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Neuro-Cardiac Collapse in Cerebral Infarction: A 25-Year CDC WONDER Mortality Analysis of Hypertensive Disease, Cardiomyopathy, and Tachyarrhythmias (1999–2024)

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ABSTRACT:

Cerebral infarction is one of the foremost causes of death in the US, and cardiovascular disorders may exacerbate the consequences of cerebrovascular injury. Hypertensive diseases, cardiomyopathy, conduction abnormalities, and tachyarrhythmias may coexist with cerebral infarction. This study observed mortality rates in the US for hypertensive diseases associated with cardiac issues and cerebral infarction.

Mortality data from 1999-2024 were taken from CDC WONDER database. Hypertensive diseases were the primary cause (I10-I15), while cardiomyopathy (I42), conduction abnormalities (I44-I45), paroxysmal tachycardia (I47), atrial fibrillation/flutter (I48), other cardiac arrhythmias (I49), cerebral infarction (I63), & stroke (I64) were the contributing factors. The AAMRs per 100,000 were estimated using the US standard population, stratified by gender, race, age, and location. Trends were examined by Joinpoint regression ($p<0.05$).
From 1999-2024, total deaths were 359,706 AAMR rose from 1.61 in 1999 to 3.18 in 2024 (AAPC: 2.39%). Males observed more increment than females (AAPC: 2.60%), while non-metropolitan areas had a greater increase (AAPC: 3.24%). White people experienced the greatest growth (AAPC: 2.92%). Non-Hispanic Black or African American individuals experienced a non-significant reduction (AAPC: -0.66%) but an increase from 2018 to 2021 (APC: 8.88%). Adults ≥ 65 years experienced the highest rise (AAPC: 2.60%). The Midwest observed the largest regional rise (AAPC: 2.87%).

Over last 25 years, mortality due to cerebral infarction with underlying hypertension illness, cardiomyopathy, and tachyarrhythmias has increased, with a

large late-period increase among non-Hispanic Black adults. Men, White, elderly, and non-metropolitan residents all continued to have higher mortality rates. These findings highlight the growing neuro-cardiac mortality burden and call for better cardiovascular risk management and early detection of cardiac problems

KEYWORDS:

1- Cerebral Infarction
2- Neuro-Cardiac Collapse
3- Cardiomyopathy
4- Tachyarrhythmias

INRODUCTION

Hypertensive heart disease (HHD), a disorder characterized by chronically elevated blood pressure, is widely regarded as one of the principal risk factors involved in the pathogenesis of coronary artery disease, peripheral artery disease, stroke and heart failure,[1,2] Affecting up to 45% of adults worldwide, it is projected that the global estimate of hypertension prevalence will reach nearly 1.56 billion by 2025, influenced by aging populations, increasing rates of obesity, and socioeconomic shifts. [3,4]

HHD can induce adverse remodeling of the myocardium which may result in degenerative electrical disease and left ventricular hypertrophy (LVH), which underlie the pathophysiology of a wide variety of arrhythmias including bradyarrhythmia and tachyarrhythmias.[2] LVH results from longstanding pressure overload and is a significant predictor of heart failure [3]while degenerative electrical disease is characterized by fibroblast proliferation, apoptosis of cardiomyocytes, gap junction remodeling, and collagen accumulation[5]

Chronically elevated blood pressure also significantly affects cerebral circulation through increased cerebrovascular resistance and is generally considered as one of the most important modifiable risk factors in the pathogenesis of ischemic stroke (IS)[6,7,8]It establishes the main vascular pathway to IS by promoting atherosclerosis and small-vessel disease.[9] It has also been observed that the risk of atrial fibrillation (AF) is elevated in cases of HHD across both genders by 50%. AF subsequently raises the risk of cerebral embolism through blood stagnation and clot formation[10].Cerebral infarction, the clinical manifestation of ischemic stroke (IS),

is one of the major causes of morbidity and long-term disability globally. It is the consequence of insufficient cerebral perfusion, whether prolonged or abrupt, which ultimately leads to localized irreversible injury in the brain.[8]There were almost 3.29 million deaths attributed to cerebral infarction in 2019 and it is projected that this number will increase to 4.90 million deaths by 2030.[11]

While there are studies analyzing atrial fibrillation[10], cardiomyopathy[12]and heart failure[13]in hypertensive adult patients discretely, there are limited national-level studies that evaluate cerebral infarction, stroke, cardiomyopathy, and arrhythmias as co-occurring causes within hypertensive deaths.

Therefore, the objective of this study is to provide a comprehensive analysis of demographic and regional disparities in mortality due to cerebral infarction in the setting of comorbid hypertensive disease, cardiomyopathies, arrhythmias and conduction disorders among adults in the United States from 1999 to 2024. Identification of vulnerable groups as well as integration of targeted prevention and management strategies can be accomplished by examining these trends.

Methods

Study Design and Data Source

We conducted a retrospective, population-based mortality analysis using the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death (MCD) database. The CDC WONDER MCD database contains national mortality data derived from death certificates of U.S. residents and provides information on one underlying cause of death and up to 20 additional multiple causes of death recorded on each death certificate.[14] Final mortality data from 1999 through 2024 were included in the present analysis[14]

Study Population and Case Definition

The study population comprised U.S. residents aged ≥25 years who died between 1999 and 2024. Deaths were identified using the International Classification of Diseases, Tenth Revision (ICD-10), according to the underlying and multiple-cause-of-death definitions.

For the primary analysis, hypertensive diseases were defined as the underlying cause of death using ICD-10 codes I10–I15. The following conditions were identified from the multiple-cause fields of the death certificate:

- Cardiomyopathy: I42
- Atrioventricular and left bundle-branch block: I44
- Other conduction disorders: I45
- Paroxysmal tachycardia: I47
- Atrial fibrillation and flutter: I48
- Other cardiac arrhythmias: I49
- Cerebral infarction: I63
- Stroke, not specified as hemorrhage or infarction: I64

The analysis therefore examined deaths in which hypertensive disease was recorded as the underlying cause and one or more of the pre-specified cardiac or cerebrovascular conditions were documented as contributing causes [2,3]. ICD-10 codes were selected according to the WHO International Classification of Diseases, 10th Revision[15]

Study Variables

The primary variables included calendar year, number of deaths, population estimates, age, sex, race/ethnicity, and geographic region. The principal outcome measure was the annual mortality rate associated with deaths meeting the specified underlying- and multiple-cause-of-death criteria.

The cardiovascular and cerebrovascular conditions were additionally evaluated individually and, where appropriate, as grouped categories to characterize the contribution of conduction disorders, tachyarrhythmia's, cardiomyopathy, cerebral infarction, and stroke to mortality associated with hypertensive disease.

Mortality Measures

Annual death counts and population estimates were obtained directly from CDC WONDER. Crude mortality rates and age-adjusted mortality rates (AAMRs) were calculated per 100,000 population. AAMRs were standardized to the 2000 U.S. standard population using the direct standardization method, consistent with CDC/NCHS mortality reporting practices [14,16]. CDC WONDER calculates age-adjusted mortality rates by applying age-specific mortality rates to the corresponding age weights of the selected standard population[16]

Ninety-five percent confidence intervals (95% CIs) were obtained for mortality rates where available. Because mortality rates are strongly influenced by differences in population age structure, age-adjusted rates were used for temporal and subgroup comparisons.[16]

Temporal Trend Analysis

Temporal trends in annual AAMRs from 1999 through 2024 were assessed using Joinpoint regression analysis. Joinpoint regression identifies statistically significant changes in mortality trends by fitting a sequence of linear segments to annual rate data. For each segment, the annual percentage change (APC) and corresponding 95% confidence interval were estimated. The average annual percentage change (AAPC) was calculated when appropriate to summarize the overall temporal trend across the study period[17]

A two-sided P value <0.05 was considered statistically significant. Trends were interpreted according to the direction and magnitude of APC and AAPC estimates rather than solely on statistical significance.

Data Reliability and Confidentiality

CDC WONDER suppresses mortality statistics when the number of deaths is fewer than 10 to protect confidentiality. Suppressed estimates were therefore excluded from quantitative interpretation. Mortality rates based on small numbers of deaths were interpreted cautiously because of increased statistical variability[14]

Ethical Considerations

The study used publicly available, de-identified, aggregate mortality data from the CDC WONDER database. No individually identifiable information was accessed. Therefore, institutional review board approval and informed consent were not required for this secondary analysis of publicly available mortality data.

