Presentation	Presenting Feature	Imaging Modality	Management	Distinctive Feature
1	Jain et al., 2012	Child (NR)	Surgically repaired ASD	Early postoperative	Severe cyanosis immediately after repair	TTE (with Doppler and contrast echocardiography)	Reoperation redirecting IVC to RA	Immediate recognition after surgery
2	Tayeh et al., 2019	5 Y	Secundum ASD (child)	Early postoperative	Persistent cyanosis, desaturation	TTE ± TEE, CT angiography	Surgical revision	Early postoperative pediatric presentation
3	Kim et al., 2021	Adult	After ASD closure	Late presentation	Dyspnea, systemic desaturation	TTE, CT angiography	Surgical septal revision	Delayed diagnosis of R-L shunt
4	Darwazah et al., 2022	Adult woman	Prior ASD repair	Delayed (years later)	Recurrent fetal loss, chronic hypoxemia	TEE, CT angiography	Surgical redirection of IVC	Rare obstetric presentation
5	Zhang et al., 2025	Mixed ages	Post-ASD repair (case series)	Early postoperative	Persistent hypoxemia	TTE, CT angiography	Surgical correction	Series highlighting early detection
6	Present case	17 Y	Low-lying inferior ASD	Early postoperative	Unexplained desaturation	TTE, CT angiography	Corrective surgical revision planned	Highlights need to confirm inferior rim and caval drainage before weaning from bypass

ASD, atrial septal defect; IVC, inferior vena cava; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; CT, computed tomography; RA, right atrium; NR, not reported.

of repair of low-lying or inferior ASDs who develop otherwise unexplained postoperative desaturation. While echocardiography remains the initial diagnostic modality, it may occasionally be inconclusive in delineating abnormal caval drainage. In such cases, CT angiography provides precise anatomical visualisation of the IVC pathway and patch configuration, enabling definitive diagnosis. In the present case, cross-sectional imaging clearly demonstrated IVC diversion into the left atrium, facilitating appropriate surgical planning for correction. Beyond the diagnostic aspect, this case highlights an important operative consideration: during repair of inferior or low-lying ASDs, meticulous identification of the true inferior rim and careful avoidance of incorporating the Eustachian valve into the repair are critical. Postoperative confirmation of appropriate caval drainage should be considered an essential step in anatomically challenging inferior ASD repairs to prevent this rare but significant complication.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research

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Informed Consent

The authors certify that appropriate consent was obtained from the patient's legal guardian for publication of clinical information and images. Identifying information has been omitted to protect patient confidentiality.

Large Language Model

None.

Author Contributions

AKP was responsible for case identification, imaging interpretation, and primary writing. RKP contributed through conceptualisation and supervision. DS provided technical review and assisted in replying to reviewer queries. RS helped refine the "Discussion" and "Conclusion" sections, while SM selected and annotated the high-quality figures.

Data Availability

No publicly available dataset was generated for this case report. All relevant clinical information and imaging findings supporting the conclusions of this article are included in the manuscript. Any additional de-identified details may be available from the corresponding author upon reasonable request, subject to patient privacy and consent restrictions.

References

1. Jain SA, Pinto R, Dalvi B. Iatrogenic diversion of IVC to left atrium after surgical closure of ASD. Ann Pediatr Cardiol. 2012;5(1):72-4.

[PMID: 22529607, PMCID: PMC3327021, https://doi.org/10.4103/0974-2069.93716].

2. Tayeh C, El Khoury M, Bitar F, Arabi M. Atrial septal defect closure complicated by anomalous inferior vena cava return to the left atrium: a case report of a 5-year-old child. Eur Heart J Case Rep. 2019;3(2). [PMID: 31449633, PMCID: PMC6601233, https://doi.org/10.1093/ehjcr/yty169].
3. Darwazah AK, Ibrahim BJ, Nairat M, Khdour I, Madi H. Iatrogenic diversion of inferior vena cava to the left atrium presented as recurrent foetal loss: a case report. Eur Heart J Case Rep. 2022;6(9):ytac348. [PMID: 36072424, PMCID: PMC9446688, https://doi.org/10.1093/ehjcr/ytac348].
4. Kim MS, Jang SY, Yang DH. Complications caused by iatrogenic right-to-left shunt after surgical closure of atrial septal defect: a case report. Eur Heart J Case Rep. 2021;5(11):ytab434. [PMID: 34917878, PMCID: PMC8669598, https://doi.org/10.1093/ehjcr/ytab434].
5. Zhang H, Liu Q, Meng H, Xiong C. Iatrogenic diversion of inferior vena cava to the left atrium presented as persistent hypoxemia: Case series. Medicine (Baltimore). 2025;104(3):e41162. [PMID: 39833084, PMCID: PMC11749782, https://doi.org/10.1097/MD.0000000000041162].
6. Fogel MA, Anwar S, Broberg C, Browne L, Chung T, Johnson T, et al. Society for Cardiovascular Magnetic Resonance/European Society of Cardiovascular Imaging/American Society of Echocardiography/Society for Pediatric Radiology/North American Society for Cardiovascular Imaging Guidelines for the use of cardiovascular magnetic resonance in pediatric congenital and acquired heart disease : Endorsed by The American Heart Association. J Cardiovasc Magn Reson. 2022;24(1):37. [PMID: 35725473, PMCID: PMC9210755, https://doi.org/10.1186/s12968-022-00843-7].
7. Anderson RH, Baker EJ, Penny DJ, Redington AN, Rigby ML, Wernovsky G. Paediatric Cardiology. Philadelphia: Churchill Livingstone Elsevier; 2010.
8. Hall JE. Guyton and Hall Textbook of Medical Physiology. Philadelphia: Elsevier; 2021.

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Original Article

Trends and Disparities of CVD Underlying-Cause Deaths with Pneumonia and Influenza Mentioned on the Death Certificate in the United States: A CDC WONDER Analysis

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Geographic variation

ABSTRACT

Background: Pneumonia and influenza (P&I) may precipitate cardiovascular decompensation, yet long-term U.S. mortality patterns of P&I co-mention at death among cardiovascular disease (CVD) deaths are not well described across sociodemographic and geographic strata.
Methods: Using CDC WONDER multiple-cause-of-death data, we identified deaths with CVD as the underlying cause (ICD-10 I00–I99) and P&I (J09–J18) mentioned anywhere on the death certificate. We calculated crude and age-adjusted mortality rates (AAMR, per 100,000; 2000 U.S. standard), assessed 1999–2023 trends with Joinpoint regression, selected descriptive subgroup and interstate mapping summaries used 1999–2020.
Results: AAMR declined from 29.58 (1999) to 8.45 (2023) (-71.4%), with joinpoints in 2005, 2009, and 2019 and a plateau after 2019. Mortality increased with age; adults ≥85 years accounted for 47.3% of deaths and the highest crude rate (277.9 per 100,000). In 2023, AAMR was higher in males than in females (10.69 vs 6.73). Rates were higher in Black than White decedents (10.7 vs 9.5 per 100,000) and highest in rural areas, with marked interstate heterogeneity.
Conclusions: AAMRs declined during 1999–2023 but plateaued after 2019, with heterogeneity by age, geography, and race/ethnicity. These descriptive co-mention patterns highlight higher-rate groups and areas that may warrant prioritization for further investigation and prevention planning; they do not establish causal pathways or quantify the impact of structural determinants.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States, making any common trigger of acute cardiovascular decompensation a major public-health concern [1]. Seasonal influenza activity has become increasingly sharp every year during the U.S. fall-winter period, resulting in predictable surges in respiratory diseases that may coincide at the population level with periods of increased acute cardiovascular events [2]. Beyond typical respiratory deaths, influenza-attributable mortality based on U.S. death certificates demonstrates substantial year-to-year variability and a disproportionate burden among older adults [3]. However, death-certificate multiple-cause coding in this study captures only co-mention at death and cannot establish infection timing, triggering, or attributable risk.

