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Is Influenza an Underrecognized Driver of Cardiovascular Mortality in the United States? A 25-Year Comprehensive Subgroup Analysis of Epidemiologic Trends, Disparities, and ARIMA-Based Mortality Forecasting (1999–2023)

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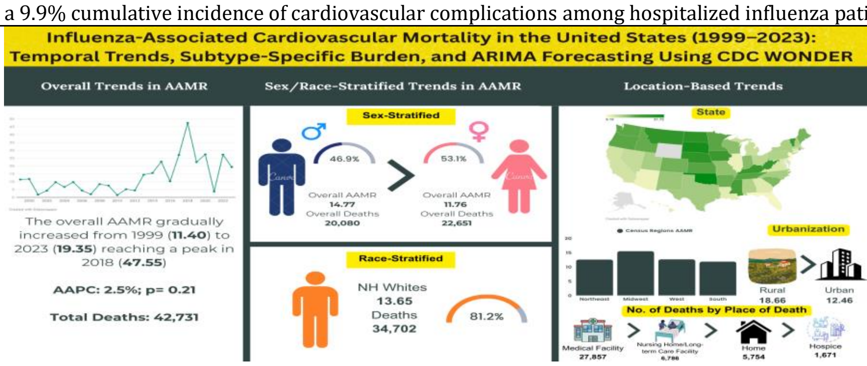
Abstract:

Influenza infection has been associated with acute cardiovascular complications: however, population level patterns of influenza-associated cardiovascular disease (CVD) mortality remains underexplored. This study aimed to evaluate temporal trends, demographic disparities, and geographic variations in influenza-associated cardiovascular disease (CVD) mortality in the United States over 25 years. A population-based observational analysis was conducted using the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death database (1999–2023). Adults aged 45 years and older whose death certificates listed both influenza and CVD were included. Cardiovascular mortality was identified using ICD-10 codes I00–I99, and influenza-related mortality using J09–J11. Age-adjusted mortality rates (AAMRs) per million population were calculated using the 2000 U.S. standard population. Temporal trends were analyzed using Joinpoint regression to estimate annual percentage change (APC) and average annual percentage change (AAPC) with 95% confidence intervals (CIs). From 1999 to 2023, a total of 42,731 deaths were attributed to influenza-related CVD. AAMRs increased from 11.4 per million in 1999 to 19.35 per million in 2023, peaking at 47.55 per million in 2018. The overall AAPC was 2.53 (95% CI: –1.71–7.43; p = 0.21). Heart failure accounted for the highest number of deaths (11,611), followed by coronary ischemic heart disease (9,746) and acute myocardial infarction (4,227). Males had higher absolute mortality, whereas females demonstrated a greater relative increase (AAPC = 6.72; $p < 0.001$). Mortality was highest among individuals aged 65 years and older, in southern regions, and in rural counties. Forecasting predicts continued increases in AAMR through 2035. Influenza infection remains a significant contributor to cardiovascular mortality in the United States. Trends align with findings from Ouranos et al. (2023), who reported a 9.9% cumulative incidence of cardiovascular complications among hospitalized influenza patients.



Keywords: Influenza; cardiovascular mortality; epidemiologic trends

Introduction:

Influenza, a highly infectious viral respiratory infection, continues to have important public health consequences globally, and is also linked with large annual morbidity and mortality, especially among the elderly and in patients with chronic comorbidities[1,2]. While the effect of influenza on the respiratory system is firmly established, there is growing evidence from literature that influenza infection has effects on the cardiovascular system. Mechanisms that include viral replication and subsequent systemic inflammation, endothelial dysfunction, and a state of hypercoagulability can cause acute cardiovascular events[3]. All of these indirect mechanisms are responsible for increased mortality risk in individuals with pre-existing cardiovascular disease (CVD) and increase the profile of influenza as an underrated but powerful precipitant of cardiovascular events.

During the past 20 years, the impact of influenza on cardiovascular mortality has been investigated in both observational and mechanistic studies. Most notably, research that has been conducted based on population data shows evidence of elevated cardiovascular hospitalization or deaths as it coincides with seasonal rises in influenza[1,3]. Furthermore, randomized trials and meta-analyses that have assessed cardiovascular protective benefits of the influenza vaccine in terms of reduction of major adverse cardiovascular events, especially in those with pre-existing CVD, indicate prevention of cardiovascular events can be achieved using vaccine-based therapy[4]. Together, these studies demonstrate influenza infection is systemic and can precipitate cardiovascular events, and even possibly prevent them using vaccination. Nevertheless, in spite of these results, the majority of earlier research was short-term, took place in a single influenza season or hospital-cased cohort and depended on mortality data lacking dual cause of death ratings. Therefore, the overall picture of influenza-associated cardiovascular mortality is predominantly uncharted, most notably in national real-world datasets. Sociodemographic group-related factors, geographic locations or urbanization levels, etc., usually are not considered in order to describe experience with dual coded mortality for influenza associated cardiovascular mortality during any period of time. Given the aging US population and the evolving burden of influenza and cardiovascular disease, it is critical and opportune to fill this gap in knowledge. Understanding the long-term mortality experience for individuals with concomitant influenza and cardiovascular disease is important for guiding a coordinated public health response, not the least of which is crafting vaccination policy, but also in pandemic planning and risk communication for vulnerable groups [5].

This present study aims to examine data in a 22-year retrospective study based on the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death (MCD) dataset. Our analysis will systematically quantify the temporal trends of dual-coded influenza-associated cardiovascular mortality, examine demographic and geographic disparities, and provide new evidence of the shared association between viral respiratory illness and cardiovascular mortality in the adult population of the US.

Methods

Study Design and Population

This study was a population-based observational analysis using the publicly available Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death (MCD) database from 1999 to 2023. The population consisted of adults aged 45 years and older whose death certificates listed both cardiovascular disease (CVD) and influenza as contributing causes of death. Cardiovascular mortality was identified using the International Classification of Diseases, 10th Revision (ICD-10) codes I00–I99, which represent diseases of the circulatory system. Concurrently, influenza-related mortality was identified using ICD-10 codes J09 (Influenza due to identified avian influenza virus), J10.0–J10.8 (influenza with pneumonia or other respiratory manifestations, virus identified), and J11.0–J11.8 (influenza with pneumonia or other manifestations, virus not identified). By intersecting these two groups of ICD codes, the analysis captured decedents for whom both cardiovascular and influenza-related pathology contributed to mortality.

Data Source and Stratification

The data were extracted from the CDC WONDER Multiple Cause of Death database, which provides access to U.S. mortality and population data for public health surveillance and research [6]. The database contains information on year of death, demographic characteristics (age, sex, race/ethnicity), and geographic identifiers. Age was categorized into five 10-year groups: 45–54, 55–64, 65–74, 75–84, and 85+ years. Sex was recorded as male or female based on death certificates. Race/ethnicity was classified into Hispanic and non-Hispanic populations, with non-Hispanic further subdivided into White and Black or African American. Due to inconsistent or low-count data, non-Hispanic Asian/Pacific Islander and non-Hispanic American Indian/Alaska Native groups were excluded. Geographic stratification included census regions (Northeast, Midwest, South, and West) as defined by the U.S. Census Bureau [7]. Urbanization was assessed using the National Center for Health Statistics (NCHS) Urban–Rural Classification Scheme, which categorizes counties into six levels: Large Central Metro, Large Fringe Metro, Medium Metro, Small Metro, Micropolitan (Nonmetro), and NonCore (Nonmetro) [8]. Place of death was grouped into Medical Facility, Decedent's Home, Hospice, Nursing Home/Long-Term Care, Other, and Unknown.

Statistical Analysis

The primary outcome was the age-adjusted mortality rate (AAMR) per 100,000 individuals for influenza-associated cardiovascular deaths, computed using the 2000 U.S. standard population. Rates were calculated per 1,000,000 people to enhance interpretability due to the lower incidence of co-coded causes. Joinpoint regression analysis was performed using the Joinpoint Regression Program, Version 5.3.0 (National Cancer Institute), to assess temporal trends in AAMR from 1999 to 2020 [9]. The Annual Percentage Change (APC) and Average Annual Percentage Change (AAPC) were estimated with 95% confidence intervals (CIs). The Monte Carlo permutation method was used to test for statistical significance of changes in trends over time [10]. The Weighted Bayesian Information Criterion (WBIC) was used to determine the optimal number of joinpoints. A p-value <0.05 was considered statistically significant for all analyses.

Exploratory time-series forecasting analyses were additionally performed to examine potential future patterns in influenza-associated cardiovascular mortality. Autoregressive integrated moving average (ARIMA) models were implemented using Python (version 3.13.2) and the statsmodels package. Model parameters (p, d, q) were iteratively tested, and the best-fitting model was selected based on minimization of root mean square error (RMSE) during internal validation [11]. These forecasts were exploratory in nature, were not intended for causal inference or policy prediction, and were interpreted cautiously given the observational design and inherent uncertainty of extrapolating beyond observed data.