RESULT

Overall Trends:

Between 1999 and 2024, the total age-adjusted mortality rate (AAMR) increased by approximately 82%. The rate increased from 4.85 (95% CI: 4.74–4.95) per 100,000 in 1999 to 5.09 (95% CI: 4.98–5.19) per 100,000 in 2000 and from 2021 to 2024, the AAMR climbed from 8.67 (95% CI: 8.56–8.79) per 100,000 in 2021 to 8.84 (95% CI: 8.73–8.95) per 100,000 in 2024, after reaching its highest point at 8.89 (95% CI: 8.78–9.00) per 100,000 in 2023.

The AAMR increased marginally but not significantly between 1999 and 2002 (APC: 1.97 [95% CI: −1.48 to 5.54]) and similarly showed a small, non-significant change between 2021 and 2024 (APC: 0.86 [95% CI: −1.48 to 3.26]). In between, the rate declined slightly but significantly from 2002 to 2012 (APC: −0.62 [95% CI: −1.23 to 0.00]), from 5.14 to 4.99 per 100,000, before rising sharply and significantly from 2012 to 2018 (APC: 4.65 [95% CI: 3.23 to 6.08]), from 4.99 to

6.50 per 100,000. The steepest rise occurred between 2018 and 2021 (APC: 10.44 [95% CI: 5.45 to 15.67]), during which the rate climbed from 6.50 to 8.67 per 100,000, after which it plateaued through 2024.

The total AAMR increased significantly overall across the full study period (1999–2024) (AAPC: 2.40 [95% CI: 1.62 to 3.19]), driven mainly by the sharp rise seen between 2012 and 2021, after which the rate stabilized at a much higher level than at the start of the study.

Sex Stratification:

Across all years from 1999 to 2024, males consistently recorded a higher AAMR (age-adjusted mortality rate) than females. In 1999, the AAMR among males was 4.75 (95% CI: 4.59–4.92) per 100,000 with 3,292 deaths recorded, while females recorded a slightly lower AAMR of 4.74 (95% CI: 4.61–4.87) per 100,000, despite a higher death count of 5,243 (reflecting the larger female population base).

Between 1999 and 2012, both sexes showed relatively stable trends, though the patterns differed slightly. Females showed a marginal, non-significant rise from 1999 to 2001 (APC: 3.31 [95% CI: −4.60 to 11.89]), followed by a small but statistically significant decline from 2001 to 2012 (APC: −0.80 [95% CI: −1.36 to −0.24]), falling from 5.05 to 4.78 per 100,000. Males, in contrast, remained essentially flat across the entire 1999–2012 span, with no significant change (APC: 0.16 [95% CI: −0.31 to 0.63]), moving from 4.75 to 5.14 per 100,000.

From 2012 to 2018, both sexes showed a significant upward trend, with males rising slightly faster than females — males from 5.14 to 6.98 per 100,000 (APC: 5.17 [95% CI: 3.49 to 6.87]) and females from 4.78 to 5.98 per 100,000 (APC: 4.04 [95% CI: 2.58 to 5.52]). The steepest acceleration for both sexes occurred between 2018 and 2021, with males climbing from 6.98 to 9.31 per 100,000 (APC: 10.53 [95% CI: 4.39 to 17.04]) and females climbing from 5.98 to 7.95 per 100,000 (APC: 10.40 [95% CI: 4.75 to 16.35]).

From 2021 to 2024, both sexes plateaued, with no statistically significant change — males (APC: 0.66 [95% CI: −1.90 to 3.28]) and females (APC: 1.04 [95% CI: −1.35 to 3.49]). The highest AAMR for both sexes was recorded in 2023, at 9.59 (95% CI: 9.41–9.77) per 100,000 for males and 8.19 (95% CI: 8.05–8.33) per 100,000 for females, before both eased slightly in 2024 — males to 9.42 (95% CI: 9.25–9.60) with 11,301 deaths, and females to 8.16 (95% CI: 8.02–8.30) with 13,259 deaths.

Across the full study period (1999–2024), the AAMR increased significantly for both sexes, with a greater average annual rise among males (AAPC: 2.61 [95% CI: 1.78–3.44]) compared to females (AAPC: 2.19 [95% CI: 1.25–3.14]), indicating that the overall upward trend in mortality was more pronounced in males.

Urbanization:

Between 1999 and 2020, metropolitan (urban) areas recorded a modestly higher AAMR than non-metropolitan (rural) areas during the earlier part of the study period, but this pattern reversed after around 2014–2015, with non-metro areas subsequently showing substantially higher mortality rates through the end of the study.

In 1999, the AAMR in metro areas was 4.92 (95% CI: 4.80–5.03) per 100,000, compared with a lower rate of 4.54 (95% CI: 4.31–4.77) per 100,000 in non-metro areas. From 1999 to 2012, the metro AAMR remained relatively flat, with no statistically significant change (APC: −0.34 [95% CI: −0.75 to 0.08]), moving from 4.92 to 5.00 per 100,000. Non-metro areas fluctuated more over roughly the same span: rising non-significantly from 1999 to 2003 (APC: 3.04 [95% CI: −0.11 to 6.28]), declining non-significantly from 2003 to 2008 (APC: −1.65 [95% CI: −4.51 to 1.29]), and rising again without statistical significance from 2008 to 2014 (APC: 1.45 [95% CI: −0.50 to 3.45]).

From 2012 onward, metro areas showed a significant upward trend, rising from 5.00 to 6.40 per 100,000 between 2012 and 2018 (APC: 4.16 [95% CI: 2.66 to 5.68]), and accelerating further to 7.60 (95% CI: 7.48–7.71) per 100,000 by 2020 (APC: 9.41 [95% CI: 2.99 to 16.24]). Non-metro areas, meanwhile, rose even more sharply — climbing from 5.14 to 7.00 per 100,000 between 2014 and 2018 (APC: 7.60 [95% CI: 3.38 to 11.98]), then surging to 9.06 (95% CI: 8.77–9.35) per 100,000 by 2020 (APC: 13.52 [95% CI: 6.10 to 21.46]) — the highest AAMR recorded for either cohort across the full study period.

Across the full period (1999–2020), the average annual increase was significantly greater in non-metro areas (AAPC: 3.24 [95% CI: 1.96 to 4.53]) than in metro areas (AAPC: 1.83 [95% CI: 1.13 to 2.53]), indicating a widening rural–urban mortality gap by 2020.

Census Region:

Across U.S. census regions, the Northeast consistently recorded the lowest AAMR throughout the study period, while the Midwest, South, and West trended higher and converged to similarly elevated levels by 2024. In 1999, the Northeast had an AAMR of 3.68 per 100,000, the Midwest 4.41, the West 5.36, and the South 5.56 per 100,000.

In the Northeast, the rate held essentially flat from 1999 to 2007 (APC: −0.10 [95% CI: −0.98 to 0.78]), then rose steadily and significantly from 2007 to 2016 (APC: 2.20 [95% CI: 1.39 to 3.02]), from 3.64 to 4.67 per 100,000. The sharpest rise followed, from 2016 to 2021 (APC: 7.78 [95% CI: 5.81 to 9.77]), climbing to 6.57 per 100,000 — the region's peak — before easing slightly, non-significantly, from 2021 to 2024 (APC: −1.22 [95% CI: −3.78 to 1.40]) to 6.33 per 100,000.

The Midwest rose modestly but significantly from 1999 to 2005 (APC: 1.90 [95% CI: 0.57 to 3.25]), from 4.41 to 5.19 per 100,000, then plateaued from 2005 to 2012 (APC: −0.92 [95% CI: −2.14 to 0.32]). A sharp, significant rise followed from 2012 to 2018 (APC: 5.09 [95% CI: 3.51 to 6.70]), from 4.71 to 6.38 per 100,000, accelerating further from 2018 to 2021 (APC: 9.35 [95% CI: 3.36 to 15.68]) to 8.44 per 100,000. Unlike the other three regions, the Midwest kept rising significantly through the final segment (APC: 3.19 [95% CI: 0.60 to 5.84]), reaching 9.26 per 100,000 in 2024 — its highest value and the highest of any region that year.

The South declined significantly from 1999 to 2013 (APC: −1.18 [95% CI: −1.67 to −0.68]), from 5.56 to 5.23 per 100,000, then reversed sharply: a significant rise from 2013 to 2018 (APC: 5.19 [95% CI: 2.19 to 8.28]) to 6.56 per 100,000, followed by the steepest increase of any region or segment, from 2018 to 2021 (APC: 12.94 [95% CI: 4.76 to 21.76]), reaching 9.24 per 100,000. The rate peaked at 9.80 per 100,000 in 2023 before easing non-significantly from 2021 to 2024 (APC: 1.17 [95% CI: −2.22 to 4.67]) to 9.48 per 100,000 — the highest 2024 value among all four regions.