There is epidemiologic evidence supporting influenza as a short-term cardiovascular trigger, and a national observational study found a higher incidence of acute myocardial infarction (AMI) during weeks with greater influenza activity, even after adjustment for meteorological effects [4]. Mechanistically, influenza may amplify systemic inflammation and coagulation signalling, thereby promoting endothelial dysfunction and plaque instability, potentially elevating thrombosis-related morbidity such as AMI and stroke [5]. Pneumonia shows a parallel cardiovascular footprint: a systematic review and meta-analysis discovered that cardiac complications are frequent in community-acquired pneumonia and are associated with worse outcomes [6]. Consistent with this, a large prospective cohort of hospitalized community-acquired pneumonia patients reported frequent in-hospital acute cardiovascular events and increased short-term mortality among those who developed such complications [7]. Accordingly, we cite the triggering-events literature for biological plausibility, but interpret our findings as descriptive co-recording of pneumonia/influenza among CVD underlying-cause deaths, not proof of causal triggering.

Because fatal illnesses are often associated with interacting conditions, analyses restricted to a single cause can undercount deaths in which influenza or pneumonia was an important contributive factor in cardiovascular deterioration [8]. The explicit fact of multiple-cause-of-death coding includes any mention of a contributing condition (up to 20 causes on a specific certificate) to achieve a more realistic determination of co-occurring respiratory infection and co-occurring CVD at death. This approach is widely used in modern burden estimations; for example, large-scale U.S. death certificate analysis

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has been used to quantify the number of influenza-related deaths over a wide time span [3].

Disparities also matter: U.S. surveillance analyses have documented racial and ethnic differences in the morbidity associated with severe influenza, including hospitalization, ICU admissions, and in-hospital death across multiple seasons [9]. At the mortality level, geographic variation in racial disparity of influenza and pneumonia has been demonstrated across U.S. regions and urbanization strata, illustrating that there is no even distribution of risk [10]. Regarding pneumonia mortality in general, many recent reports in the U.S. show consistent differences by sex, race, and rurality, which confirms the possibility of structural and access-related contributors to unequal outcomes [11].

Although there is biological plausibility and growing evidence linking influenza and pneumonia to cardiovascular events and adverse outcomes, long-horizon descriptions of how often these conditions co-occur on death certificates – and how that pattern varies over time, by age, race/ethnicity, and state – remain fragmented. Although prior U.S. work has described influenza- and pneumonia-related mortality trends using death certificates, key gaps remain in characterizing how P&I are co-recorded with cardiovascular mortality across time and place. Specifically, it is not well described (i) whether the long-term declines in P&I co-mentions among CVD deaths changed after 2019 (including potential plateauing), (ii) how patterns vary simultaneously by age, race/ethnicity, urbanization, and state. We therefore aimed to describe annual trends and subgroup/state gradients of U.S. death certificates in which P&I co-occur with CVD characterize recent trend changes. We focused the primary analysis on deaths with CVD as the underlying cause and P&I recorded anywhere on the death certificate to anchor inference to the burden of CVD mortality with concurrent respiratory infection conditions. This objective is conceptually distinct from studying primary respiratory mortality (P&I as the underlying cause), where CVD may be listed incidentally as a comorbidity.

2. Methods

2.1. Study Design and Data Source

This retrospective, population-based study analyzed U.S. nationwide mortality data from 1999 – 2023 from the CDC WONDER Multiple Cause of Death database that is derived from the National Vital Statistics System, which includes all conditions reported on death certificates and therefore allows for determining deaths in which an influenza or pneumonia co-occurred with CVD, independent of the underlying cause of death designation. All crude and AAMRs used general population denominators (U.S. resident population) and therefore represent population mortality rates of CVD underlying-cause deaths with P&I mentioned on the death certificate, rather than mortality rates among a cohort of individuals living with diagnosed CVD. To enable reproducibility, the exact CDC WONDER extraction specification (request type, years, ICD-10 filters, groupings, and output options) is provided in the Supplement. Briefly, we used the CDC WONDER Multiple Cause of Death (Detailed Mortality) request to obtain annual counts and rates, applying the ICD-10 filters described below and grouping by year and the relevant stratifying variables (sex, race/ethnicity, urbanization, and state). CDC WONDER suppression rules were respected: cells suppressed for confidentiality (small counts) were treated as missing (not zero), and strata with suppressed/unstable estimates were not interpreted; where suppression affected rate calculations or mapping stability, the affected strata were excluded from those specific comparisons and flagged in the corresponding tables/figures. The final 1999 – 2023 analytic series was assembled from two separate CDC WONDER extracts: one covering 1999 – 2020 and a second covering 2018 – 2023. For the three overlapping calendar years (2018 – 2020), annual death counts and age-adjusted mortality rates from both extracts were cross-checked prior to constructing the final series; counts and rates for each overlapping year matched exactly across the two extractions, and no discontinuity or artificial inflection was identified at the merge point.

CDC WONDER suppresses cells with deaths <10; however, in our extracted annual series none of the analytic strata-years met the suppression threshold for the time-series analyses, so no values were suppressed in the joinpoint. An exception is Table 1, where a small number of 'Unknown/Not stated' records were excluded from the displayed subgroup rows (per WONDER's output categories), which is why section totals may not fully reconcile.

Place of death was obtained from the CDC WONDER Multiple Cause of Death "Place of Death" variable and is reported as counts and percentages (rates not applicable). Categories included inpatient, outpatient/ER, dead on arrival, status unknown (1999 – 2002 only), home, hospice (2003+), nursing home/long-term care, other, and unknown. Percentages used the total deaths shown in the table as the denominator, with "other" and "unknown" included.

2.2. Case Definition

This study included all deaths in the United States with CVD as the underlying cause of death. We defined the outcome as deaths with CVD as the underlying cause of death (ICD-10 I00 – I99) and pneumonia and/or influenza (P&I; ICD-10 J09 – J18) mentioned anywhere on the death certificate among multiple causes of death (i.e., a co-mention, not a causal attribution). A death was included if influenza or pneumonia was mentioned anywhere on the death certificate, as a contributing cause in conjunction with a cardiovascular diagnosis. Analyses were restricted to decedents aged ≥15 years. Deaths among individuals <15 years were excluded because CVD is rare in childhood, and small cell counts in younger age strata are frequently suppressed in CDC WONDER for confidentiality. All totals and percentages reported in age-stratified analyses reflect inclusion of decedents aged 15 years and older only.

2.3. Outcome Measures

The main outcome was the age-adjusted mortality rate (AAMR), which was expressed per 100,000 people. Age adjustment was done under the direct standardization method with the 2000 U.S. standard population as the reference. The rates of mortality were estimated in the general population and stratified by sex, race/ethnicity, and urbanization level. Place of death was summarized descriptively (counts and percentages) using the CDC WONDER 'Place of Death' variable from death certificates. For between-group comparisons (e.g., sex, race/ethnicity, urbanization, and state), we used age-adjusted rates throughout; crude rates were reserved only for within-age-band descriptions (i.e., age-specific rates) and are explicitly labeled as such when presented. Descriptive subgroup analyses, including age-group summaries, place of death, urbanization gradients, and state-level choropleth maps, were restricted to 1999 – 2020 due to CDC WONDER suppression and instability in small cells across certain subgroup cross-tabulations in more recent years; these analyses are therefore presented as pre-pandemic historical summaries and should not be interpreted as reflecting the contemporary post-pandemic context described in the full 1999 – 2023 trend analyses. The COVID-19 pandemic and post-pandemic period (2020 onward) may have materially altered care-setting patterns, geographic distributions, and subgroup disparities; readers should exercise caution when

extrapolating the 1999 – 2020 descriptive findings to the current period.