Ethical Considerations

The analysis used publicly available, de-identified data, exempting it from institutional review board approval. All potentially identifiable or incomplete records were excluded to maintain privacy. The study was conducted for public health and epidemiological purposes only, in accordance with the Public Health Service Act (42 U.S.C. 242m(d)). No external funding was received, and the authors declare no conflicts of interest.

Results:

OVERALL

Influenza related cardiovascular disease (CVD) caused a total of 35260 deaths in the US from 1999 to 2020 and an additional 7471 deaths from 2021 to 2023 resulting in a total 42731 deaths. The age adjusted mortality rates (AAMRs) ranged between 11.4 per million (95% CI 10.72-11.08) in 1999 to 19.35 per million (95% CI 18.64-20.07) in 2023. The highest AAMR per million was reported in 2018 at 47.55. The average AAMR for

1999-2020 reported to be 13.53 per million (95% CI 13.39-13.67) and 16.98 per million (95% CI 16.59-17.37) for years 2021-2023. These trends highlight large variations in AAMR in different time periods with an average annual percentage change (AAPC) of 2.53* (95% CI -1.71 – 7.43) (p-value < 0.21). Notable changes in APCs were from 1999-2010, 2010-2018 and 2018-2023 with APCs -5.78 (95% CI -45.40 – 6.43), 27.47 (95% CI 15.71 – 111.70) and -12.80 (95% CI -45.85 – 0.61) respectively. When looking at the AAMR from 2015-2023 a drop in AAMR is seen in 2021 to 3.68 from 27.42 in 2020 and increases to 27.3 in 2022, representing a deviation from preceding trends.

CVD was further segregated into Heart Failure (HF), Coronary Ischemic Heart Disease (CIHD) and Acute Myocardial Infarction (AMI) to show correlation between each of these with influenza. Mortality trends assessments from 1999-2023 revealed HF had the most deaths (11,611), followed by CIHD (9,746) and finally AMI (4,227). CIHD had the greatest AAPC of 4.92 (95% CI 2.13-10.43) (p value<0.05 followed by HF with AAPC 2.42*(-1.68 – 7.27) (p value <0.21) while in contrast HF had barely any rise in AAPC. For HF rates declined non-significantly from 1999–2010 (APC = −7.11; 95% CI: −43.15 to 5.37; p value< 0.228), rose significantly from 2010–2018 (APC = 29.88*; 95% CI: 17.20 to 122.03; p value < 0.004), and declined significantly again from 2018–2023 (APC = −13.17*; 95% CI: −43.37 to −0.43; p value < 0.048). CIHD only showed a significant increase from 1999-2023 (APC = 4.93; 95% CI: 2.13 to 10.43; p value < 0.005), while AMI mortality decreased sharply from 1999–2011 (APC = −4.97; 95% CI: −29.99 to 3.90 (p value< 0.257), increased significantly from 2011–2018 (APC = 26.94*; 95% CI: 13.46 to 86.34; p value < 0.004), and finally fell from 2018–2023 (APC = −17.40*; 95% CI: −41.28 to −6.70; p value < 0.006).

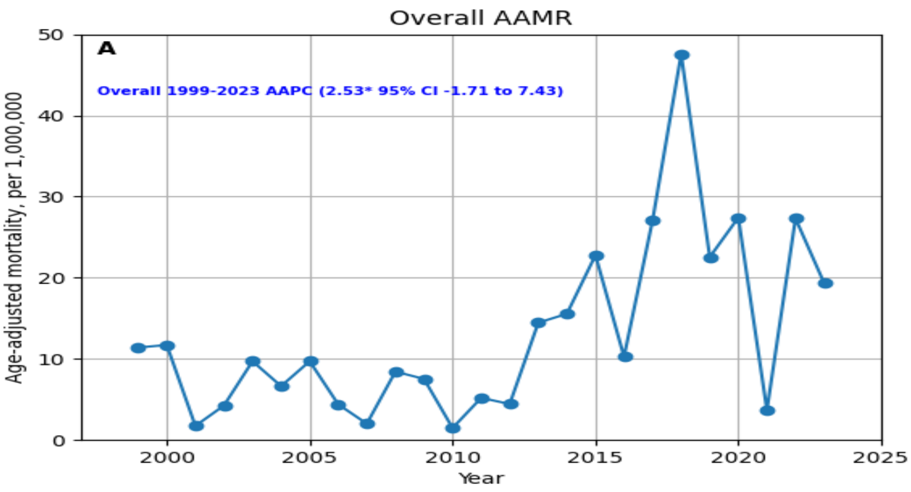


Figure 1 Overall Influenza and CVD-related AAMR per 1,000,000 in the United States, 1999 to 2023

GENDER

Segregation of the database by gender shows mirrored trends for both the groups but males had consistently higher AAMR compared to females. Male population had a total of 20080 deaths and the female population had a total of 22651 deaths from 1999 to 2023, respectively. The AAMRs for males was recorded to be 15.74 per million (95% CI 15.5-15.98) for years 1999-2020 and 18.57 per million (95% CI 17.95-19.19) for 2021-2023. AAMRs for females was recorded to be 11.95 per million (95%CI 11.78-12.13) for years 1999-2020 and 15.68 per million (95%CI 15.18-16.18) for 2021-2023. The highest AAMR per million for males was recorded in 2018 at 54.75 (95% CI 52.83-56.67) and for females at 42.22 (95% CI 40.79-43.64) in 2018. Mortality trends increased in both genders from 1999-2023 however females had a much higher AAPC of 6.72* (95% CI 3.86-12.56) (p value < 0.001) while males had an AAPC of 2.61 (95% CI -0.98 – 6.87) (p value < 0.15) from 1999-2023. While mortality trends in both genders varied significantly yet notable APCs were only seen for males mainly from 2010-2018 and 2018-2023 with APCs 27.87 (95% CI 16.62-86.67) and -13.84 (95% CI -37.80 – -3.01). .

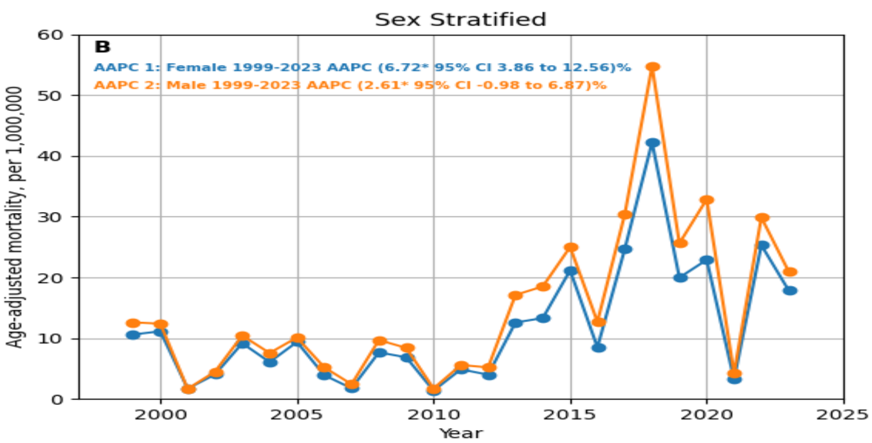


Figure 2 Sex-stratified Influenza and CVD-related AAMRs per 1,000,000 in the United States, 1999 to 2023

RACE / ETHNICITY

Data for Mortality trends for Influenza related CVD was divided into two main categories: HISPANIC or LATINO and NON-HISPANIC ORIGIN which included four races (American Indians or Alaska Native, Asian or Pacific Islander, Black or African American, White). AAMRs for American Indians, Asians and Blacks were mostly unavailable. From the available data it can be seen that the highest AAMR per million for Asians was 32.22 (95% CI 27.81-36.62) in 2018, 42.14 (95% CI 38.73-45.54) per million in 2020 for Blacks, 50.94 (95% CI 49.58-52.31) per million in 2018 for whites, and 35.37 (95% CI 32.19-38.54) per million in 2020 for Hispanics. AAPCs could not be compared due to unavailability of data except for in Whites where AAPC was 2.18 (95% CI -2.36--6.97) (p value < 0.3) from 1999-2023. Notable trends for APCs were seen for Asians from 2013–2018 and 2018-2023 with APC 31.04 (95% CI 12.41 – 215.37) and -17.30 (95% CI -46.92 – -3.56) respectively, NH Blacks from 2008–2020 and 2020–2023 with APC 21.76 (95% CI 16.65 – 55.61) and -21.99 (95% CI -61.27 – 4.76) respectively, for NH white from 2010–2018 and 2018-2023 with APC 27.62 (95% CI 15.57 – 114.73) and -13.64 (95% CI -50.11 – 0.60) respectively, finally for Hispanics From 2008–2023, APC was 7.82 (95% CI 1.29 – 20.62).