The West rise non-significantly from 1999 to 2002 (APC: 3.45 [95% CI: −0.81 to 7.91]), eased non-significantly from 2002 to 2010 (APC: −0.77 [95% CI: −1.79 to 0.25]), then rose significantly from 2010 to 2018 (APC: 3.72 [95% CI: 2.83 to 4.62]), from 5.58 to 7.64 per 100,000. A sharp, significant rise followed from 2018 to 2021 (APC: 8.27 [95% CI: 2.49 to 14.38]) to the region's peak of 9.71 per

100,000, before declining slightly and non-significantly from 2021 to 2024 (APC: −0.66 [95% CI: −3.11 to 1.86]) to 9.32 per 100,000.

Across the full study period (1999–2024), AAMR increased significantly in all four regions, with the largest average annual rise in the Midwest (AAPC: 2.88 [95% CI: 2.00 to 3.76]), followed by the West (AAPC: 2.23 [95% CI: 1.33 to 3.13]), the Northeast (AAPC: 2.12 [95% CI: 1.53 to 2.72]), and the South (AAPC: 1.97 [95% CI: 0.87 to 3.08]). By 2024, the Midwest, South, and West had converged at similarly high levels (9.26–9.48 per 100,000), while the Northeast remained distinctly lower at 6.33 per 100,000.

Race:

At the start of the study period, Black or African American people had by far the highest AAMR (12.50 per 100,000 in 1999), followed by Asian or Pacific Islander people (4.28), White people (4.12), Hispanic or Latino people (4.05), and American Indian or Alaska Native people (3.56). The Black or African American rate peaked early, at 12.74 per 100,000 in 2000.

Among Black or African American people, the rate was stable from 1999 to 2002 (APC: −0.16 [95% CI: −4.67 to 4.55]), then fell significantly from 2002 to 2011 (APC: −4.04 [95% CI: −5.04 to −3.04]), from 12.44 to 8.57 per 100,000. It then held steady from 2011 to 2018 (APC: 0.16 [95% CI: −1.37 to 1.72]), with a low of 8.40 per 100,000 in 2014. A significant rise followed from 2018 to 2021 (APC: 8.88 [95% CI: 0.54 to 17.91]), to 11.21 per 100,000, before a non-significant decline from 2021 to 2024 (APC: −1.87 [95% CI: −5.52 to 1.92]), to 10.63 per 100,000.

Among White people, the rate was essentially stable from 1999 to 2012 (APC: 0.40 [95% CI: −0.04 to 0.85]), moving from 4.12 to 4.66 per 100,000. It then rose sharply and significantly from 2012 to 2018 (APC: 5.22 [95% CI: 3.59 to 6.87]), to 6.34 per 100,000, and faster still from 2018 to 2021 (APC: 11.13 [95% CI: 4.45 to 18.24]), to 8.60 per 100,000. From 2021 to 2024 the change was non-significant (APC: 1.57 [95% CI: −0.98 to 4.18]), with a peak of 8.94 per 100,000 in 2023 and 8.92 in 2024.

Hispanic or Latino people showed a small but significant decline from 1999 to 2014 (APC: −0.71 [95% CI: −1.34 to −0.07]), from 4.05 to 3.84 per 100,000, with a low of 3.68 in 2012. A significant rise followed from 2014 to 2022 (APC:

5.45 [95% CI: 4.03 to 6.89]), to 5.68 per 100,000, and then a non-significant decline from 2022 to 2024 (APC: −3.06 [95% CI: −10.67 to 5.19]), to 5.34 per 100,000. The peak was 5.69 per 100,000 in 2023.

Among American Indian or Alaska Native people, the rate changed non-significantly from 1999 to 2011 (APC: −1.01 [95% CI: −3.95 to 2.03]), fluctuating from 3.56 to 2.62 per 100,000 with a low of 2.36 in 2009. A sharp, significant rise followed from 2011 to 2022 (APC: 8.38 [95% CI: 5.78 to 11.05]), to 6.57 per 100,000, with a peak of 6.63 in 2020. From 2022 to 2024 the rate declined non-significantly (APC: −12.58 [95% CI: −31.04 to 10.82]), to 5.15 per 100,000. The wide confidence intervals reflect small numbers.

Among Asian or Pacific Islander people, the rate declined significantly from 1999 to 2014 (APC: −1.52 [95% CI: −2.84 to −0.18]), from 4.28 to 3.04 per 100,000 (low of 2.89 in 2012). It then rose significantly from 2014 to 2020 (APC: 4.21 [95% CI: 0.51 to 8.04]), to 4.62 per 100,000. From 2021, CDC WONDER reports this group as Asian alone. The rate moved from 4.26

to 4.03 per 100,000 between 2021 and 2024, a non-significant decline (APC: −2.20 [95% CI: −5.68 to 1.41]).

Across the full study period, AAMR increased significantly among White people (AAPC: 2.93 [95% CI: 2.06 to 3.80]) and Hispanic or Latino people (AAPC: 1.03 [95% CI: 0.21 to 1.86]). There was no significant overall change among American Indian or Alaska Native people (AAPC: 2.00 [95% CI: −0.46 to 4.52]), Black or African American people (AAPC: −0.66 [95% CI: −1.84 to 0.53]), or Asian or Pacific Islander people (AAPC 1999–2020: 0.09 [95% CI: −1.22 to 1.41]). By 2024, Black or African American people still had the highest AAMR (10.63 per 100,000), followed by White people (8.92), Hispanic or Latino people (5.34), American Indian or Alaska Native people (5.15), and Asian people (4.03). The gap between Black or African American and White people narrowed from roughly 3-fold in 1999 (12.50 vs 4.12) to about 1.2-fold in 2024.

Age Groups:

In every year of the study, AAMR rose sharply with age. In 1999, the AAMR was 0.26 (95% CI: 0.23-0.30) per 100,000 for adults aged 25-44 (246 deaths), 1.87 (95% CI: 1.76-1.98) for those aged 45-64 (1,117 deaths), and 20.89 (95% CI: 20.41-21.38) for those aged 65 and older (7,172 deaths). The oldest group's rate

was about 80 times that of the youngest group and about 11 times that of the middle group.

Adults aged 25-44 showed a small but significant increase across the whole study period, with no join points (APC = AAPC: 1.20 [95% CI: 0.61 to 1.80]). The rate rose from 0.26 in 1999 to 0.42 (95% CI: 0.38-0.46) per 100,000 in 2024 (343 deaths), matching its earlier high of 0.42 in 2021.

Among adults aged 45-64, the rate declined significantly from 1999 to 2012 (APC: -0.76 [95% CI: -1.26 to -0.25]), from 1.87 to 1.69 per 100,000, with a low of 1.67 (95% CI: 1.58-1.76) in 2007. A significant rise followed from 2012 to 2017 (APC: 3.34 [95% CI: 0.59 to 6.17]), to 2.01 per 100,000, and then a steeper rise from 2017 to 2021 (APC: 8.45 [95% CI: 4.67 to 12.37]), to a peak of 2.82 (95% CI: 2.71-2.94) per 100,000. From 2021 to 2024 the rate declined non-significantly (APC: -2.69 [95% CI: -6.02 to 0.75]), to 2.58 (95% CI: 2.48-2.69) per 100,000 (2,351 deaths).

The 65-85+ group had the highest rates and the largest increase. The rate rose non-significantly from 1999 to 2001 (APC: 3.68 [95% CI: -4.15 to 12.15]), to 22.25 per 100,000, and then remained essentially flat from 2001 to 2012 (APC: -0.49 [95% CI: -1.05 to 0.08]), at 21.84 per 100,000 in 2012. A significant rise followed from 2012 to 2018 (APC: 4.79 [95% CI: 3.32 to 6.28]), to 28.66 per 100,000, accelerating from 2018 to 2021 (APC: 10.74 [95% CI: 5.09 to 16.70]), to 38.42 per 100,000. From 2021 to 2024 the rate plateaued (APC: 1.30 [95% CI: -1.01 to 3.67]). It peaked at 39.93 (95% CI: 39.39-40.47) per 100,000 in 2023 and stood at 39.69 (95% CI: 39.16-40.22) per 100,000 in 2024, with 21,866 deaths.

Across the full study period (1999-2024), AAMR increased significantly in all three age groups, with the largest average annual rise in adults aged 65 and older (AAPC: 2.61 [95% CI: 1.67 to 3.56]), followed by those aged 45-64 (AAPC: 1.24 [95% CI: 0.38 to 2.11]) and those aged 25-44 (AAPC: 1.20 [95% CI: 0.61 to 1.80]). As a result, the gap between age groups widened: by 2024, the AAMR in the oldest group was about 95 times that of the youngest group and about 15 times that of the middle group.