2.4. Temporal and Geographic Analyses

Temporal trends in AAMRs were measured using joinpoint regression with the National Cancer Institute Joinpoint Regression Program. The log-transformed rates in mortality were modeled in order to determine statistically significant inflections over time, corresponding to changes in trend direction or magnitude. The annual percent change (APC) was estimated for each of the identified segments, and the average annual percent change (AAPC) across the full study period. The maximum number of joinpoints was four, and the selection of the model was based on using the permutation tests. The statistical significance was evaluated by having a two-sided alpha level of 0.05, and all estimates were presented with the 95% confidence intervals (CI). Within-year (monthly or seasonal) variation in AAMRs was not evaluated in this study.

Geographic strata in CDC WONDER reflect the decedent's legal place of residence at the time of death (state and county of residence), not the county of occurrence. Urbanization level was obtained from the CDC WONDER Multiple Cause of Death dataset "Urbanization" variable, which assigns each death to an NCHS urban – rural category based on the decedent's county of residence (Large Central Metro, Large Fringe Metro, Medium Metro, Small Metro, Micropolitan, and Noncore). Place of death was analyzed separately using death-certificate place-of-death categories and should not be interpreted as a residence-based measure. Records with missing/unknown residence geography (and therefore unassigned urbanization) were excluded from geography- and urbanization-stratified tabulations, but were retained in national-level totals.

Geographic variation in mortality rates of CVD as the underlying cause and P&I mentioned as contributing causes was examined using state-level age-adjusted mortality rates. These rates in the mortality burden throughout the U.S. were visualized using choropleth maps. Where mapping stability was a concern (e.g., small counts/suppression), we applied stability rules described in the Supplementary Methods and avoided interpretation of unstable strata; maps are labeled consistently as age-adjusted and based on residence state. Reproducible techniques were used for all data representation and computational workflows.

2.5. Statistical Analysis and Ethics

All mortality rates were expressed per 100,000 population. Using reproducible computational workflows, statistical analyses, and data visualization, while Joinpoint analyses were performed using the National Cancer Institute Joinpoint software. Subgroup-specific descriptive summaries (e.g., sex, race/ethnicity, urbanization, and place of death) were derived from CDC WONDER tabulations that exclude records with missing or unknown values for the stratifying variable. Therefore, subgroup totals may not equal the overall national death count because records with unknown or suppressed characteristics are omitted from those stratified tabulations. All subgroup percentages are calculated using the total number of deaths available within each stratified extraction as the denominator. Race/ethnicity on death certificates is subject to misclassification (notably for American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander decedents) and may be affected by changes in coding/bridging practices over time; because CDC WONDER provides aggregated tabulations, no individual-level mitigation was possible, and we interpret disparity estimates with this limitation in mind. The present research involved publicly available, de-identified data; therefore, it did not require informed consent or approval from the institutional review board (IRB).

3. Results

3.1. Crude mortality rates by age group

In the U.S., between 1999 and 2023, 772,865 deaths were identified from the U.S. death certificates in which CVD was listed as the underlying cause of death and P&I was listed as a contributing cause of death, with an absolute decrease of 21.13 per 100,000 and 71.4% relative reduction in the AAMR between 1999 and 2023 (29.58 and 8.45, respectively). Unless otherwise specified, temporal trend analyses. Among decedents aged ≥15 years, crude mortality in age-stratified descriptive analyses (1999 – 2020) increased steeply with age. Age-stratified crude-rate summaries are shown for 1999 – 2020 because WONDER suppression/instability in small cells (particularly in younger strata and some subgroup cross-tabulations) limited stable tabulation of certain descriptive strata through 2023; the full-period (1999 – 2023) trend analyses remain based on annual AAMRs.

The lowest rate of crude mortality was noted among persons aged 15 – 24 years (0.1 per 100,000; 696 deaths, 0.1%), and the highest count of crude mortality was found among persons aged 85 years and over (277.9 per 100,000; 332,093 deaths, 47.3%). Another significant burden was noticed among adults aged between 75 – 84 years (216,833 deaths, 30.9%; 72.6 per 100,000), which shows that the majority of CVD underlying-cause deaths with P&I mentioned on the death certificate concentrated in older age groups **(Figure 1)**.

3.2. Age-adjusted mortality by sex, race, and ethnicity

In 2023, the male AAMR was 10.69 per 100,000 compared to 6.73 per 100,000 in females (1999: 37.21 vs 24.97 per 100,000, respectively). In descriptive summaries (1999 – 2020), female deaths were 365,859 (51.9%) and a rate of 8.1 per 100,000, while male deaths were 339,161 (48.1%) with a higher rate of 11.8 per 100,000 (Table 1). All between-group comparisons reported as "#/100,000" reflect age-adjusted rates (AAMRs); crude rates are presented only for within-age-band descriptions **(Figure 1)** and age-group rows in **(Table 1)**.

Racial/ethnic distributions (1999 – 2020 descriptive summaries) showed that the largest number of deaths in the country were White decedents (613,213 deaths, 87.0%; 9.5 per 100,000). Black or African American decedents had a higher mortality rate (10.7 per 100,000) with 69,456 deaths (9.9%). Asian or Pacific Islander decedents accounted for 19,078 deaths (2.7%; 7.4 per 100,000), and American Indian or Alaska Native decedents accounted for 3,273 deaths (0.5%; 7.3 per 100,000). By Hispanic origin (1999 – 2020 descriptive summaries), Hispanic or Latino decedents accounted for 39,443 deaths (5.6%; 8.0 per 100,000), while non-Hispanic decedents accounted for 663,895 deaths (94.4%; 9.7 per 100,000) (Table 1). To prevent false precision, 95% CIs (or stability flags where applicable) for subgroup AAMRs, and strata affected by WONDER suppression/instability are explicitly flagged and not over-interpreted.

3.3. Place of death

During 1999 – 2020, the majority of CVD underlying-cause deaths with P&I mentioned on the death certificate took place in inpatient medical facilities (419,228 deaths, 59.6%). A large percentage was in the nursing homes/long-term care facilities (178,070 deaths, 25.3%), and 7.1% was at the decedent's home (50,162 deaths). Fewer were found in the hospice facilities (2.4%) or outpatient/emergency departments (3.2%).

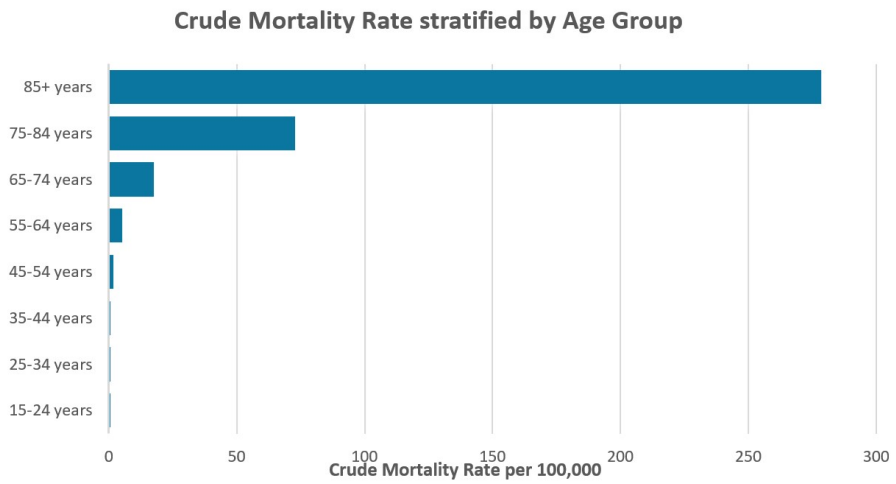

Figure 1: Crude mortality rates for CVD underlying-cause deaths with P&I mentioned on the death certificate, by age group (1999–2020).