The data for race reveals an even more interesting trend where AAMR in 2021 falls so low that data is unavailable for NH American Indians and Blacks while for other races and Hispanics it is in the single digits.

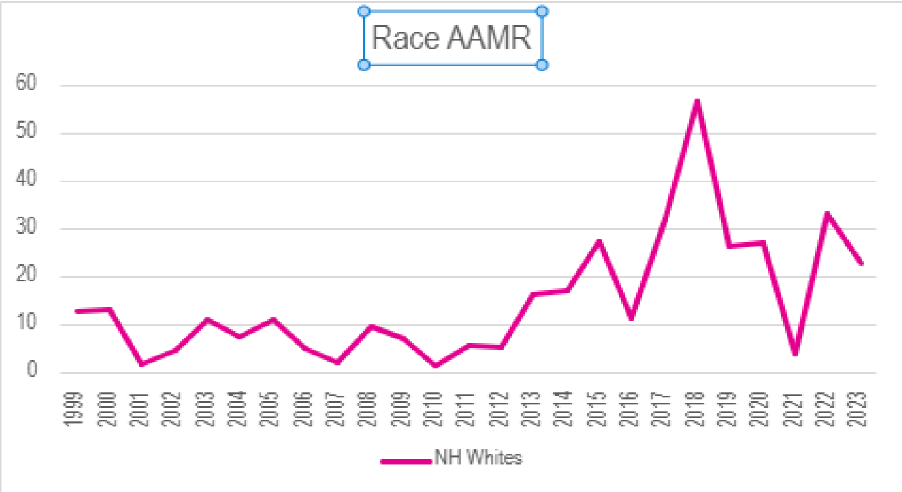


Figure 3 Race/ Ethnicity Stratified Influenza and CVD-related AAMR per 1,000,000 deaths in the United States, 1999 to 2023

AGE GROUPS

The mortality trends for Influenza related CVD were divided into the two main groups, population (45-64 years) and population (65+). The total number of deaths in these age groups are as follows: for age groups 45-64 8014 deaths between 1999-2023, for age groups 65+ 34717 deaths between 1999-2023. The AAMRs varied widely between these age groups i.e. 3.66 per million (95% CI 3.57-3.75) for population (45-64 years) in 1999-2020 and 5.36 per million (95% CI 5.08-5.65) in 2021-2023 {with the highest AAMR of 11.93 per million (95%CI 11.2-12.65) in 2020} , for population (65 +) 30.88 in 1999-2020 (95%CI 30.52-31.24) and 37.38 in 2021-2023 (95%CI 36.43-38.34) {with the highest AAMR of 110.35 per million (95%CI 107.44-113.26) in 2018} , respectively. Both age groups had rise in mortality trends however AAPC was higher for age group 45-64 respectively with an AAPC of 10.29* (95% CI 7.52 – 16.97) (p value < 0.01) and 1.58 (95% CI -2.68-6.29) (p value <0.42) for age group 65+. Notable APC trends were seen only in age group 65+ from 2010-2018 and 2018-2023 with APCs 28.58 (95% CI 15.94-119.97) and -14.48 (95% CI -45.68 -- -0.78).

GEOGRAPHICAL REGIONS (CENSUS & STATES)

Mortality trends for Influenza related CVD were segregated into four geographical areas i.e. Northeast, Midwest, South and Western regions. The highest number of casualties occurred in South (14,406) deaths, followed by Midwest (11,116), West (9,066) and Northeast (8,143) from 1999 to 2023. The highest average AAMR was recorded in the Midwest at 16.03 (95% CI 15.7-16.35) per million in 1999-2020 while the highest average AAMR in 2021-2023 was in the South region reported as 18.17 (95% CI 17.51-18.82) per million. South region had the lowest average AAMR 12.15 per million (95% CI 11.93-12.37) in 1999-2020 and Northeast with lowest in 2021-2023 with average AAMR of 15.57 per million (95%CI 14.71-16.43) Each region had a rise in AAPCs however Northeast had the maximum rise with AAPC 8.89* (95% CI 6.26-15.21)(p value<0.01) while lowest AAPC was reported for West with AAPC 2.93* (95% CI -1.19- 7.64)(p value <0.14). Joinpoint analysis reveals no notable APCs for Northeast and Midwest however it highlights APCs in regions South and West. For both South and West APCs increased significantly from 2010-2018 with APCs 28.61* (95% CI 17.56-101.84) and 31.63* (95% CI 18.12-104.13) followed by a drastic fall in APCs from 2018-2023 with APC for South as -10.9 (95% CI -36.74 – 0.99) and for West as -14.20* (95% CI -42.82– -2.53) .

From 1999–2020, the highest AAMR for Influenza-associated CVD was observed in South Dakota, with an AAMR of 33.64 per million and a total of 278 deaths, ranking at the 100th percentile among all U.S. states. The lowest AAMR was noted in the District of Columbia, with 27 deaths and an AAMR of 5.72 per million at the 0th percentile. The average AAMR across all states during this period was approximately 13.53 per million, with a cumulative total of 35,260 deaths. States with mortality rates at or above the 90th percentile included South Dakota, Nebraska, Vermont, North Dakota, Montana, and West Virginia, whereas those at or below the 10th percentile included Georgia, Louisiana, New Jersey, Nevada, Florida, and the District of Columbia.

From 2021–2023, the highest AAMR Influenza related CVD was reported in Oklahoma, with 216 deaths and an AAMR of 41.65 per million, ranking at the 100th percentile. The lowest reliable estimate was seen in New Jersey, with 134 deaths and an AAMR of 10.46 per million, ranking at the 0th percentile. Several states, including Alaska, Delaware, Wyoming, and the District of Columbia, had unreliable or suppressed data due to small sample sizes. The average AAMR across all states was unavailable. States at or above the 90th percentile included Oklahoma, Kentucky, Mississippi, North Dakota, and Montana, while those at or below the 10th percentile were Hawaii, Arizona, Connecticut, and New Jersey.

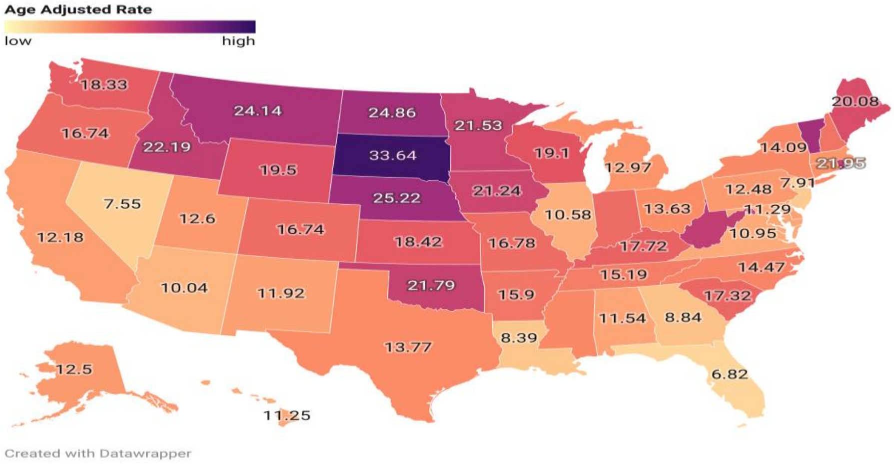


Figure 4 State-Stratified Influenza and CVD-related AAMRs per 1,000,000 in United States 1999-2020

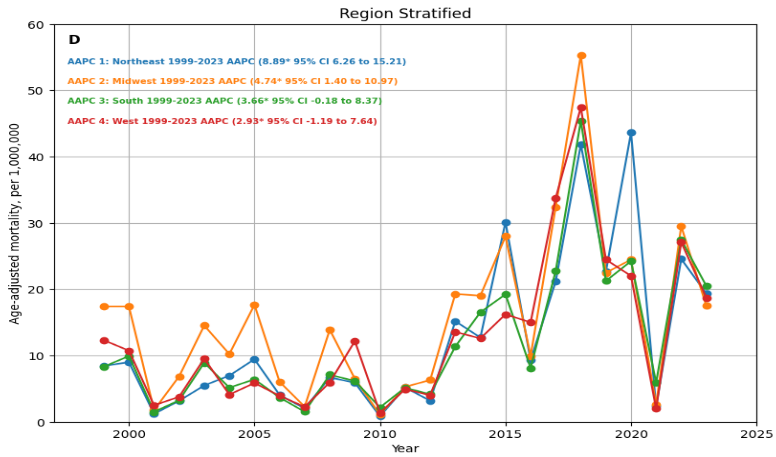


Figure 5 Influenza and CVD-related AAMR per 1,000,000 Stratified by Regions in the United States, 1999 to 2023

Urbanization

Data for urbanization revealed that in the years 1999-2020 Urban areas had the larger number of deaths 26,718 with the average AAMR 12.46 per million (95% CI 12.31-12.61) and the highest AMR reported in 2018 at 44.19 per million (95% CI 42.97-42.54). Rural areas had 8,542 deaths in these years with the average AAMR 18.66 per million (95% CI 18.27-19.06) and the highest AAMR reported in 2018 at 64.57 per million (95% CI 61.27-67.88). Both Urban and Non-Urban areas had significant increase in mortality rates with AAPCs of 4.97* (95% CI 1.22-10.84) (p value <0.016) and 2.28* (95% CI -1.45-6.78) (p value <0.17) respectively.