Discussion

This study examined national trends and disparities in mortality associated with neuro-cardiac collapse in adults with cerebral infarction in the United States from 1999 to 2024. Using the CDC WONDER database, this 25-year nationwide analysis identified 359,706 deaths among adults aged ≥25 years in whom cerebral

infarction (ICD-10: I63) and stroke (I64) were documented alongside hypertensive diseases (I10–I15), cardiomyopathy (I42), and tachyarrhythmias or conduction disorders (I44–I49). Overall, age-adjusted mortality increased substantially during the study period, from 4.85 per 100,000 in 1999 to 8.84 per 100,000 in 2024, representing an approximately 82.3% increase (AAPC 2.40%, $p < 0.000001$). This pattern is notable because it occurred despite advances in acute stroke treatment and secondary prevention. Increasing evidence recognizes that ischemic stroke and cardiovascular disease are closely interconnected, with cardiac complications contributing importantly to morbidity and mortality after stroke[18,19,20,21,22]

After a period of relative stability or mild decline from 2002 to 2012 (APC −0.62%, $p = 0.049$), a clear inflection point occurred in 2012, followed by a significant increase from 2012 to 2018 (APC 4.65%, $p < 0.00001$). The most pronounced increase occurred between 2018 and 2021 (APC 10.44%, $p = 0.0005$), with mortality reaching a peak AAMR of 8.89 per 100,000 in 2023. Although mortality subsequently plateaued from 2021 to 2024 (APC 0.86%, $p = 0.441$), the rate remained substantially higher than during the early study period. National cardiovascular surveillance has similarly demonstrated that previous improvements in cardiovascular mortality have slowed or reversed in selected populations, particularly among individuals with multiple cardiometabolic risk factors [23,24]

Disparities by Sex, Race/Ethnicity, Age, and Geography

Marked differences were observed according to sex, race/ethnicity, age, and geographic location. Male individuals consistently demonstrated higher mortality than females throughout the study period, with a somewhat greater long-term increase among males (AAPC 2.61%) than females (AAPC 2.19%). By 2024, mortality reached 9.42 per 100,000 in males compared with 8.16 per 100,000 in females. Sex differences in cardiovascular outcomes after ischemic stroke have also been documented, although both sexes remain at substantial risk of post-stroke cardiovascular events[21,23]

Important racial and ethnic disparities were also evident. Black African and American individuals had the highest baseline mortality in 1999 (12.50 per 100,000) and continued to experience a high mortality rate in 2024 (10.63 per 100,000). Although the overall AAPC among Black individuals was −0.66%, reflecting substantial reductions during the earlier study period, mortality increased significantly between 2018 and 2021 (APC 8.88%, $p = 0.038$). Previous national analyses have demonstrated persistent Black-White disparities in cardiovascular mortality. Kyalwazi et al. reported substantially higher cardiovascular mortality among Black adults compared with White adults during 1999–2019, although the

absolute mortality gap narrowed over time[25]. Geographic analyses have additionally demonstrated substantial variation in both absolute and relative Black-White stroke mortality disparities across U.S. counties.[26]

In contrast, White populations demonstrated the largest continuous long-term increase in our analysis (AAPC 2.93%, $p < 0.000001$), reducing the absolute Black-White mortality gap from approximately three-fold in 1999 to approximately 1.2-fold in 2024. American Indian or Alaska Native populations experienced a marked mid-to-late period increase, particularly from 2011 to 2022 (APC 8.38%), while Hispanic or Latino populations demonstrated a significant increase from 2014 to 2022 (APC 5.45%). These findings emphasize that racial and ethnic disparities are dynamic and may vary according to the underlying cardiovascular and cerebrovascular conditions being studied[25,26]

Geographic differences were similarly pronounced. Non-metropolitan areas demonstrated a greater long-term increase in mortality than metropolitan areas (AAPC 3.24% vs. 1.83%). Although metropolitan areas had higher mortality earlier in the study period, a crossover occurred around 2014–2015, after which mortality in rural areas increased substantially, reaching 9.06 per 100,000 in 2020 (APC 13.52%, $p = 0.0025$). This finding is consistent with recent national evidence demonstrating persistent rural-urban differences in stroke mortality in the United States[27] Similar urban-rural disparities have been observed in mortality involving cardiovascular disease and diabetes [28]

Regional variation was also observed, with the Midwest demonstrating the largest overall long-term increase (AAPC 2.88%). The Midwest, West, and South subsequently converged at similarly elevated mortality levels by 2024. Such regional heterogeneity may reflect differences in hypertension prevalence, diabetes, obesity, healthcare access, socioeconomic conditions, and preventive-care utilization. National cardiovascular surveillance has repeatedly demonstrated substantial geographic variation in cardiovascular mortality across the United States[23,24,28]

Age-specific patterns further demonstrated a changing risk profile. Adults aged ≥65 years continued to carry the greatest absolute mortality burden, reaching an AAMR of 39.69 per 100,000 in 2024. However, younger adults aged 25–44 years demonstrated a significant long-term increase (AAPC 1.20%, $p = 0.0003$). This finding is particularly relevant because increasing cardiovascular and cardiometabolic mortality among younger and middle-aged adults has also been reported in national CDC WONDER analyses

Integration With Contemporary Research

The observed mortality pattern is biologically consistent with the increasingly recognized concept of stroke-heart syndrome or the neuro-cardiac axis. Acute ischemic stroke can produce cardiac injury through complex interactions involving autonomic dysfunction, catecholamine excess, inflammation, endothelial dysfunction, and alterations in myocardial electrophysiology[18,19,22,30] Contemporary reviews describe cardiac complications after stroke as including myocardial injury, acute coronary syndromes, ventricular dysfunction, arrhythmias, and heart failure[18,19,22,29].The relationship between cerebral infarction and cardiovascular disease is also bidirectional. Chronic hypertension contributes to vascular remodeling and cardiac structural abnormalities, while cardiomyopathy and atrial disease can provide an arrhythmogenic substrate for thromboembolism.[18,19] Hypertension remains one of the most important modifiable risk factors for both stroke and cardiovascular disease, and contemporary hypertension guidelines continue to emphasize sustained blood-pressure control as a central component of cardiovascular and cerebrovascular prevention[31]

Atrial fibrillation is particularly important within this neuro-cardiac pathway. AF may contribute to cerebral infarction through cardioembolism, while acute stroke itself can precipitate autonomic and inflammatory disturbances that increase the likelihood of cardiac arrhythmias[18,19]Recent systematic reviews have demonstrated that AF may be detected after stroke even when it was not initially identified, supporting prolonged rhythm surveillance in appropriately selected patients[32,33]A recent systematic review and meta-analysis further found that AF detection increases with longer cardiac rhythm monitoring after stroke[34]

The temporal increase observed after 2012 may therefore reflect the combined effect of an increasingly complex cardiometabolic risk environment and the growing recognition of multimorbidity. Obesity, hypertension, diabetes, and heart failure frequently coexist and can amplify both cerebrovascular and cardiovascular risk. The American Heart Association has emphasized the direct relationship between obesity and cardiovascular risk factors, including hypertension, dyslipidemia, and type 2 diabetes[35]Similarly, national CDC WONDER analyses have demonstrated increasing cardiovascular and diabetes-related mortality among younger adults and persistent demographic and geographic disparities[28]

The sharp increase observed during 2018–2021 also overlaps with the COVID-19 pandemic. Although the present ecological analysis cannot establish causality, the temporal association is biologically plausible. A CDC WONDER-based national study reported a 4.6% increase in cardiovascular mortality in 2020 compared with 2019, with particularly pronounced increases among younger adults, Black adults,

and Hispanic adults[36]Increases were also observed in hypertensive and cerebrovascular mortality. COVID-19 has additionally been associated with endothelial dysfunction, inflammation, platelet activation, and thromboid inflammatory responses, providing potential biological mechanisms for increased cardiovascular and cerebrovascular risk[37]Therefore, pandemic-related disruption of healthcare access and chronic disease management may have contributed alongside direct biological effects, although these mechanisms cannot be separated using mortality data alone.

The place-of-death findings provide an additional important perspective. Between 2018 and 2024, 41.49% of deaths occurred at home, 24.08% in nursing homes or long-term care facilities, and only 14.77% in inpatient medical units. This distribution indicates that a substantial proportion of deaths occurred outside conventional acute hospital settings. Consequently, prevention of neuro-cardiac mortality may need to extend beyond hospital-based stroke treatment and include earlier identification of arrhythmias, improved outpatient blood-pressure management, remote monitoring, and timely access to emergency services.