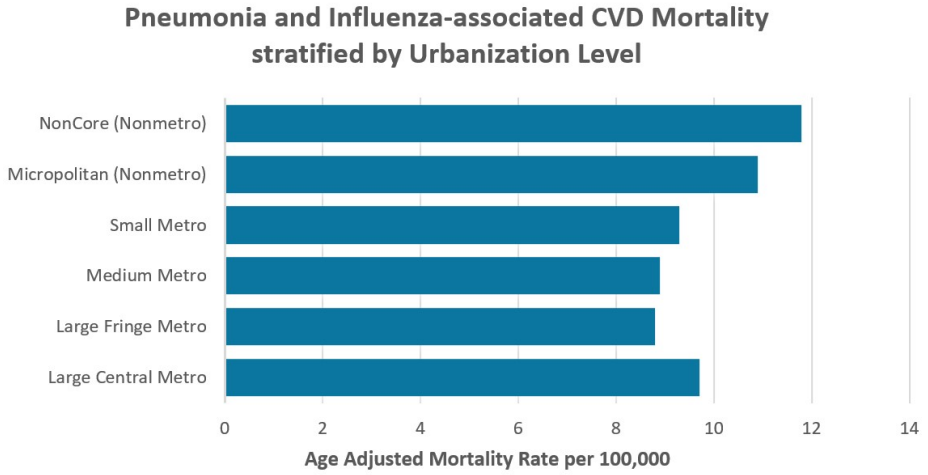

Figure 2: AAMRs of CVD underlying-cause deaths with P&I mentioned on the death certificate in the United States, stratified by urbanization level, 1999–2020.

3.4. Geographic and urbanization-level variation

Urbanization studies (1999 – 2020 descriptive summaries) found that the mortality rates were higher in nonmetropolitan areas. AAMR was highest in noncore (nonmetro) areas (11.8 per 100,000), followed by micropolitan (10.9), large fringe metropolitan (8.8), intermediate values in large central metro (9.7), medium metro (8.9), and small metro (9.3) areas **(Figure 2)**. State-level age-adjusted mortality rates (AAMR; 1999 – 2020) demonstrated pronounced geographic heterogeneity. Specifically, AAMR ranged from 7.61 per 100,000 in Arizona (lowest) to 17.71 per 100,000 in West Virginia (highest), underscoring substantial interstate variation in CVD deaths with P&I listed as contributing causes **(Figure 3)**.

3.5. Overall temporal trends (joinpoint regression)

Joinpoint regression identified three inflection points (2005, 2009, 2019) and four segments: there was a significant drop in mortality in 1999 – 2005 (APC -6.18%, 95% CI -6.97 to -5.38; p<0.000001), followed by an even sharper decline in 2005 – 2009 (APC -10.84%, 95% CI -13.48 to -8.11; p<0.000001), a continuation of this downward trend in 2009 – 2019 (APC -3.72%, 95% CI -4.32 to -3.12; p<0.000001), and a flattening with no statistically significant change of the trend in 2019 – 2023 (APC +0.10%, 95% CI -2.10 to +2.36; p=0.922. The AAPC over the entire duration was -4.94% (95% CI: -5.56 to -4.32; p<0.000001) **(Figure 4)**.

3.6. Sex-specific trends

Sex-stratified joinpoint models showed that the patterns were largely similar, with early decline and more recent attenuation; AAMR declined significantly among females in 1999 – 2005 (APC -6.27%), 2005 – 2009 (APC -10.80%), and 2009 – 2019 (APC -4.10%), and then did not change significantly in 2019 – 2023 (APC -0.64%, p=0.612), while mortality declined significantly among males in 1999 – 2005 (APC -6.26%), 2005 – 2009 (APC -10.92%), and 2009 – 2017 (APC -4.00%), and then did not change significantly in 2017 – 2023 (APC -0.70%, p=0.345); AAPC was significantly negative for both females (-5.23%) and males (-4.95%) for the entire period **(Figure 5)**.

3.7. Race-specific time trends

All of the racial/ethnic groups showed statistically significant long-term decline during 1999 – 2023, which were represented by significant full-period AAPCs: American Indian/Alaska Native -5.42%, Asian/Pacific Islander -6.05%, Black or African American -4.58%, White -4.97%, and Hispanic or Latino -5.14% (all p<0.000001).

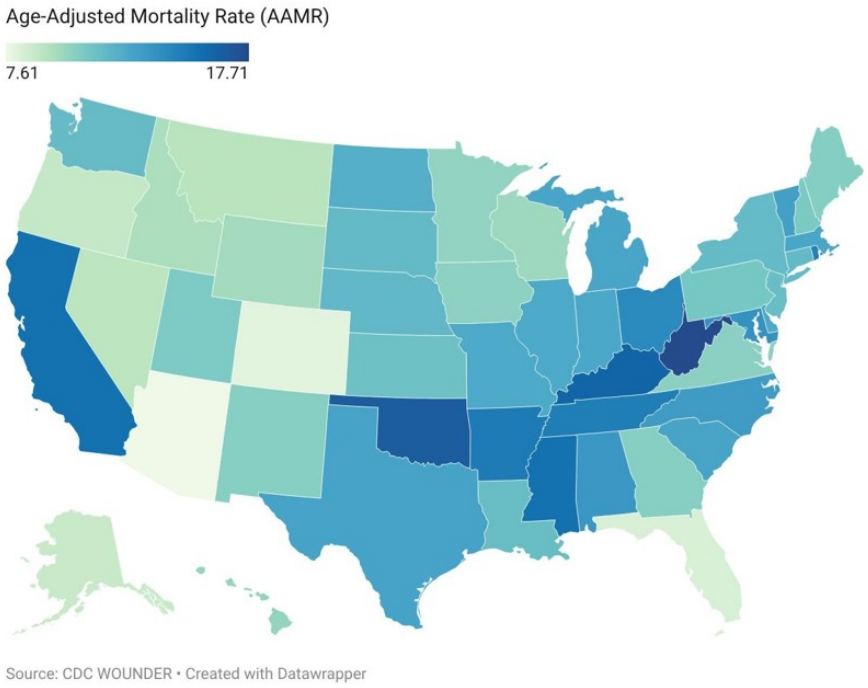

Figure 3: State-Level Geographic Variation in AAMRs of CVD Underlying-Cause of Deaths with Pneumonia and Influenza Mentioned on the Death Certificate, United States (1999–2020).

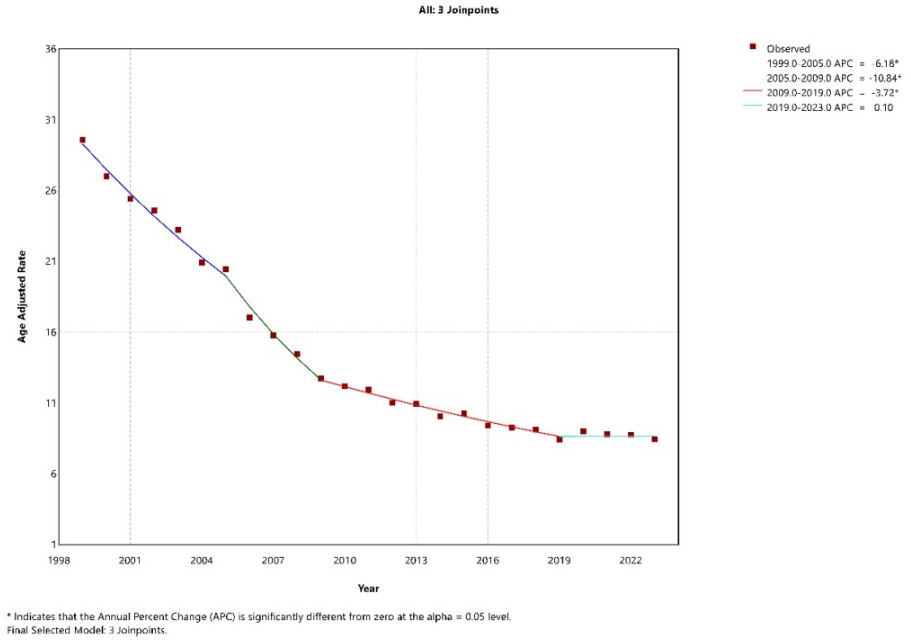

Figure 4: Joinpoint regression of overall AAMR for CVD underlying-cause deaths with P&I mentioned on the death certificate per 100,000 population, United States, 1999–2023.