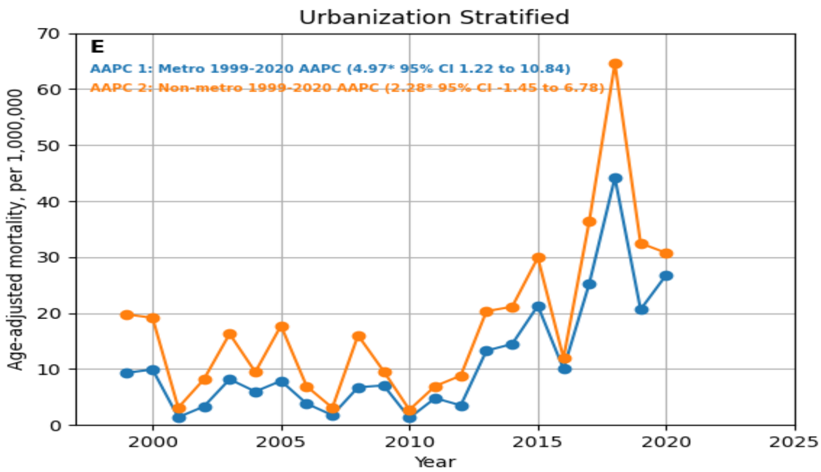


Figure 6 Urbanization Stratified Influenza and CVD-related AAMR per 1,000,000 in the United States, 1999 to 2023

Place of Death

Database trends from 1999-2023 showed that medical facility in-patient had the greatest number of deaths (25,534), with the highest number of deaths in 2018 (4025) and lowest number of deaths in 2001(61). It was followed by Nursing Home (6,786), Decedent's Home (5,754), and Hospice Facility (1,671),

Forecast

Forecasting database trends till 2035 reveals rising mortality trends with Overall AAMR peaking at 61.77 in 2035 (-22.04 – 145.58). Trends forecasted based on gender shows a similar trend and significant rise in AAMRs peaking in 2035 to 69.5 per million (95% CI -23.67 – 162.68) for males and 39.66 (95% CI -31.17 – 110.49) in females. Overall mortality trends increased significantly till 2035 with AAPCs of 5.38 (95% CI: 5.32 – 5.43; $p < 0.01$). Mortality trends in males also increased significantly during the same period with AAPCs of 5.31 (95% CI: 5.25 – 5.36; $p < 0.01$), while females demonstrated a significant upward trend as well with AAPCs of 4.36 (95% CI: 4.32 – 4.40; $p < 0.01$).

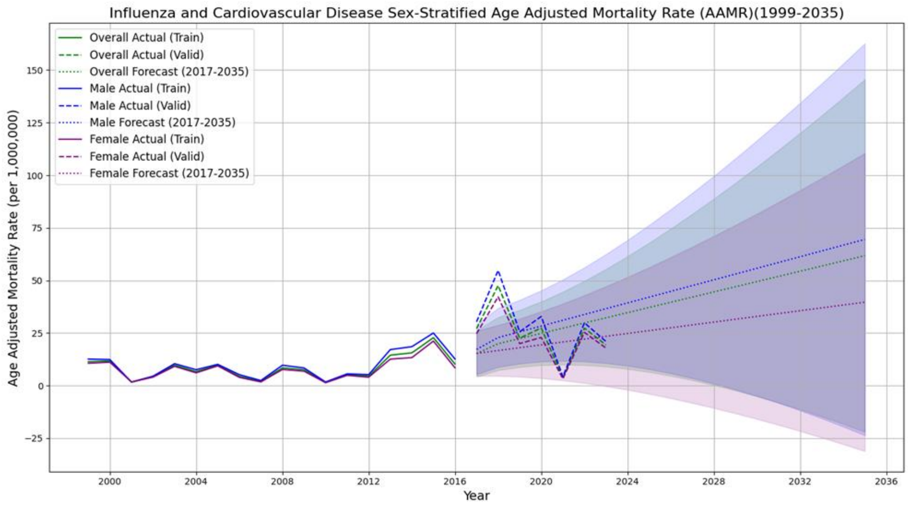


Figure 7 ARIMA Future Forecast of Influenza and CVD-related AAMR per 1,000,000 in the United States, 1999 to 2023

Discussion:

This national population-based study spanning 1999–2023 provides compelling population-level evidence of temporal patterns and disparities that influenza-associated cardiovascular disease (CVD) remains a substantial contributor to mortality in the United States. By leveraging CDC WONDER mortality data, our analysis highlights pronounced fluctuations in influenza-related cardiovascular deaths across time, demographic groups, and geographic regions. The findings charatcerize co-occurring influenza and cardiovascular mortality trends and their evolution over major public health events, such as the COVID-19 pandemic. Over 42,000 influenza-related CVD deaths were identified during the study period, emphasizing the public health relevance of this intersection between infectious and cardiovascular conditions. The increase in age-adjusted mortality rate (AAMR) from 11.4 per million in 1999 to 19.35 per million in 2023, peaking at 47.55 per million in 2018, reflects the recurring periods of severe influenza epidemics rather than a monotonic rise. The upward inflection observed between 2010 and 2018, characterized by a positive annual percentage change (APC) of 27.47, coincided with years dominated by influenza A(H3N2) strains, which are known for higher virulence and poorer vaccine effectiveness. These data are consistent with prior epidemiologic observations that severe influenza seasons coincide with spikes in all-cause and cardiac mortality [12].

The sharp dip in 2021 (AAMR = 3.68 per million) represents an epidemiological outlier and likely reflects the suppression of influenza circulation during the COVID-19 pandemic due to non-pharmaceutical interventions such as masking and social distancing. Reduced influenza testing and diagnostic displacement under SARS-CoV-2 coding further explain the decline. The subsequent rebound in 2022–2023, as influenza activity normalized, validates this interpretation. These oscillations highlight the sensitivity of influenza-associated cardiovascular mortality to both viral ecology and health system disruptions. When analyzed by subtype, heart failure (HF) accounted for the greatest number of influenza-associated deaths, followed by coronary ischemic heart disease (CIHD) and acute myocardial infarction (AMI) [13]. This gradient aligns with the pathophysiological vulnerability of individuals with pre-existing myocardial dysfunction. HF mortality rose sharply between 2010–2018, paralleling increased influenza severity during those years. CIHD, however, demonstrated the highest average annual percentage change (AAPC 4.92; $p < 0.05$), suggesting that ischemic pathology may be particularly sensitive to infectious stressors. . Proposed mechanisms described in prior literature include endothelial activation, procoagulant effects, and sympathetic stress [14].

Interestingly, AMI mortality exhibited a biphasic pattern declining through 2011, surging by 2018, then decreasing post-2018 mirroring both influenza virulence cycles and evolving cardiovascular care quality. These findings collectively suggest that influenza infection may act as a precipitating factor in susceptible individuals, particularly during high-virulence seasons [15].

The present findings complement and extend those of Ouranos et al. (2023), [16] who conducted a *systematic review and meta-analysis* of 6,936 hospitalized patients with laboratory-confirmed influenza to quantify the cumulative incidence and in-hospital mortality of cardiovascular complications. They reported a 17.47% cumulative incidence of heart failure, 2.19% for AMI, 6.12% for arrhythmias, 2.56% for myocarditis, and 1.14% for stroke or TIA, with an overall in-hospital cardiovascular mortality rate of 1.38%. Our analysis, though population-level and mortality-focused rather than hospital incidence-based, converges on similar conclusions: influenza infection may carry a clinically meaningful cardiovascular burden, with HF and ischemic events predominating. While Ouranos et al. measured *in-hospital* cardiovascular complications during acute infection, our findings capture population-level mortality perspective based on death certificate data, capturing both acute and *post-infectious outcomes* . The considerably lower absolute mortality rate in our dataset compared to the meta-analysis's in-hospital figures can be attributed to denominator differences in population-wide mortality per million versus patient-level incidence among hospitalized cases. However, both datasets underscore the same hierarchy of risk: heart failure as the most frequent manifestation, followed by ischemic and arrhythmic complications. Importantly, the meta-analysis demonstrated a near 10% cumulative rate of cardiovascular events among hospitalized influenza patients, supporting the biological plausibility of the long-term population-level mortality burden observed in this study [17]. The parallel trends between our longitudinal U.S. mortality data and the pooled international hospital data suggests that cardiovascular surveillance should be considered during influenza management.