Implications for Public Health and Clinical Practice

From a public-health perspective, these findings support a shift toward integrated prevention of neurological and cardiovascular disease rather than considering cerebral infarction and cardiac disease as isolated conditions. The simultaneous increase observed across several demographic and geographic groups indicates that improvements in acute treatment alone may be insufficient when underlying risk factors and healthcare-access barriers remain substantial. National cardiovascular surveillance has emphasized the continuing importance of hypertension, diabetes, obesity, and other modifiable risk factors in determining population-level cardiovascular outcomes[38]

The higher and more rapidly increasing mortality observed in non-metropolitan populations highlights the importance of reducing geographic barriers to specialized care. Potential approaches include strengthening regional stroke networks, improving emergency medical transport, expanding tele-stroke services, and integrating cardiac monitoring into post-stroke pathways. Recent evidence demonstrating persistent rural-urban differences in stroke mortality further supports the need for geographically targeted strategies[28]

Clinically, the findings reinforce the importance of coordinated neurological and cardiovascular evaluation after ischemic stroke. Stroke-heart syndrome can manifest through arrhythmias, myocardial injury, ventricular dysfunction, and other cardiovascular complications[30,18,29]The European Society of Cardiology

Council on Stroke has similarly emphasized integrated management of stroke and associated heart disease, including antithrombotic therapy, cardiovascular risk-factor control, and multidisciplinary care[39]

Extended cardiac monitoring may be particularly relevant in patients with suspected occult AF or cryptogenic/embolic stroke. Recent systematic reviews indicate that longer-duration monitoring improves AF detection compared with limited monitoring strategies ,The AHA/ASA guidelines also recommend cardiac rhythm monitoring for occult AF when no other cause of stroke is identified[23].For patients with confirmed AF, anticoagulation remains an important component of secondary prevention when clinically appropriate, although the timing of initiation after acute ischemic stroke requires individualized assessment [40].

Heart failure and cardiomyopathy should also be incorporated into post-stroke risk assessment. Contemporary heart-failure guidelines emphasize guideline-directed medical therapy and multidisciplinary management for patients with heart failure, while emerging evidence continues to demonstrate the clinical importance of cardiac dysfunction after stroke [41].

Strengths and Limitations

This study has several important strengths. First, the CDC WONDER database provides a large national dataset allowing longitudinal examination of mortality patterns across the United States over 25 years. Second, the study evaluates multiple demographic and geographic dimensions, including age, sex, race/ethnicity, urbanization, census region, and place of death. Third, the use of age-adjusted mortality rates and join point-based APC and AAPC estimates allows identification of changes in temporal trends that may be obscured by crude mortality rates.

Several limitations should nevertheless be considered. First, CDC WONDER mortality data are based on death certificates and therefore depend on the accuracy and completeness of cause-of-death documentation and ICD coding. Misclassification or under-recognition of cardiac complications may therefore affect the observed estimates. Second, the ecological nature of the analysis prevents adjustment for individual-level clinical variables, including left ventricular ejection fraction, stroke severity, infarct location, specific anticoagulant or antiarrhythmic treatment, thrombectomy status, medication adherence, and comorbid disease burden. Third, the presence of a condition on a death certificate does not establish a direct causal relationship between cerebral infarction and cardiac disease. Fourth, temporal associations, particularly during the COVID-19

period, cannot establish causality. Finally, suppression of small cell counts in certain demographic or geographic subgroups may limit the precision of some subgroup estimates.

Future Prospects

Future studies should link population-level mortality surveillance with patient-level clinical and cardiovascular registries. Such linkage could clarify how stroke severity, cardiac function, arrhythmia burden, anticoagulation, heart-failure treatment, and acute reperfusion therapies contribute to long-term neuro-cardiac outcomes. Further research should also evaluate whether contemporary therapeutic strategies, including direct oral anticoagulants, SGLT2 inhibitors, guideline-directed heart-failure therapy, and prolonged rhythm monitoring, are associated with changes in neuro-cardiac mortality [24,25,26].

Future research should additionally investigate whether AI-assisted risk stratification can identify patients at particularly high risk for post-stroke arrhythmia, myocardial injury, or autonomic dysfunction. Recent evidence suggests that prediction models for AF after stroke may have potential utility, although prospective validation and assessment of clinical impact remain necessary before routine implementation [34]. Integration of wearable cardiac monitoring, remote blood-pressure monitoring, telemedicine, and electronic-health-record-based prediction models may facilitate earlier detection of cardiovascular complications after cerebral infarction. Furthermore, data from the Centers for Disease Control and Prevention (CDC) WONDER multiple cause of death database provide the foundation for tracking these mortality trends [42].

Overall, the present findings demonstrate substantial changes in mortality involving cerebral infarction and coexisting cardiovascular disease in the United States between 1999 and 2024. The persistent differences according to sex, race/ethnicity, age, and geography indicate that neuro-cardiac mortality represents a complex intersection of cerebrovascular disease, cardiovascular risk, multimorbidity, and healthcare access. Continued integration of stroke and cardiovascular prevention, improved detection of occult cardiac disease, and attention to geographic and demographic disparities will be important areas for future investigation.

Conclusion

Over the 25-year study period (1999–2024), mortality involving cerebral infarction with underlying hypertensive disease, cardiomyopathy, and tachyarrhythmias/conduction disorders in the United States increased significantly by 82.3%, reaching an age-adjusted mortality rate of 8.84 per 100,000 population in 2024. This increase was characterized by a marked acceleration between 2018 and 2021. Substantial demographic and geographic disparities persisted throughout the study period, with males, adults aged ≥65 years, and residents of non-metropolitan areas experiencing higher mortality and greater long-term increases. Black or African American individuals consistently had the highest absolute mortality rates; however, the disparity between Black and White populations narrowed over time because of a sustained increase in mortality among White adults. Notably, more than 65% of deaths occurred outside acute inpatient hospital settings. These findings underscore the growing public health burden of neuro-cardiac comorbidity and support the need for integrated secondary prevention, early recognition and surveillance of arrhythmias, and improved access to cardiovascular and cerebrovascular care, particularly among rural and other high-risk populations.

DECLARATIONS

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Ethical Approval

Not applicable.

Data availability statement

The data that support the findings of this study are publicly available from the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) system at https://wonder.cdc.gov/

Competing interests

The authors declare no competing interests

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Consent

Not applicable.

Consent for Publication

All authors have agreed to this study.