However, trend patterns varied by group. The mortality of Asian/Pacific Islanders declined sharply from 1999 – 2015 (APC: -7.54%), then continued to decline during 2015 – 2023 (APC: -3.00%, p=0.0013). White mortality improved considerably until the year 2019 (1999 – 2005 APC -6.20%; 2005–2009 APC -10.92%; 2009 – 2019 APC -3.68%) and then plateaued without significant change in 2019 – 2023 (APC -0.07%, p=0.952). Hispanic or Latino mortality declined significantly between 1999 – 2014 (APC -7.25%) with a continued but slower significant decline between 2014–2023 (APC -1.53%, p=0.0436). Mortality of Blacks or African Americans was characterized by several periods of significant decrease until 2018, then a non-significant increase from 2018 – 2021 (APC +6.52%, p=0.145), followed by a non-significant decline from 2021 – 2023 (APC -6.39%, p=0.124), which indicates late-period instability in the trend estimates **(Figure 6)**.

Table 1: Distribution of Deaths with CVD as the underlying cause and P&I mentioned as contributing causes by demographic and contextual characteristics, United States, 1999–2020

Characteristics	Category	Deaths	% of Total Deaths	Rate per 100,000
Ten-Year Age Groups	15-24 years	696	0.10%	0.1
	25-34 years	1988	0.30%	0.2
	35-44 years	5493	0.80%	0.6
	45-54 years	16121	2.30%	1.7
	55-64 years	39205	5.60%	5.1
	65-74 years	90084	12.80%	17.6
	75-84 years	216833	30.90%	72.6
	85+ years	332093	47.30%	277.9
Sex	Female	365859	51.90%	8.1
	Male	339161	48.10%	11.8
Race	American Indian or Alaska Native	3273	0.50%	7.3
	Asian or Pacific Islander	19078	2.70%	7.4
	Black or African American	69456	9.90%	10.7
	White	613213	87.00%	9.5
Hispanic Origin	Hispanic or Latino	39443	5.60%	8
	Not Hispanic or Latino	663895	94.40%	9.7
Urbanization	Large Central Metro	196023	27.90%	9.7
	Large Fringe Metro	152245	21.60%	8.8
	Medium Metro	139708	19.90%	8.9
	Small Metro	67706	9.60%	9.3
	Micropolitan (Nonmetro)	79358	11.30%	10.9
	NonCore (Nonmetro)	68298	9.70%	11.8
Place of Death	Medical Facility - Inpatient	419243	59.60%	-
	Medical Facility - Outpatient or ER	22431	3.20%	-
	Medical Facility - Dead on Arrival	1478	0.20%	-
	Medical Facility - Status unknown	974	0.10%	-
	Decedent's home	50187	7.10%	-
	Hospice facility	16649	2.40%	-
	Nursing home/long-term care	177711	25.30%	-
	Other	13087	1.90%	-
	Place of death unknown	1578	0.20%	-

AAMRs, age-adjusted mortality rates. Rates (#) are AAMRs, except for age groups, which reflect crude mortality rates. Age-stratified analyses were restricted to decedents aged ≥15 years. Urbanization reflects the NCHS urban–rural classification of the decedent's county of residence. Place of death is from the CDC WONDER "Place of Death" variable and is reported as counts and percentages (no rates). Note: Totals within sections may not equal the overall total because CDC WONDER may suppress small cells and/or code records as "Unknown/Not stated," and these categories are not always displayed as separate rows. Thus, percentages within each section use the section-specific denominator (non-missing/non-suppressed records for that characteristic, unless an "Unknown/Other" row is shown).

4. Discussion

This was a population-based retrospective study using the CDC WONDER Multiple Cause of Death database to evaluate U.S. national mortality trends from 1999 – 2023, defining CVD as the underlying cause of death (ICD-10 I00 – I99) with P&I listed as a contributing cause (ICD-10 J09 – J18). Over the entire period, 772,865 deaths were certified, with a general downward trend in age-adjusted mortality, which declined from 29.58 to 8.45 per 100,000 (a 71.4% decrease). The trend, however, reached its lowest point in 2019 and flattened during 2019 – 2023, with higher rates in 2020 – 2022, followed by a return to the 2019 level in 2023. Such findings are important, as descriptive co-mention patterns on death certificates: while respiratory infections can trigger sudden cardiovascular events [12], this study does not confirm infection timing or causal triggering and instead identifies groups/periods in which P&I and CVD are co-recorded at death. The recent attenuation/plateau suggests that

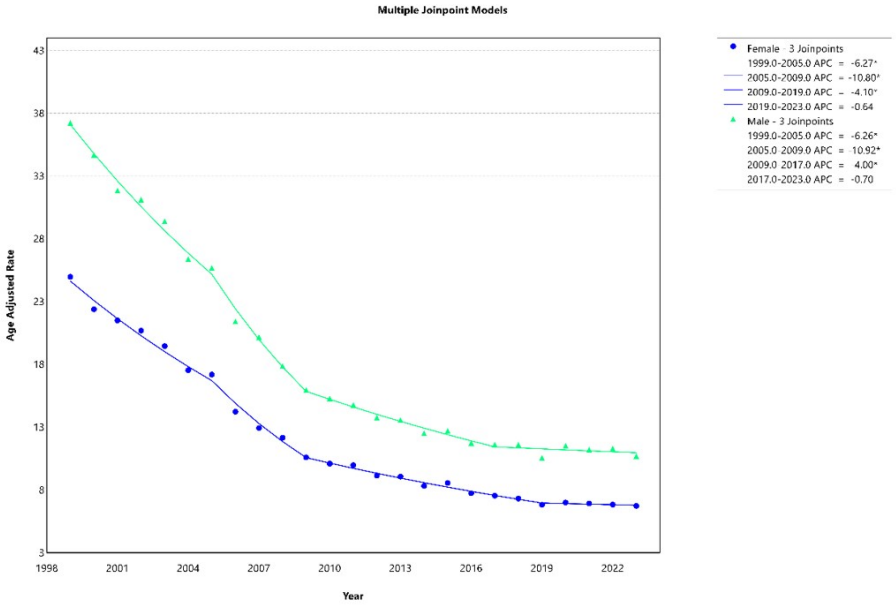

Figure 5: Sex-stratified joinpoint regression of AAMRs for CVD underlying-cause deaths with P&I mentioned on the death certificate per 100,000 population, United States, 1999–2023.