Our results also reveal sex-specific differences, with males exhibiting higher absolute AAMRs but females showing a sharper proportional rise (AAPC = 6.72; p < 0.001). This pattern mirrors shifting demographic and behavioral trends, including increasing cardiovascular risk among women and underutilization of preventive therapies. Immunological sex differences may play a role in female hormonal and immune responses amplifying inflammatory signaling during infection, potentially worsening cardiac injury [18]. The parallel rise in both sexes, followed by the pandemic-associated dip in 2021, confirms that these disparities operate within broader epidemiologic cycles rather than in isolation. Racially disaggregated results revealed the highest mortality among non-Hispanic Whites, followed by episodic surges in Black and Hispanic populations [19]. These disparities likely reflect structural determinants, such as healthcare access, vaccine coverage, and comorbidity prevalence shape influenza-related CVD mortality. The absence of reliable data for American Indian/Alaska Native populations reflects long-standing underrepresentation in public health surveillance, a limitation that continues to obscure the full scope of influenza's cardiovascular impact in minority communities. Older adults (≥65 years) experienced the majority of deaths (34,717), consistent with immunosenescence and accumulated cardiovascular pathology. Yet, the younger cohort (45–64 years) demonstrated the steepest growth in mortality (AAPC 10.29; p < 0.01) [20]. This mirrors Ouranos et al.'s findings where cardiovascular events occurred even among middle-aged hospitalized patients, reinforcing that influenza-associated cardiac risk is not restricted to the elderly. Rising baseline prevalence of obesity, hypertension, and diabetes in the 45–64 demographic may explain this accelerating risk curve. These findings advocate broadening preventive strategies beyond traditional geriatric vaccination campaigns. Geographic patterns further highlight the role of environment and healthcare infrastructure. The South recorded the highest number of deaths. The Midwest, though less populous, displayed the highest average AAMR, while the Northeast experienced the fastest relative increase (AAPC 8.89). These trends may reflect regional differences in climate, healthcare access, and socioeconomic conditions. The consistency of mortality peaks in colder northern states such as South Dakota and Montana suggests climatic facilitation of influenza spread and heightened cardiovascular stress during winter months. The temporal association between influenza activity and cardiovascular mortality aligns with recent evidence that respiratory infections may act as important precipitating stressors for vascular events in susceptible population. Van Royen et al. (2024) argued that acute respiratory infections "fuel" cardiovascular disease by amplifying inflammation, thrombogenesis, and metabolic stress in vulnerable individuals. Their commentary in the Journal of the American College of Cardiology supports the biological plausibility of population-level mortality fluctuations observed in our analysis, emphasizing that respiratory infections have been associated with atherosclerotic plaques destabilization and acute coronary syndromes. Derqui et al. (2022), in a nine-season observational analysis from Valencia, Spain, identified age, chronic cardiac disease, and renal impairment as predictors of influenza severity among hospitalized adults. These predictors parallel the high-risk subgroups driving mortality in our dataset of older adults with pre-existing CVD reinforcing the transnational consistency of influenza-related cardiovascular vulnerability [21-24].

The higher AAMR observed in rural compared to urban populations (18.66 vs. 12.46 per million) likely results from healthcare access disparities, fewer vaccination campaigns, and delayed recognition of influenza complications [25]. The predominance of deaths in inpatient medical settings underscores that influenza-associated cardiovascular events often culminate in acute hospital presentations, consistent with Ouranos et al.'s hospital-based analysis. The substantial proportion of deaths at home or in long-term care facilities emphasizes missed opportunities for diagnosis or timely intervention among frail populations. Chow et al. (2020), showed that one in eight hospitalized adults with influenza experienced an acute cardiovascular event, most commonly HF decompensation or myocardial ischemia. Likewise, the NEJM study by Kwong et al. (2018) demonstrated a six-fold increase in acute myocardial infarction (AMI) risk within one week of laboratory-confirmed influenza infection. Beyond acute ischemia, Sellers et al. (2017) detailed a spectrum of extrapulmonary complications, including myocarditis, arrhythmias, and vascular inflammation, resulting from viral invasion and systemic immune activation. Experimental evidence by Wu and Huang (2017) provided mechanistic support, showing that influenza infection synergistically upregulates matrix metalloproteinase-9 and pro-inflammatory cytokines in endothelial cells exposed to oxidized LDL, promoting plaque instability. The significant post-2010 increases in HF- and CIHD-related mortality observed in our data align with these mechanistic pathways. Exploratory mortality forecasting through 2035 suggests a continuing upward trend, with projected AAMRs exceeding 60 per million. Though, the projections should be interpreted with caution, they mirrors global predictions that aging populations and persistent cardiovascular comorbidity will amplify influenza's cardiac impact unless vaccination rates improve. Integrating annual influenza vaccination into cardiovascular prevention frameworks especially for patients with heart failure or coronary artery disease could significantly reduce both infection-related morbidity and cardiovascular mortality. Clinical trials have shown that influenza vaccination can lower major adverse cardiac events by 15–45%, positioning it as a low-cost, high-impact intervention [26-29].

Limitations

This study's strengths include its nationwide scope, long follow-up period, and rigorous trend analysis using Joinpoint regression, enabling nuanced detection of shifts in mortality over time. However, limitations include reliance on death certificate data, which may underestimate influenza contribution, and inability to distinguish between direct viral cardiac injury and indirect triggers of decompensation. In contrast to the meta-analysis by Ouranos et al., which captured only hospitalized and laboratory-confirmed cases, our study cannot confirm influenza infection status at the individual level but provides broader external validity by encompassing the entire population.

Conclusions

This nationwide analysis spanning more than two decades demonstrates persistent and heterogeneous population-level associations between influenza and cardiovascular mortality in the United States, particularly among older adults and those with underlying heart failure or ischemic heart disease. The study revealed temporal associations in mortality, with peaks corresponding to severe influenza seasons, and a transient decline during the COVID-19 pandemic suggestive of reduced viral circulation and diagnostic displacement. Sex-based, racial, and regional disparities highlight that influenza's cardiovascular impact is not evenly distributed. Males exhibited higher absolute mortality rates, while females showed a faster rate of increase. Similarly, rural populations and southern regions experienced greater mortality, underscoring the influence of access to care and vaccination coverage. The younger adult population (45–64 years) demonstrated a steeper rise in mortality, indicating a shifting epidemiologic burden that parallels increasing cardiometabolic risk factors in middle age. Future studies incorporating individual-level clinical data are needed to clarify causal pathways and inform targeted interventions.

Supplementary Data

Supplemental Table 1: Number of Influenza and CVD-Related Deaths, Stratified by Sex and Race in Adults in the United States 1999-2023.

Year	Overall	Women	Men	NH American Indian or Alaskan Native	NH Asian or Pacific Islander	NH Black or African American	NH White	Hispanic or Latino	Population
1999	1075	651	424	Suppressed	13	52	975	30	95153686
2000	1124	688	436	Suppressed	11	48	1034	24	96944389
2001	168	104	64	0	Suppressed	15	145	Suppressed	99781854
2002	420	257	163	Suppressed	Suppressed	15	386	10	102217733
2003	978	585	393	Suppressed	Suppressed	41	900	20	104692428
2004	679	393	286	Suppressed	Suppressed	33	630	Suppressed	107138553
2005	1014	626	388	Suppressed	Suppressed	37	941	22	109787199
2006	467	258	209	Suppressed	Suppressed	13	437	11	112380379
2007	221	117	104	Suppressed	Suppressed	Suppressed	197	Suppressed	114894084
2008	950	537	413	Suppressed	Suppressed	46	868	20	117395131
2009	893	448	445	15	28	76	645	127	119895863
2010	182	91	91	0	Suppressed	21	132	24	121757429
2011	636	358	278	Suppressed	12	50	524	43	124174484
2012	552	302	250	Suppressed	11	33	485	18	126000296
2013	1840	967	873	Suppressed	50	136	1543	108	127788037
2014	2024	989	1035	14	45	167	1612	180	129779643
2015	3005	1700	1305	26	74	168	2608	116	131826832

2016	1383	651	732	Suppressed	49	118	1082	122	133494018
2017	3727	2021	1706	16	112	239	3115	241	135229289
2018	6677	3477	3200	42	210	523	5505	387	136335528
2019	3239	1646	1593	39	113	294	2548	240	137381702
2020	4006	1882	2124	35	204	622	2615	509	138429175
Total	35260	18748	####	187	932	2747	28927	2252	2622477732
2021	528	254	274	Suppressed	16	69	378	61	139339453
2022	4061	2147	1914	47	95	367	3192	325	140311934
2023	2882	1502	1380	31	67	286	2205	252	141596553
Total	7471	3903	3568	78	178	722	5775	638	421247940