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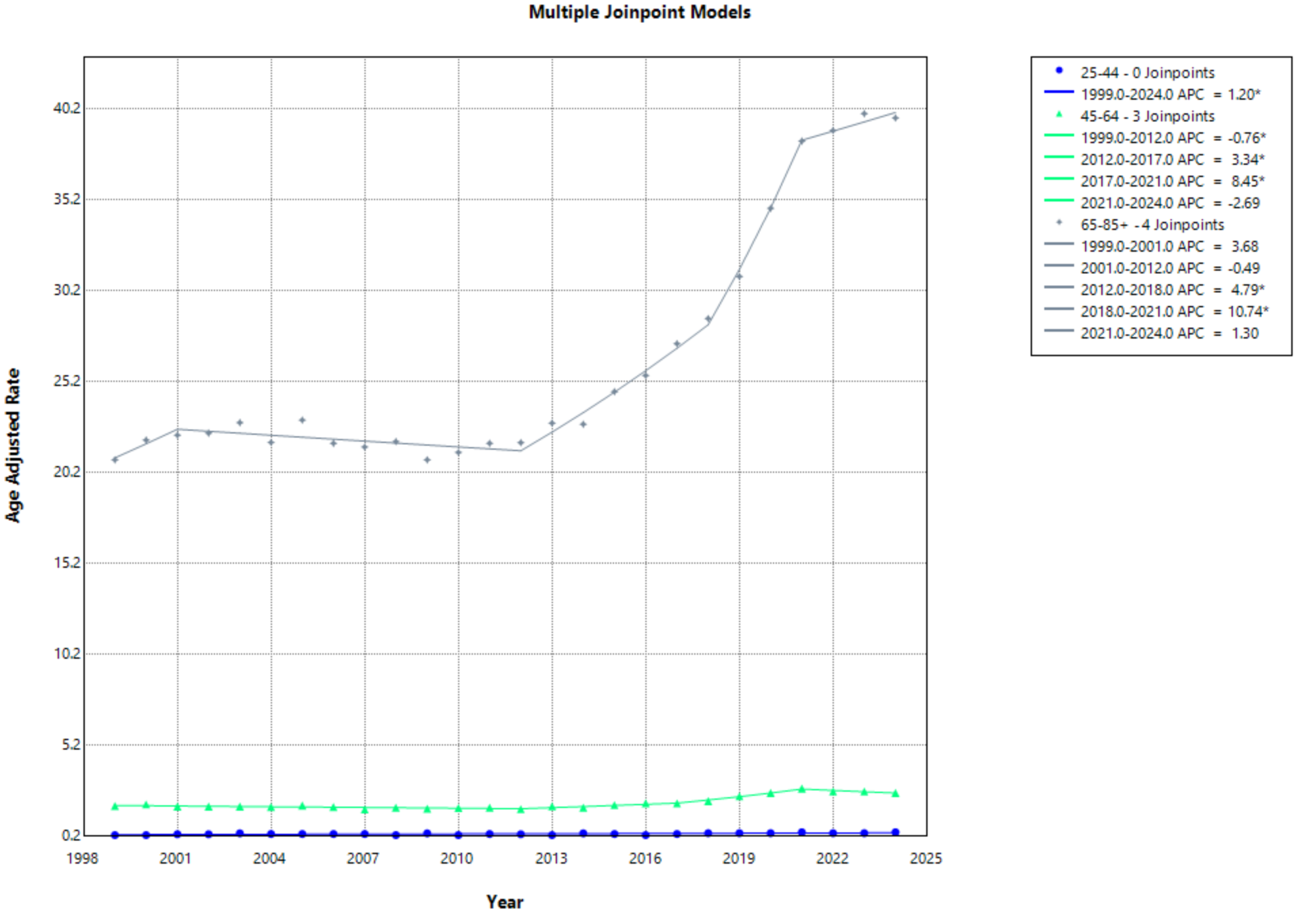
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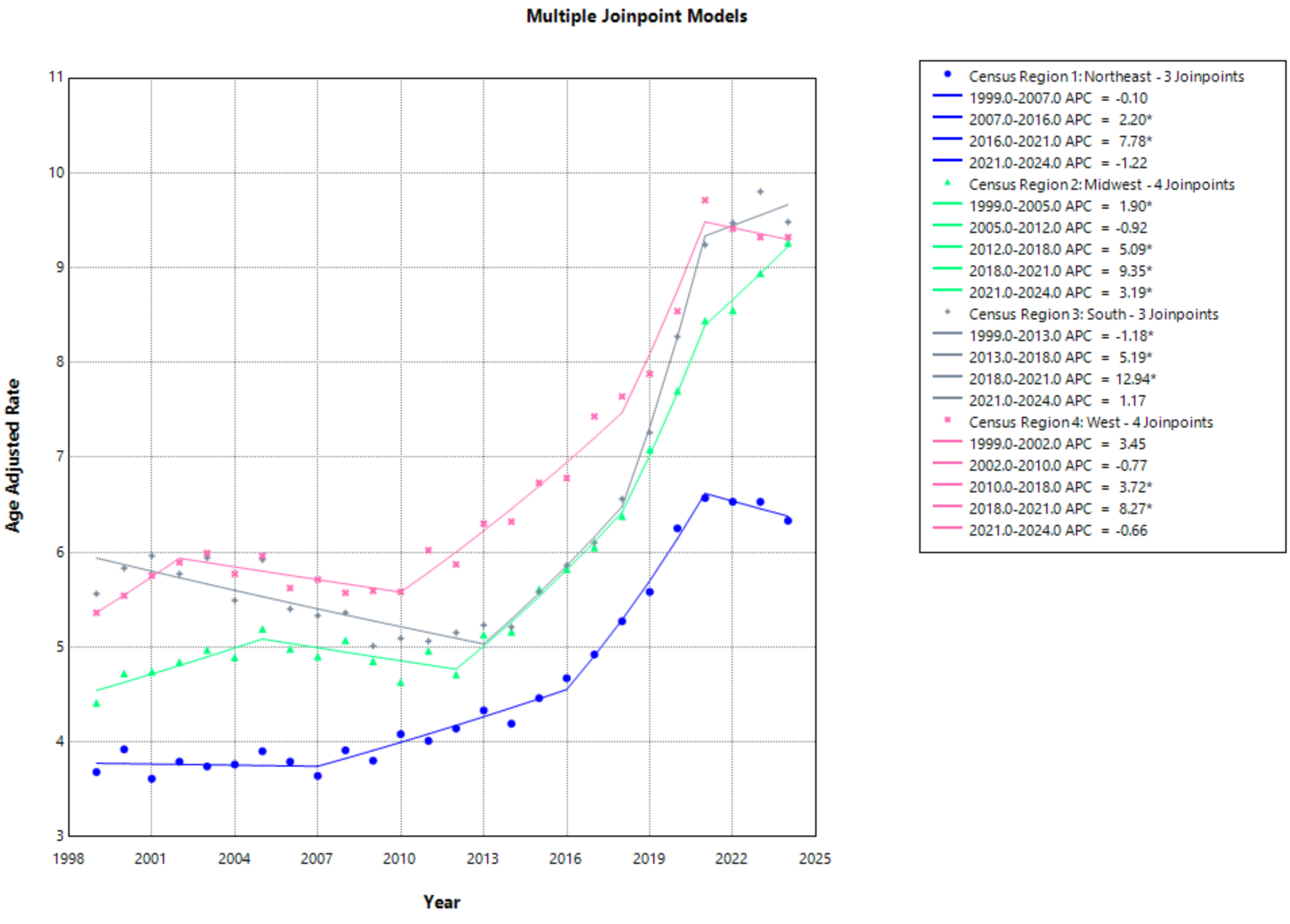
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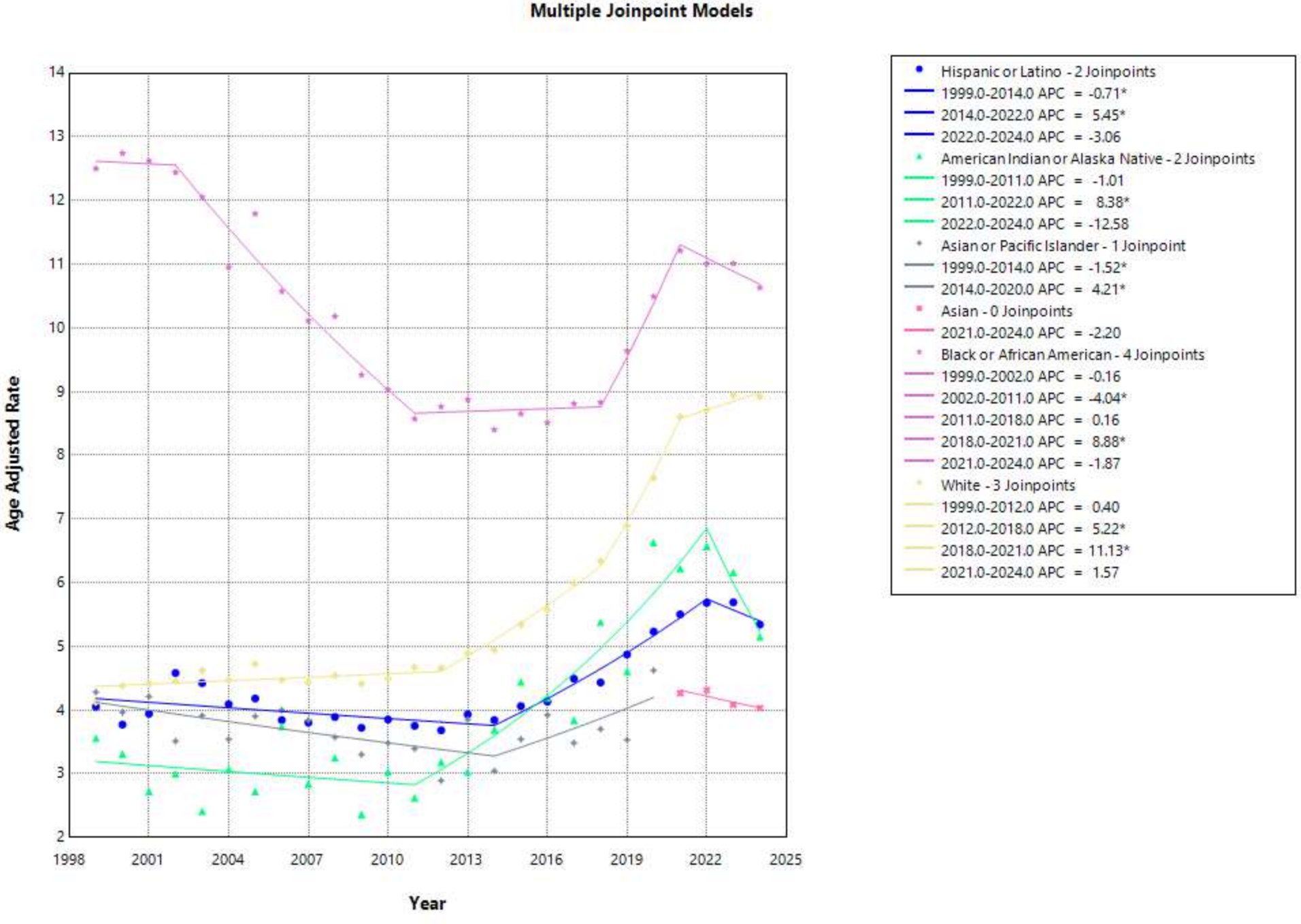