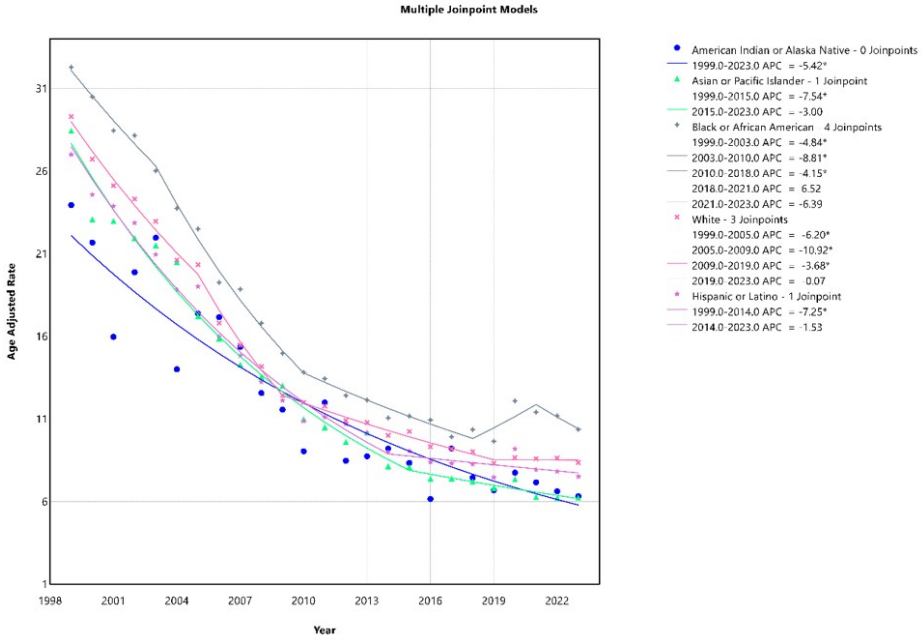

Figure 6: Joinpoint regression of AAMR for CVD underlying-cause deaths with P&I mentioned on the death certificate per 100,000 population, stratified by race/ethnicity, United States, 1999–2023.

some high-risk groups may still be missing effective prevention and care, but alternative explanations should also be considered.

The steep drop between 1999 and the mid-2000s, and the subsequent improvement through 2019, are likely due to broader developments in cardiovascular prevention and care in the United States. The mortality burden of CVD may have been decreased during this period by population-level improvements in blood pressure and cholesterol, smoking cessation, and emergency and hospital care of heart attacks and stroke. Meanwhile, improved prevention and treatment of respiratory diseases, such as seasonal influenza and pneumococcal immunization in the elderly and persons with chronic illness, could have helped reduce heart stress due to infections [13].

To our knowledge, no prior study has comprehensively examined these long-term national patterns and disparities in CVD underlying-cause deaths with P&I mentioned on the death certificate. Kwong et al. demonstrated a sharp short-term increase in acute myocardial infarction after laboratory-confirmed influenza, supporting influenza as an acute cardiovascular trigger. However, that design is more concerned with a short-term post-infection risk period and clinical

events, not with national patterns of multiple causes of death, long-term trend variations, and geographical/urbanization disparities in deaths in which P&I co-occur with CVD as the underlying cause of death [14]. Likewise, Corrales-Medina et al. found higher short- and long-term risk of incident cardiovascular disease after pneumonia hospitalization in community-based cohorts. However, this approach cannot quantify the frequency of pneumonia/influenza that is recorded as a contributing condition in cardiovascular deaths at the population level, nor can it capture nationwide disparities by race/ethnicity and state, or changes in this pattern since 2019 [15].

One important result is that the previous improvement did not persist after 2019. Many different reasons could explain it. To begin with, the COVID-19 pandemic (2020 – 2022) disrupted routine health care, including preventive appointments and early treatment of acute manifestations, which could have provided an additional opportunity to prevent the emergence of infection and cardiovascular issues in the later stages. Second, a combination of long-term increases in the cardiometabolic risk factors (obesity, diabetes, and hypertension) can predispose people to more severe outcomes if they are diagnosed with pneumonia or influenza [16, 17]. Third, mortality patterns might also be influenced by changes in the population exposed and by the severity of respiratory infections, in direct proportion to some settings (such as long-term care facilities). Since the data are based on death certificate coding, there is no record of what factor caused the plateau, but it should be a focus of follow-up research and societal action. In addition, the apparent post-2019 plateau may partly reflect measurement threats, including pandemic-era documentation and coding changes, competing causes (e.g., COVID-19) affecting what is recorded on death certificates, and potential shifts in underlying-cause assignment practices; these factors could bias observed trends independent of true incidence and should be considered when interpreting late-period segmentation.

In 2023, the AAMR was 10.69 per 100,000 in males compared with 6.73 per 100,000 in females (1999: 37.21 vs 24.97 per 100,000, respectively). This male excess in co-mention mortality persisted across the full study period. The observed sex differential is consistent with higher baseline CVD prevalence in men, differences in health behaviors, and differences in preventive care utilization [18–20]. However, this descriptive design cannot adjudicate these mechanisms. Males constitute a higher-rate group that may warrant prioritization in further epidemiologic investigation of P&I and CVD co-occurrence.

Descriptive analyses (1999 – 2020) showed that Black or African American decedents had a higher AAMR (10.7 per 100,000) than White decedents (9.5 per 100,000), despite White decedents constituting the numerically larger group. Joinpoint regression identified late-period instability in Black mortality trends after 2018, with non-significant APC fluctuations of +6.52% and -6.39%; these should be interpreted cautiously, as they may reflect small-number instability and pandemic-era coding disruptions rather than a confirmed trend reversal. These racial/ethnic gradients are hypothesis-generating within this descriptive framework and cannot be attributed to specific structural or clinical mechanisms; death-certificate race/ethnicity is also subject to misclassification. Prior literature has identified differential access to cardiovascular preventive services and differences in cardiometabolic comorbidity burden as plausible contributors [21, 22], but causal inference is not possible from this design.

Mortality was highest in noncore (nonmetropolitan) areas (AAMR 11.8 per 100,000) and lowest in large fringe metropolitan areas (8.8 per 100,000). State-level rates ranged from 7.61 per 100,000 in Arizona to 17.71 per 100,000 in West Virginia during 1999 – 2020. Because these geographic and urbanization analyses are restricted to the pre-pandemic period, the COVID-19 pandemic and its aftermath may have materially altered care-setting patterns, geographic distributions of mortality, and interstate disparities; these findings should therefore be interpreted as pre-2021 historical context rather than as current estimates of disparities. These geographic gradients are consistent with prior evidence of higher cardiovascular mortality in rural areas [23, 24] and are presented as descriptive patterns; crude-rate mapping without covariate adjustment precludes causal inference, and these gradients should be evaluated in follow-up analyses incorporating age-adjusted comparisons with additional ecological covariates.

As anticipated, death rates sharply increased with age. The crude mortality was greatest in adults aged 85 years and above, accounting for almost half of the total number of deaths in the descriptive analysis. This may reflect increased comorbidity burden, reduced immune response, and increased exposure in the long-term care setting [15, 25]. A majority of the deaths occurred in inpatient medical facilities, and approximately a quarter in nursing homes or long-term care facilities. These place-of-death patterns are drawn from the 1999 – 2020 descriptive period; the pandemic era is known to have substantially shifted care settings (e.g., increased home and hospice deaths), so these figures should be treated as pre-2021 historical context rather than reflections of current patterns.

On a mechanistic level, the following pathways are provided as context from prior literature and are not adjudicated by death-certificate co-mention data. On a mechanistic level, the contemporary cardiology surveys synthesize the potential of influenza to trigger cardiovascular events by direct cardiac infection, endothelial maladaptation resulting in plaque destabilization and rupture, and systemic mechanisms (hypoxemia, inflammation) that elevate the metabolic load, biomechanical load and hypercoagulability thereby increasing the likelihood that an individual with vulnerable coronary or cerebrovascular disease will move past a clinical endpoint (myocardial infarction, stroke, acute heart failure) during and immediately after infection [26].