Supplemental Table 2: Annual Percent Change (APC) and Average Annual Percent Change (AAPC) of Influenza and CVD–related Age-Adjusted Mortality Rates per 1,000,000 in Adults in the United States 1999-2023

Year	AAPC (95% CI)	Year2	APC (95% CI)
Overall		**1999-2010**	-5.7855 (-45.4072 to 6.4338)
1999-2023	2.5375(-1.711 to 7.4338)	**2010-2018**	27.4787* (15.718 to 111.7039)
		2018-2023	-12.8075 (-45.8534 to 0.6192)
Female		**1999-2023**	6.7284* (3.8658 to 12.5675)
1999-2023	6.7284*(3.8658 to 12.5675)		
Male		**1999-2010**	-5.3284 (-41.4982 to 5.6233)
1999-2023	2.615(-0.989 to 6.8763)	**2010-2018**	27.8763* (16.6298 to 86.6793)
		2018-2023	-13.8479* (-37.8057 to -3.0152)
NH Asian		**2013-2018**	31.0449* (12.4133 to 215.3718)
2013-2023	4.1039(-8.5372 to 25.8289)	**2018-2023**	-17.2985* (-46.921 to -3.5611)
NH Black		**2008-2020**	21.7616* (16.6457 to 55.6059)
2008-2023	11.3880*(5.4247 to 25.9688)	**2020-2023**	-21.9898 (-61.267 to 4.7568)
NH White		**1999-2010**	-6.1661 (-43.4076 to 6.0577)
1999-2023	2.1803(-2.3653 to 6.9723)	**2010-2018**	27.6163* (15.5683 to 114.7288)
		2018-2023	-13.6382 (-50.1066 to 0.5991)

Hispanics		**2008-2023**	7.8199* (1.289 to 20.6212)
2008-2023	7.8199*(1.289 to 20.6212)		
Northeast		**1999-2023**	8.8995* (6.2608 to 15.2161)
1999-2023	8.8995*(6.2608 to 15.2161)		
Midwest		**1999-2023**	4.7477* (1.4058 to 10.9712)
1999-2023	4.7477*(1.4058 to 10.9712)		
South		**1999-2010**	-5.0634 (-42.606 to 6.7563)
1999-2023	3.6686(-0.1879 to 8.3786)	**2010-2018**	28.6197* (17.5643 to 101.8486)
		2018-2023	-10.9034 (-36.7406 to 0.9939)
West		**1999-2011**	-3.796 (-42.9604 to 6.7697)
1999-2023	2.934(-1.1952 to 7.6436)	**2011-2018**	31.6394* (18.1279 to 104.1323)
		2018-2023	-14.2015* (-42.8277 to -2.5348)
Metro		**1999-2010**	-5.4161 (-36.0146 to 9.2063)
1999-2020	4.9721*(1.2201 to 10.8469)	**2010-2018**	29.7613* (7.2072 to 103.2075)
		2018-2020	-20.2556 (-44.5107 to 17.3215)
Non-Metro		**1999-2011**	-5.666 (-24.9686 to 3.8079)
1999-2020	2.2848(-1.4582 to 6.7816)	**2011-2018**	30.3951* (14.3987 to 93.0621)
		2018-2020	-28.9454 (-53.5228 to 11.0449)
45-64		**1999-2023**	10.2997* (7.5246 to 16.9782)
1999-2023	10.2997*(7.5246 to 16.9782)		
65+		**1999-2010**	-7.4558 (-44.3114 to 4.7315)
1999-2023	1.5821(-2.6829 to 6.2991)	**2010-2018**	28.5890* (15.9451 to 119.9763)
		2018-2023	-14.4877* (-45.6876 to -0.7809)
HF		**1999-2010**	-7.1102 (-43.1539 to 5.3676)
1999-2023	2.4207(-1.687 to 7.2758)	**2010-2018**	29.8795* (17.2001 to 122.0293)
		2018-2023	-13.1707* (-43.3655 to -0.4297)
CIHD			
1999-2023	4.9265*(2.1337 to 10.4304)	**1999-2023**	4.9265* (2.1337 to 10.4304)
AMI		**1999-2011**	-4.9733 (-29.9861 to 3.899)
1999-2023	0.4257(-3.3475 to 4.0349)	**2011-2018**	26.9382* (13.4571 to 86.3437)

		2018-2023	-17.3968* (-41.2812 to -6.6976)

*=indicates statistically significant value ($p < 0.05$)

Supplementary Table 3: Influenza and CVD-related Age-Adjusted Mortality Rates per 1,000,000, Stratified by Race in Adults in the United States 1999-2023

	Age Adjusted Rates (95% CI)				
Year	**NH American Indian or Alaskan Native**	**NH Asian or Pacific Islander**	**NH Black or African American**	**NH White**	**Hispanic or Latino**
1999	Suppressed(Suppressed to Suppressed)	Unreliable(3.79 to 12.8)	6.7(4.99 to 8.81)	12.02(11.27 to 12.78)	6.72(4.43 to 9.78)
2000	Suppressed(Suppressed to Suppressed)	Unreliable(2.62 to 10.04)	6.12(4.49 to 8.13)	12.66(11.89 to 13.43)	6.24(3.96 to 9.37)
2001	Unreliable(0 to 0)	Suppressed(Suppressed to Suppressed)	Unreliable(1.03 to 3.03)	1.75(1.47 to 2.04)	Suppressed(Suppressed to Suppressed)
2002	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	Unreliable(1.05 to 3.09)	4.59(4.13 to 5.05)	Unreliable(0.96 to 3.97)
2003	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	4.82(3.43 to 6.59)	10.57(9.88 to 11.27)	3.86(2.29 to 6.1)
2004	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	3.77(2.58 to 5.32)	7.3(6.73 to 7.87)	Suppressed(Suppressed to Suppressed)
2005	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	4.24(2.97 to 5.87)	10.66(9.98 to 11.34)	3.59(2.19 to 5.54)
2006	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	Unreliable(0.74 to 2.5)	4.92(4.46 to 5.38)	Unreliable(0.83 to 3.18)
2007	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	2.13(1.83 to 2.43)	Suppressed(Suppressed to Suppressed)
2008	Suppressed(Suppressed to Suppressed)	Suppressed(Suppressed to Suppressed)	4.67(3.38 to 6.3)	9.3(8.68 to 9.92)	2.94(1.74 to 4.65)
2009	Unreliable(10.84 to 34.8)	5.61(3.67 to 8.23)	6.3(4.93 to 7.94)	7.05(6.5 to 7.6)	11.75(9.6 to 13.9)

2010	Unreliable(0 to 0)	Suppressed(Suppressed to Suppressed)	1.73(1.06 to 2.67)	1.4(1.16 to 1.64)	2.69(1.69 to 4.07)
2011	Suppressed(Suppressed to Suppressed)	Unreliable(1.51 to 5.1)	4.39(3.22 to 5.83)	5.33(4.87 to 5.79)	4.38(3.12 to 5.99)
2012	Suppressed(Suppressed to Suppressed)	Unreliable(1.3 to 4.66)	2.9(1.97 to 4.12)	4.82(4.39 to 5.26)	Unreliable(1.29 to 3.43)
2013	Suppressed(Suppressed to Suppressed)	10.49(7.74 to 13.91)	11.31(9.35 to 13.27)	15.23(14.46 to 16)	10.99(8.84 to 13.14)
2014	Unreliable(9.26 to 29.74)	8.12(5.88 to 10.94)	13.12(11.06 to 15.18)	16.07(15.27 to 16.86)	15.6(13.21 to 17.98)
2015	36.7(23.51 to 54.6)	13.84(10.85 to 17.41)	14.22(12.02 to 16.43)	24.84(23.87 to 25.8)	11.39(9.27 to 13.51)
2016	Suppressed(Suppressed to Suppressed)	8.44(6.23 to 11.19)	8.36(6.81 to 9.92)	10.54(9.9 to 11.18)	10.33(8.42 to 12.23)
2017	Unreliable(11.17 to 32.91)	18.36(14.92 to 21.79)	18.77(16.32 to 21.22)	29.09(28.06 to 30.12)	20.51(17.85 to 23.17)
2018	51.81(36.84 to 70.82)	32.22(27.81 to 36.62)	38.91(35.49 to 42.34)	50.94(49.58 to 52.31)	31.28(28.08 to 34.48)
2019	41.44(29.02 to 57.36)	15.65(12.72 to 18.58)	20.9(18.45 to 23.36)	23.5(22.57 to 24.43)	17.61(15.31 to 19.91)
2020	35.11(24.17 to 49.3)	26.98(23.23 to 30.73)	42.14(38.73 to 45.54)	23.94(23.01 to 24.88)	35.37(32.19 to 38.54)
2021	Suppressed(Suppressed to Suppressed)	Unreliable(1.34 to 3.81)	4.73(3.65 to 6.03)	3.54(3.18 to 3.9)	4.38(3.32 to 5.68)
2022	47.7(34.79 to 63.83)	12.75(10.29 to 15.61)	25.1(22.46 to 27.75)	28.99(27.97 to 30.01)	22.06(19.59 to 24.53)
2023	31.52(21.27 to 45)	8.66(6.7 to 11.02)	19.24(16.94 to 21.53)	20.13(19.28 to 20.98)	16.56(14.45 to 18.68)