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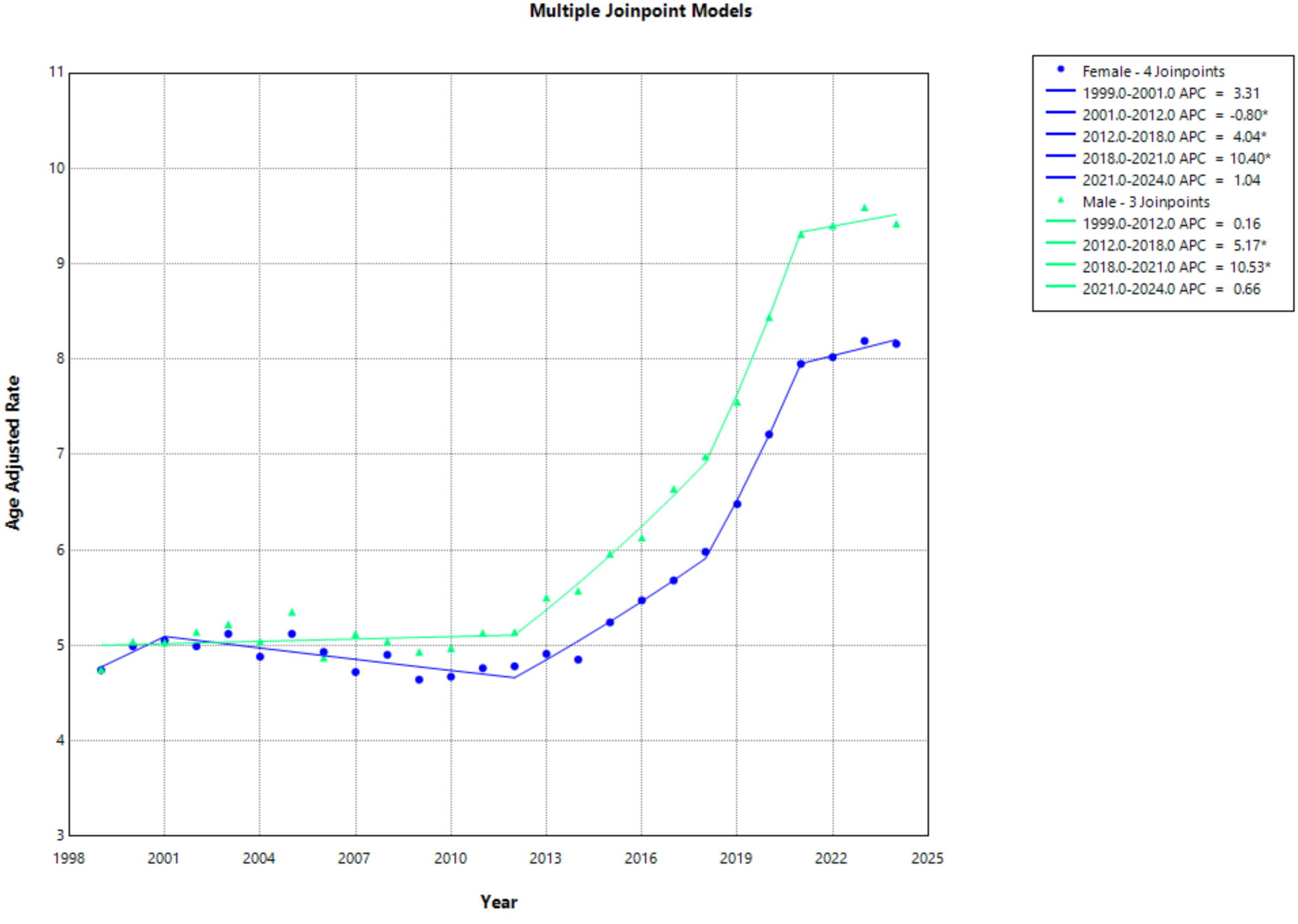
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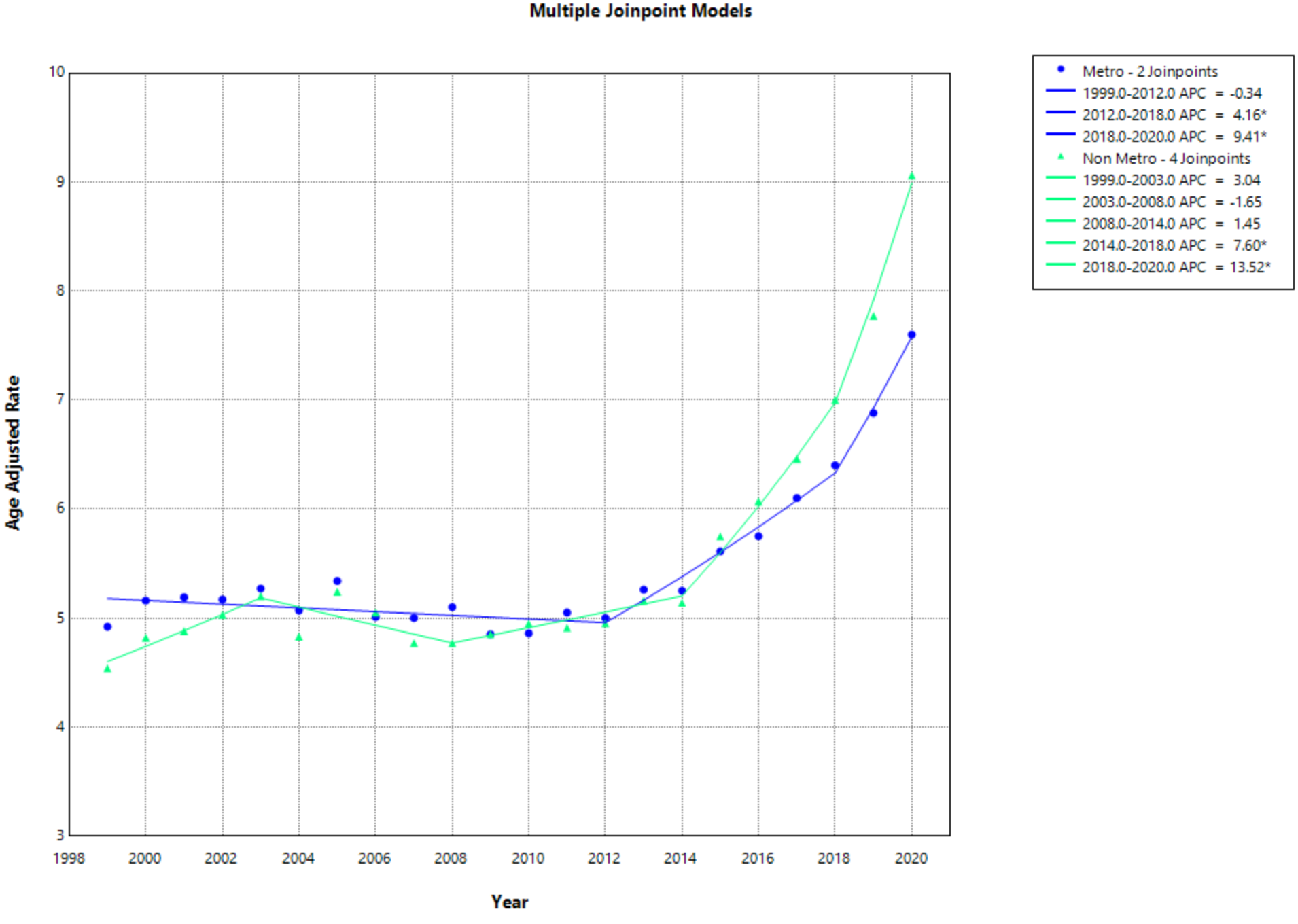
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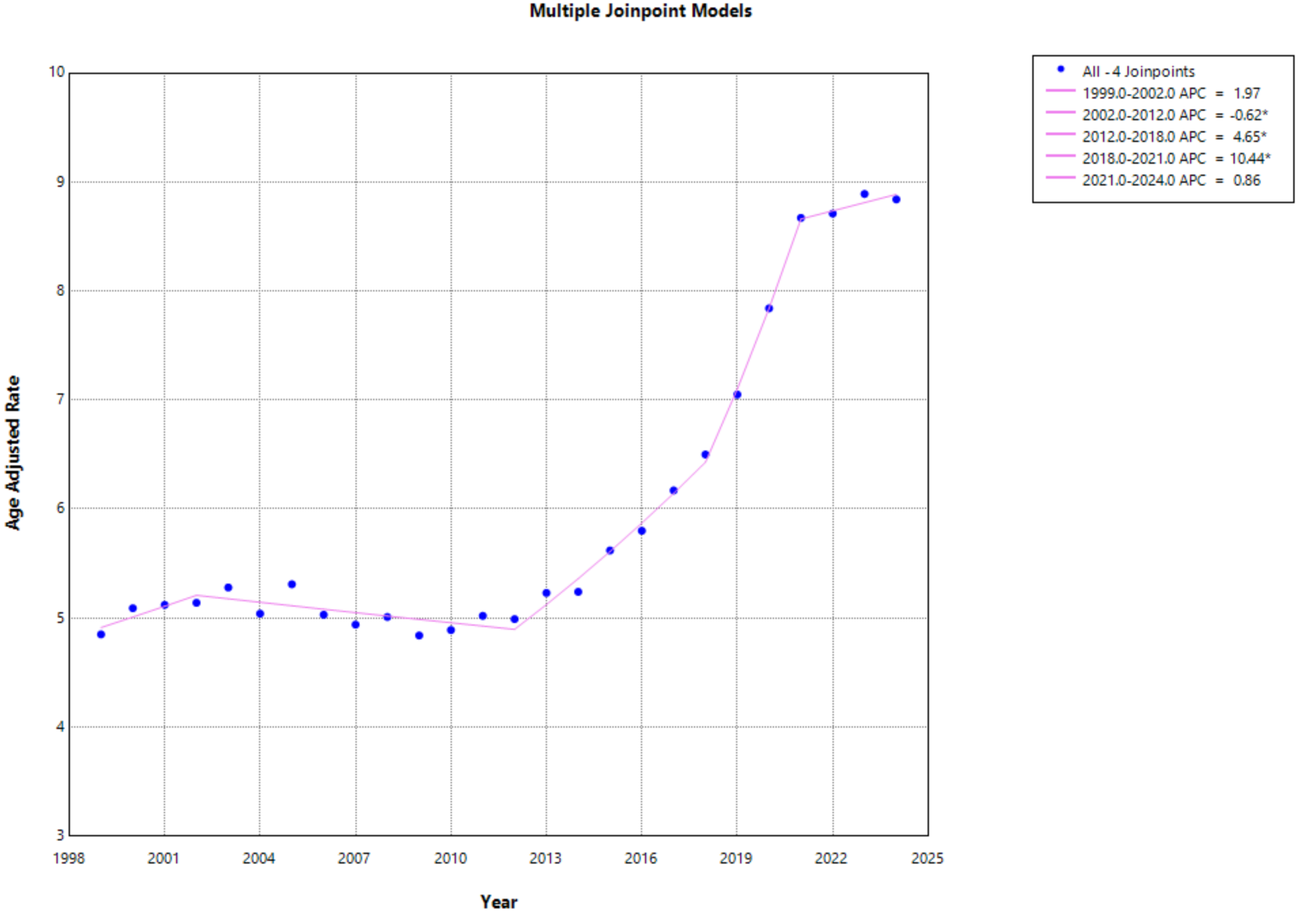