In the case of pneumonia, cohort data of large size show that hospitalization for pneumonia is a predictor of short-term and long-term risk of CVD, supporting pneumonia as a clinically relevant risk factor. For instance, the physiologic triad: Hypoxemia + tachycardia/fever + hypotension or adrenergic surge may result in supply-demand mismatch (type 2 myocardial infarction) and exacerbate cardiac failure by increasing afterload/volume changes, as well as trigger ventricular dysfunction due to ischemia in patients with limited cardiac reserve [26, 27].

Simultaneously, systemic inflammation facilitates endothelial activation and a prothrombotic state (e.g., heightened coagulation activity and microvascular dysfunction), which offers a pathway between respiratory infection and coronary thrombosis or microvascular ischemia despite the absence of the typical plaque rupture, and these vascular-inflammatory changes are commonly featured in surveys of the cardiovascular complications of influenza [12]. Pneumonia is also highly arrhythmogenic; population data reveal that new-onset atrial fibrillation (AF) after community-acquired pneumonia is associated with increased thromboembolic risk and is not necessarily transient (significant recurrence during follow-up), which is clinically significant because there is another infection-mediated pathway to cardiovascular mortality, AF-related embolic stroke risk [28].

Sepsis-induced cardiomyopathy, where cardiac dysfunction is mediated by a cascade of dysregulated inflammatory mediators, oxidative

stress, mitochondrial dysfunction, calcium-handling imbalance, autonomic disruption, and endothelial dysfunction is another significant contributor, particularly in the presence of severe pneumonia with sepsis physiology; this may manifest as reversible global systolic/diastolic depression, and may have a synergistic effect with underlying CVD to increase the risk of short-term mortality [29].

Critically, the long term risk of pneumonia has biologic evidence, although after apparent clinical recovery, a significant percentage of patients are still discharged with evidence of subclinical inflammation, and increased levels of IL-6 and IL-10 which are positively related to subsequent mortality, high IL-6 is specifically related to CVD-related death (among other causes); this supports the hypothesis that the unresolved systemic inflammation is a cause of subsequent mortality and death after a CVD event [30].

Although the mechanistic literature identifies infection-mediated pathways, conventional cardiometabolic risk factors – hypertension, diabetes, and chronic kidney disease – are prevalent among CVD decedents and constitute relevant background for interpreting co-mention patterns. This study cannot quantify the relative contribution of these factors to the observed rates, nor can it evaluate the effect of any specific preventive strategy; such questions require designs with individual-level covariate data and intervention follow-up.

Several limitations warrant consideration. First, death certificate data lack critical individual-level information (e.g., smoking status, body mass index, vaccination status, and medication use), limiting confounding control. Second, cause-of-death coding is imperfect; P&I may be underreported or misclassified on death certificates. Third, as a population-level observational analysis based on co-mentions on death certificates, the study cannot demonstrate that pneumonia or influenza induced particular cardiovascular deaths. Nevertheless, major strengths include the long study period (1999 – 2023) and complete national coverage, enabling robust characterization of long-term trends and subgroup and state-level disparities. Additionally, because analyses were conducted at the annual level, this study does not evaluate within-year seasonal variation in mortality.

Overall, U.S. mortality of CVD underlying-cause deaths with P&I mentioned on the death certificate decreased strongly in the period between 1999 and 2019 but was followed by a plateau in 2019 – 2023, with a slight increase observed in 2020 – 2022. Older adults, males, nonmetropolitan, and selected racial/ethnic groups continued to have a higher mortality rate. These results describe co-mention patterns in CVD underlying-cause deaths and identify higher-rate groups/areas for prioritization of prevention planning and further investigation, while recognizing measurement limitations and alternative explanations for late-period trends. These results justify reinforcing cardiovascular prevention and infection prevention strategies as components of heart-health approaches, in particular among older adults and individuals with established CVD. These descriptive patterns suggest areas for prioritization in prevention planning and future research to connect mortality with patient-specific clinical data (vaccination, comorbidities) and the effectiveness of access to short- and long-term care with the environment, and test interventions that may decrease the post-infection cardiovascular complications.

5. Conclusion

This comprehensive 25-year analysis describes mortality trends in CVD underlying-cause deaths with P&I mentioned on the death certificate in the United States. The findings demonstrate a marked reduction in deaths, with overall AAMR declining by nearly 5% per year from 1999 to 2023. A recent stabilization in mortality rates was observed in the late period, which descriptively identifies a potential plateau and highlights high-rate groups/areas that may warrant prioritization for further investigation and prevention planning. Both males and females have benefited from improvements, with females showing a greater decline. However, some disparities across racial and ethnic groups persist, with non-Hispanic Black or African American populations showing the smallest overall decline and greater late-period uncertainty/volatility in trend estimates.

These observed differences should be interpreted cautiously, as they may reflect variation in death-certificate coding practices, suppression/instability in small strata, pandemic-era documentation changes, and unmeasured structural confounding that cannot be addressed in this descriptive design. Future research should evaluate plausible mechanisms using designs that can better adjudicate timing and causality, rather than inferring triggering pathways from co-mention data. Ultimately, our findings provide descriptive surveillance of co-mention patterns over time and geography and should be used to motivate and prioritize confirmatory epidemiologic and health-systems research rather than to claim intervention effects. Next-step analyses will include separating influenza (J09 – J11) from pneumonia (J12 – J18), stratifying by CVD subtypes (e.g., ischemic heart disease, stroke, heart failure).

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Institutional Review Board (IRB)

Not applicable. This study used publicly available, de-identified data; IRB approval and informed consent were not required.

Large Language Model

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Author Contributions

Conceptualization was carried out by MB and AZ, while methodology and data curation were handled by MB, AZ, and MMA. The software and formal analysis were performed by AZ, MMA, and MB, and visualization was completed by AZ and MMA. Investigation involved MB, AZ, and MMA. The original draft was written by AAB, ASI, MAB, AMS, and AMB, while all authors contributed to reviewing and editing the manuscript. Supervision and project administration were led by MB, and all authors contributed to resources and validation.

Data Availability

All data used in this study are publicly available. U.S. multiple-cause-of-death mortality data (1999–2023) were obtained from

the CDC WONDER Multiple Cause of Death database (accessed October 2025). Deaths were identified with cardiovascular disease (CVD) as the underlying cause of death (ICD-10 codes I00–I99) and pneumonia and influenza (P&I) listed as contributing causes (ICD-10 codes J09–J18), where P&I was mentioned anywhere on the death certificate in conjunction with a cardiovascular diagnosis. These data can be queried and downloaded directly from CDC WONDER, and no individual-level or identifiable information was used. Aggregated analysis-ready annual series (including deaths, denominators, and age-adjusted mortality rates by subgroup) used to generate the figures are provided in the Supplementary Data file.