Supplementary Table 4: Overall and Sex-Stratified Influenza and CVD–related Age-Adjusted Mortality Rates per 1,000,000 in Adults in the United States 1999-2023

	Age Adjusted Rates (95% CI)		
year	**Female**	**Male**	**Overall**
1999	10.6 (9.78 to 11.41)	12.6 (11.38 to 13.83)	11.4 (10.72 to 12.08)
2000	11.13 (10.29 to 11.96)	12.38 (11.2 to 13.57)	11.71 (11.03 to 12.4)
2001	1.7 (1.37 to 2.03)	1.66 (1.27 to 2.13)	1.74 (1.48 to 2)
2002	4.01 (3.52 to 4.5)	4.48 (3.78 to 5.18)	4.25 (3.84 to 4.66)
2003	9.16 (8.41 to 9.9)	10.42 (9.37 to 11.47)	9.71 (9.1 to 10.32)
2004	6.06 (5.46 to 6.67)	7.55 (6.66 to 8.44)	6.64 (6.14 to 7.14)
2005	9.37 (8.64 to 10.11)	10.1 (9.08 to 11.12)	9.71 (9.11 to 10.31)
2006	3.91 (3.43 to 4.39)	5.2 (4.49 to 5.92)	4.39 (3.99 to 4.79)
2007	1.74 (1.42 to 2.06)	2.41 (1.94 to 2.89)	2.01 (1.75 to 2.28)
2008	7.65 (7 to 8.31)	9.68 (8.74 to 10.63)	8.43 (7.89 to 8.96)
2009	6.85 (6.21 to 7.49)	8.4 (7.61 to 9.2)	7.53 (7.03 to 8.02)
2010	1.36 (1.09 to 1.67)	1.72 (1.37 to 2.12)	1.48 (1.27 to 1.7)
x2011	4.86 (4.34 to 5.37)	5.58 (4.91 to 6.24)	5.19 (4.78 to 5.59)
2012	3.99 (3.53 to 4.44)	5.19 (4.54 to 5.84)	4.44 (4.06 to 4.81)
2013	12.58 (11.78 to 13.39)	17.11 (15.96 to 18.27)	14.46 (13.79 to 15.13)
2014	13.3 (12.45 to 14.14)	18.51 (17.36 to 19.66)	15.55 (14.87 to 16.24)
2015	21.16 (20.14 to 22.19)	25 (23.62 to 26.37)	22.78 (21.96 to 23.6)
2016	8.48 (7.82 to 9.14)	12.67 (11.74 to 13.61)	10.26 (9.71 to 10.81)
2017	24.65 (23.56 to 25.75)	30.36 (28.9 to 31.83)	27.09 (26.21 to 27.97)
2018	42.22 (40.79 to 43.64)	54.75 (52.83 to 56.67)	47.55 (46.4 to 48.7)
2019	19.97 (18.99 to 20.95)	25.61 (24.33 to 26.89)	22.54 (21.76 to 23.33)
2020	22.89 (21.84 to 23.94)	32.86 (31.44 to 34.28)	27.42 (26.56 to 28.28)
Total	11.95 (11.78 to 12.13)	15.74 (15.5 to 15.98)	13.53 (13.39 to 13.67)
2021	3.2 (2.81 to 3.6)	4.23 (3.72 to 4.75)	3.68 (3.36 to 3.99)
2022	25.3 (24.22 to 26.39)	29.86 (28.5 to 31.23)	27.3 (26.46 to 28.15)

2023	17.86 (16.94 to 18.77)	20.96 (19.83 to 22.09)	19.35 (18.64 to 20.07)
Total	15.68 (15.18 to 16.18)	18.57 (17.95 to 19.19)	16.98 (16.59 to 17.37)

Supplementary Table 5: Influenza and CVD-related Age-Adjusted Mortality Rate per 1,000,000 Stratified by Census Region in Adults in the United States 1999-2023

	Age Adjusted Rates (95% CI)			
Year	**Northeast**	**Midwest**	**South**	**West**
1999	8.43 (7.17 to 9.69)	17.4 (15.7 to 19.1)	8.32 (7.33 to 9.31)	12.33 (10.73 to 13.94)
2000	9.01 (7.71 to 10.3)	17.4 (15.71 to 19.1)	9.94 (8.86 to 11.01)	10.74 (9.26 to 12.23)
2001	1.21 (0.78 to 1.78)	1.78 (1.29 to 2.41)	1.52 (1.14 to 2)	2.5 (1.85 to 3.3)
2002	3.18 (2.47 to 4.03)	6.87 (5.82 to 7.91)	3.25 (2.65 to 3.86)	3.79 (2.98 to 4.75)
2003	5.49 (4.5 to 6.48)	14.54 (13.02 to 16.07)	8.93 (7.94 to 9.92)	9.54 (8.2 to 10.89)
2004	6.98 (5.88 to 8.09)	10.23 (8.97 to 11.5)	5.16 (4.41 to 5.9)	4.12 (3.3 to 5.09)
2005	9.45 (8.18 to 10.73)	17.66 (16.02 to 19.31)	6.42 (5.59 to 7.25)	5.86 (4.84 to 6.89)
2006	4.07 (3.27 to 5)	6.05 (5.09 to 7.02)	3.68 (3.06 to 4.29)	3.94 (3.15 to 4.85)
2007	2.03 (1.49 to 2.7)	2.29 (1.74 to 2.95)	1.53 (1.17 to 1.98)	2.27 (1.7 to 2.98)
2008	6.7 (5.65 to 7.75)	13.9 (12.48 to 15.32)	7.11 (6.27 to 7.94)	5.96 (4.97 to 6.95)
2009	5.91 (4.91 to 6.91)	6.5 (5.52 to 7.47)	6.17 (5.42 to 6.91)	12.19 (10.84 to 13.55)
2010	0.85 (0.52 to 1.32)	1.11 (0.75 to 1.57)	2.19 (1.78 to 2.68)	1.35 (0.93 to 1.89)
2011	5.19 (4.29 to 6.08)	5.28 (4.43 to 6.13)	5.15 (4.47 to 5.83)	4.93 (4.08 to 5.79)
2012	3.19 (2.54 to 3.96)	6.31 (5.39 to 7.24)	4.17 (3.56 to 4.78)	4.02 (3.24 to 4.8)
2013	15.19 (13.65 to 16.72)	19.3 (17.69 to 20.92)	11.36 (10.38 to 12.34)	13.58 (12.19 to 14.98)
2014	12.72 (11.31 to 14.13)	19.03 (17.42 to 20.64)	16.54 (15.38 to 17.71)	12.59 (11.28 to 13.89)
2015	30.12 (27.99 to 32.24)	27.98 (26.05 to 29.91)	19.24 (17.99 to 20.5)	16.23 (14.74 to 17.72)
2016	9.29 (8.1 to 10.49)	9.95 (8.8 to 11.11)	8.13 (7.33 to 8.93)	15.01 (13.59 to 16.42)
2017	21.21 (19.45 to 22.96)	32.42 (30.36 to 34.47)	22.77 (21.44 to 24.09)	33.77 (31.68 to 35.87)
2018	41.8 (39.34 to 44.25)	55.31 (52.66 to 57.97)	45.4 (43.55 to 47.25)	47.41 (44.96 to 49.86)
2019	22.69 (20.86 to 24.52)	22.5 (20.81 to 24.2)	21.26 (20.02 to 22.51)	24.47 (22.74 to 26.2)
2020	43.61 (41.08 to 46.14)	24.47 (22.71 to 26.23)	24.24 (22.92 to 25.55)	22.02 (20.4 to 23.64)
Total	13.03 (12.72 to 13.34)	16.03 (15.7 to 16.35)	12.15 (11.93 to 12.37)	13.44 (13.13 to 13.74)