References

1. Tejada-Vera B, Bastian BA, Curtin SC. Deaths: Leading Causes for 2023. Natl Vital Stat Rep. 2025;(10):1. [PMID: 41021892, PMCID: PMC12498176, https://doi.org/10.15620/cdc/174607].
2. Flu Season | Influenza (Flu) | CDC [Internet]; 2026. Cited 2026 Jan 23. Available from: https://www.cdc.gov/flu/about/season.html.
3. Hansen CL, Chaves SS, Demont C, Viboud C. Mortality Associated With Influenza and Respiratory Syncytial Virus in the US, 1999-2018. JAMA Netw Open. 2022;5(2):e220527. [PMID: 35226079, PMCID: PMC8886548, https://doi.org/10.1001/jamanetworkopen.2022.0527].
4. Mohammad MA, Tham J, Koul S, Rylance R, Bergh C, Erlinge D, et al. Association of acute myocardial infarction with influenza: A nationwide observational study. PLoS One. 2020;15(8):e0236866. [PMID: 32760080, PMCID: PMC7410234, https://doi.org/10.1371/journal.pone.0236866].
5. Gopal R, Marinelli MA, Alcorn JF. Immune Mechanisms in Cardiovascular Diseases Associated With Viral Infection. Front Immunol. 2020;11:570681. [PMID: 33193350, PMCID: PMC7642610, https://doi.org/10.3389/fimmu.2020.570681].
6. Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med. 2011;8(6):e1001048. [PMID: 21738449, PMCID: PMC3125176, https://doi.org/10.1371/journal.pmed.1001048].
7. Pieralli F, Vannucchi V, Nozzoli C, Augello G, Dentali F, De Marzi G, et al. Correction to: Acute cardiovascular events in patients with community acquired pneumonia: results from the observational prospective FADOI-ICECAP study. BMC Infect Dis. 2021;21(1):195. [PMID: 33607965, PMCID: PMC7893753, https://doi.org/10.1186/s12879-021-05891-5].
8. CDC. Multiple Cause of Death 1999-2020 [Internet];. Cited 2026 Jan 23. Available from: https://wonder.cdc.gov/wonder/help/mcd.html.
9. O'Halloran AC, Holstein R, Cummings C, Daily Kirley P, Alden NB, Yousey-Hindes K, et al. Rates of Influenza-Associated Hospitalization, Intensive Care Unit Admission, and In-Hospital Death by Race and Ethnicity in the United States From 2009 to 2019. JAMA Netw Open. 2021;4(8):e2121880. [PMID: 34427679, PMCID: PMC8385599, https://doi.org/10.1001/jamanetworkopen.2021.21880].
10. Donaldson SV, Thomas AN, Gillum RF, Mehari A. Geographic Variation in Racial Disparities in Mortality From Influenza and Pneumonia in the United States in the Pre-Coronavirus Disease 2019 Era. Chest. 2021;159(6):2183-90. [PMID: 33400931, https://doi.org/10.1016/j.chest.2020.12.029].
11. Holland E, Jabbar ABA, Asghar MS, Asghar N, Mistry K, Mirza M, et al. Demographic and regional trends of pneumonia mortality in the United States, 1999 to 2022. Sci Rep. 2025;15(1):10103. [PMID: 40128337, PMCID: PMC11933369, https://doi.org/10.1038/s41598-025-94715-6].
12. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004;351(25):2611-8. [PMID: 15602021, https://doi.org/10.1056/NEJMoa041747].
13. Ananth CV, Brandt JS, Keyes KM, Graham HL, Kostis JB, Kostis WJ. Epidemiology and trends in stroke mortality in the USA, 1975-2019. Int J Epidemiol. 2023;52(3):858-66. [PMID: 36343092, PMCID: PMC10244057, https://doi.org/10.1093/ije/dyac210].
14. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med. 2018;378(4):345-53. [PMID: 29365305, https://doi.org/10.1056/NEJMoa1702090].
15. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA. 2015;313(3):264-74. [PMID: 25602997, PMCID: PMC4687729, https://doi.org/10.1001/jama.2014.18229].
16. Huang D, He D, Gong L, Wang W, Yang L, Zhang Z, et al. Clinical characteristics and risk factors associated with mortality in patients with severe community-acquired pneumonia and type 2 diabetes mellitus. Crit Care. 2021;25(1):419. [PMID: 34876193, PMCID: PMC8650350, https://doi.org/10.1186/s13054-021-03841-w].
17. Zhao X, Gang X, He G, Li Z, Lv Y, Han Q, et al. Obesity Increases the Severity and Mortality of Influenza and COVID-19: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2020;11:595109. [PMID: 33408692, PMCID: PMC7779975, https://doi.org/10.3389/fendo.2020.595109].
18. Marma AK, Lloyd-Jones DM. Systematic examination of the updated Framingham heart study general cardiovascular risk profile. Circulation. 2009;120(5):384-90. [PMID: 19620502, https://doi.org/10.1161/CIRCULATIONAHA.108.835470].
19. Towfighi A, Markovic D, Ovbiagele B. Current national patterns of comorbid diabetes among acute ischemic stroke patients. Cerebrovasc Dis. 2012;33(5):411-8. [PMID: 22456491, https://doi.org/10.1159/000334192].
20. Vaidya V, Partha G, Karmakar M. Gender differences in utilization of preventive care services in the United States. J Womens Health (Larchmt). 2012;21(2):140-5. [PMID: 22081983, https://doi.org/10.1089/jwh.2011.2876].
21. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke. 2014;45(1):315-53. [PMID: 24309587, PMCID: PMC5995123, https://doi.org/10.1161/01.str.0000437068.30550.cf].
22. Matthews KA, Spears KS, Anderson-Lewis C. Rural Health Disparities: Contemporary Solutions for Persistent Rural Public Health Challenges. Prev Chronic Dis. 2025;22:E27. [PMID: 40539904, PMCID: PMC12199730, https://doi.org/10.5888/pcd22.250202].
23. Golembiewski EH, Gravholt DL, Torres Roldan VD, Lincango Naranjo EP, Vallejo S, Bautista AG, et al. Rural Patient Experiences of Accessing Care for Chronic Conditions: A Systematic Review and Thematic Synthesis of Qualitative Studies. Ann Fam Med. 2022;20(3):266-72. [PMID: 35606138, PMCID: PMC9199043, https://doi.org/10.1370/afm.2798].
24. Smith CL, Bednarchik B, Aung H, Wilk DJ, Boxer RS, Daddato AE, et al. Humoral and Cellular Immunity Induced by Adjuvanted and Standard Trivalent Influenza Vaccine in Older Nursing Home Residents. J Infect Dis. 2023;228(6):704-14. [PMID: 36951196, https://doi.org/10.1093/infdis/jiad071].
25. Thomas RE. Reducing Morbidity and Mortality Rates from COVID-19, Influenza and Pneumococcal Illness in Nursing Homes and Long-Term Care Facilities by Vaccination and Comprehensive Infection Control Interventions. Geriatrics (Basel). 2021;6(2). [PMID: 34066781, PMCID: PMC8162358, https://doi.org/10.3390/geriatrics6020048].
26. Skaarup KG, Modin D, Nielsen L, Jensen JUS, Biering-Sorensen T. Influenza and cardiovascular disease pathophysiology: strings attached. Eur Heart J Suppl. 2023;25(Suppl A):A5-A11. [PMID: 36937370, PMCID: PMC10021500, https://doi.org/10.1093/eurheartjsupp/suac117].
27. Kalantar Neyestanaki MH, Kalantar Neyestanaki M. Influenza and its cardiovascular complications: a comprehensive review. Acta Angiologica. 2024;30(2):69-78. [https://doi.org/10.5603/aa.99211].
28. Sogaard M, Skjoth F, Nielsen PB, Smit J, Dalager-Pedersen M, Larsen TB, et al. Thromboembolic Risk in Patients With Pneumonia and New-Onset Atrial Fibrillation Not Receiving Anticoagulation Therapy. JAMA Netw Open. 2022;5(5):e2213945. [PMID: 35616941, PMCID: PMC9136621, https://doi.org/10.1001/jamanetworkopen.2022.13945].
29. Liu YC, Yu MM, Shou ST, Chai YF. Sepsis-Induced Cardiomyopathy: Mechanisms and Treatments. Front Immunol. 2017;8:1021. [PMID: 28970829, PMCID: PMC5609588,

https://doi.org/10.3389/fimmu.2017.01021].

30. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. Am J Respir Crit Care Med. 2008;177(11):1242-7. [PMID: 18369199, PMCID: PMC2720087, https://doi.org/10.1164/rccm.200712-1777OC].