2021	2.36 (1.81 to 3.01)	2.62 (2.07 to 3.26)	5.92 (5.26 to 6.59)	1.98 (1.52 to 2.54)
2022	24.57 (22.72 to 26.42)	29.51 (27.58 to 31.44)	27.47 (26.09 to 28.85)	27.1 (25.31 to 28.89)
2023	19.35 (17.69 to 21.01)	17.5 (16.02 to 18.97)	20.5 (19.31 to 21.69)	18.73 (17.25 to 20.2)
Total	15.57 (14.71 to 16.43)	16.75 (15.91 to 17.6)	18.17 (17.51 to 18.82)	16.18 (15.37 to 16.98)

Supplementary Table 6: Influenza and CVD-related Age-Adjusted Mortality Rates per 1,000,000 in the Metropolitan and Non-metropolitan areas in Adults in the United States 1999-2020

	Age Adjusted Rates (95% CI)	
Year	**Metro**	**Non-Metro**
1999	9.33 (8.64 to 10.01)	19.75 (17.72 to 21.78)
2000	9.92 (9.22 to 10.62)	19.15 (17.15 to 21.14)
2001	1.38 (1.12 to 1.64)	3.09 (2.34 to 4)
2002	3.31 (2.92 to 3.71)	8.17 (6.87 to 9.46)
2003	8.17 (7.55 to 8.79)	16.29 (14.47 to 18.1)
2004	5.98 (5.45 to 6.5)	9.46 (8.08 to 10.84)
2005	7.88 (7.28 to 8.48)	17.74 (15.87 to 19.62)
2006	3.82 (3.41 to 4.23)	6.91 (5.74 to 8.07)
2007	1.75 (1.48 to 2.03)	3.07 (2.36 to 3.93)
2008	6.74 (6.21 to 7.27)	16.02 (14.28 to 17.76)
2009	7.07 (6.55 to 7.6)	9.59 (8.23 to 10.95)
2010	1.27 (1.04 to 1.49)	2.71 (2.04 to 3.51)
2011	4.8 (4.37 to 5.22)	6.94 (5.81 to 8.06)
2012	3.51 (3.15 to 3.88)	8.82 (7.56 to 10.08)
2013	13.28 (12.57 to 13.98)	20.33 (18.43 to 22.22)
2014	14.46 (13.74 to 15.19)	21.12 (19.17 to 23.07)
2015	21.3 (20.43 to 22.17)	29.9 (27.61 to 32.18)
2016	10 (9.41 to 10.59)	11.94 (10.47 to 13.41)
2017	25.22 (24.29 to 26.15)	36.33 (33.83 to 38.82)
2018	44.19 (42.97 to 45.4)	64.57 (61.27 to 67.88)
2019	20.63 (19.81 to 21.45)	32.47 (30.13 to 34.82)
2020	26.81 (25.89 to 27.74)	30.74 (28.45 to 33.04)

Total	12.46 (12.31 to 12.61)	18.66 (18.27 to 19.06)

Supplementary Table 7: Influenza and CVD–related Age-Adjusted Mortality Rates per 1,000,000, Stratified by States in Adults in the United States 1999-2020

State	Age Adjusted Rates (95% CI)
Alabama	11.54 (10.49 to 12.59)
Alaska	12.5 (8.8 to 17.23)
Arizona	10.04 (9.19 to 10.89)
Arkansas	15.9 (14.36 to 17.45)
California	12.18 (11.77 to 12.59)
Colorado	16.74 (15.38 to 18.1)
Connecticut	13.25 (12.04 to 14.45)
Delaware	11.76 (9.47 to 14.44)
District of Columbia	5.72 (3.77 to 8.32)
Florida	6.82 (6.45 to 7.18)
Georgia	8.84 (8.11 to 9.57)
Hawaii	11.25 (9.41 to 13.1)
Idaho	22.19 (19.54 to 24.85)
Illinois	10.58 (9.96 to 11.2)
Indiana	16.88 (15.78 to 17.98)
Iowa	21.24 (19.62 to 22.86)
Kansas	18.42 (16.75 to 20.09)
Kentucky	17.72 (16.33 to 19.1)
Louisiana	8.39 (7.44 to 9.34)
Maine	20.08 (17.69 to 22.48)
Maryland	11.29 (10.32 to 12.27)
Massachusetts	12.67 (11.78 to 13.56)
Michigan	12.97 (12.21 to 13.73)
Minnesota	21.53 (20.2 to 22.87)
Mississippi	13.98 (12.47 to 15.49)
Missouri	16.78 (15.68 to 17.88)

Montana	24.14 (20.97 to 27.32)
Nebraska	25.22 (22.81 to 27.62)
Nevada	7.55 (6.34 to 8.77)
New Hampshire	16.04 (13.73 to 18.35)
New Jersey	7.91 (7.29 to 8.53)
New Mexico	11.92 (10.24 to 13.59)
New York	14.09 (13.53 to 14.64)
North Carolina	14.47 (13.61 to 15.33)
North Dakota	24.86 (21.13 to 28.59)
Ohio	13.63 (12.92 to 14.33)
Oklahoma	21.79 (20.15 to 23.42)
Oregon	16.74 (15.37 to 18.11)
Pennsylvania	12.48 (11.88 to 13.09)
Rhode Island	21.95 (19.13 to 24.78)
South Carolina	17.32 (15.99 to 18.65)
South Dakota	33.64 (29.64 to 37.63)
Tennessee	15.19 (14.13 to 16.26)
Texas	13.77 (13.2 to 14.34)
Utah	12.6 (10.84 to 14.37)
Vermont	24.89 (20.85 to 28.94)
Virginia	10.95 (10.12 to 11.78)
Washington	18.33 (17.18 to 19.48)
West Virginia	22.36 (20.16 to 24.55)
Wisconsin	19.1 (17.91 to 20.29)
Wyoming	19.5 (15.59 to 24.08)
Total	**13.53 (13.39 to 13.67)**

Supplementary Table 8: Influenza and CVD-related Mortality, Stratified by Place of Death in Adults in the United States 1999-2023

	Deaths		
Year	**Medical Facility - Inpatient**	**Decedent's home**	**Nursing home/long term care**
1999	462	157	379
2000	536	186	309
2001	61	41	41
2002	184	56	159
2003	527	119	266
2004	375	81	182
2005	501	106	337
2006	265	63	114
2007	103	47	52
2008	500	126	234
2009	612	129	55
2010	113	37	12
2011	402	59	128
2012	318	62	115
2013	1017	232	376
2014	1364	216	226
2015	1719	232	721
2016	1003	153	99
2017	2337	355	624
2018	4025	858	1017
2019	2154	368	346
2020	2314	955	310
2021	329	92	30
2022	2546	590	373
2023	1767	434	281
Total	25534	5754	6786

Supplementary Table 9: Influenza and CVD–related Age-Adjusted Mortality Rates per 1,000,000, Stratified by States in Adults in the United States 1999-2020 ranked according to Percentiles.

State	Deaths	Age Adjusted Rate	Rank	Percentile
South Dakota	278	33.64	1	100
Nebraska	429	25.22	2	98
Vermont	147	24.89	3	96
North Dakota	176	24.86	4	94
Montana	225	24.14	5	92
West Virginia	402	22.36	6	90
Idaho	271	22.19	7	88
Rhode Island	238	21.95	8	86
Oklahoma	686	21.79	9	84
Minnesota	1019	21.53	10	82
Iowa	673	21.24	11	80
Maine	272	20.08	12	78
Wyoming	87	19.5	13	76
Wisconsin	1000	19.1	14	74
Kansas	475	18.42	15	72
Washington	992	18.33	16	70
Kentucky	639	17.72	17	68
South Carolina	663	17.32	18	66
Indiana	913	16.88	19	64
Missouri	900	16.78	20	62
Colorado	595	16.74	21	58
Oregon	578	16.74	21	58
New Hampshire	187	16.04	23	56
Arkansas	410	15.9	24	54
Tennessee	792	15.19	25	52
North Carolina	1102	14.47	26	50
New York	2470	14.09	27	48

Mississippi	333	13.98	28	46
Texas	2303	13.77	29	44
Ohio	1431	13.63	30	42
Connecticut	472	13.25	31	40
Michigan	1133	12.97	32	38
Massachusetts	795	12.67	33	36
Utah	198	12.6	34	34
Alaska	42	12.5	35	32
Pennsylvania	1643	12.48	36	30
California	3446	12.18	37	28
New Mexico	196	11.92	38	26
Delaware	92	11.76	39	24
Alabama	468	11.54	40	22
Maryland	519	11.29	41	20
Hawaii	146	11.25	42	18
Virginia	674	10.95	43	16
Illinois	1132	10.58	44	14
Arizona	540	10.04	45	12
Georgia	583	8.84	46	10
Louisiana	306	8.39	47	8
New Jersey	632	7.91	48	6
Nevada	155	7.55	49	4
Florida	1375	6.82	50	2
District of Columbia	27	5.72	51	0

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