Multiple Joinpoint Models
Age Adjusted Rate
Year
40.2
35.2
30.2
25.2
20.2
15.2
10.2
5.2
0.2
1998
2001
2004
2007
2010
2013
2016
2019
2022
2025
25-44 - 0 Joinpoints
1999.0-2024.0 APC = 1.20*
45-64 - 3 Joinpoints
1999.0-2012.0 APC = -0.76*
2012.0-2017.0 APC = 3.34*
2017.0-2021.0 APC = 8.45*
2021.0-2024.0 APC = -2.69
65-85+ - 4 Joinpoints
1999.0-2001.0 APC = 3.68
2001.0-2012.0 APC = -0.49
2012.0-2018.0 APC = 4.79*
2018.0-2021.0 APC = 10.74*
2021.0-2024.0 APC = 1.30


Multiple Joinpoint Models
Age Adjusted Rate
Year
11
10
9
8
7
6
5
4
3
1998
2001
2004
2007
2010
2013
2016
2019
2022
2025
Census Region 1: Northeast - 3 Joinpoints
1999.0-2007.0 APC = -0.10
2007.0-2016.0 APC = 2.20*
2016.0-2021.0 APC = 7.78*
2021.0-2024.0 APC = -1.22
Census Region 2: Midwest - 4 Joinpoints
1999.0-2005.0 APC = 1.90*
2005.0-2012.0 APC = -0.92
2012.0-2018.0 APC = 5.09*
2018.0-2021.0 APC = 9.35*
2021.0-2024.0 APC = 3.19*
Census Region 3: South - 3 Joinpoints
1999.0-2013.0 APC = -1.18*
2013.0-2018.0 APC = 5.19*
2018.0-2021.0 APC = 12.94*
2021.0-2024.0 APC = 1.17
Census Region 4: West - 4 Joinpoints
1999.0-2002.0 APC = 3.45
2002.0-2010.0 APC = -0.77
2010.0-2018.0 APC = 3.72*
2018.0-2021.0 APC = 8.27*
2021.0-2024.0 APC = -0.66


Multiple Joinpoint Models
Age Adjusted Rate
Year
14
13
12
11
10
9
8
7
6
5
4
3
2
1998
2001
2004
2007
2010
2013
2016
2019
2022
2025
Hispanic or Latino - 2 Joinpoints
1999.0-2014.0 APC = -0.71*
2014.0-2022.0 APC = 5.45*
2022.0-2024.0 APC = -3.06
American Indian or Alaska Native - 2 Joinpoints
1999.0-2011.0 APC = -1.01
2011.0-2022.0 APC = 8.38*
2022.0-2024.0 APC = -12.58
Asian or Pacific Islander - 1 Joinpoint
1999.0-2014.0 APC = -1.52*
2014.0-2020.0 APC = 4.21*
Asian - 0 Joinpoints
2021.0-2024.0 APC = -2.20
Black or African American - 4 Joinpoints
1999.0-2002.0 APC = -0.16
2002.0-2011.0 APC = -4.04*
2011.0-2018.0 APC = 0.16
2018.0-2021.0 APC = 8.88*
2021.0-2024.0 APC = -1.87
White - 3 Joinpoints
1999.0-2012.0 APC = 0.40
2012.0-2018.0 APC = 5.22*
2018.0-2021.0 APC = 11.13*
2021.0-2024.0 APC = 1.57

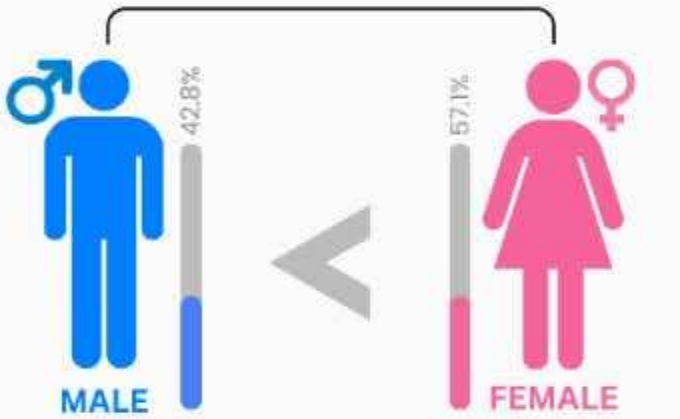

Multiple Joinpoint Models
Female - 4 Joinpoints
1999.0-2001.0 APC = 3.31
2001.0-2012.0 APC = -0.80*
2012.0-2018.0 APC = 4.04*
2018.0-2021.0 APC = 10.40*
2021.0-2024.0 APC = 1.04
Male - 3 Joinpoints
1999.0-2012.0 APC = 0.16
2012.0-2018.0 APC = 5.17*
2018.0-2021.0 APC = 10.53*
2021.0-2024.0 APC = 0.66
Age Adjusted Rate
Year
11
10
9
8
7
6
5
4
3
1998
2001
2004
2007
2010
2013
2016
2019
2022
2025


Multiple Joinpoint Models
Age Adjusted Rate
Year
10
9
8
7
6
5
4
3
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
Metro - 2 Joinpoints
1999.0-2012.0 APC = -0.34
2012.0-2018.0 APC = 4.16*
2018.0-2020.0 APC = 9.41*
Non Metro - 4 Joinpoints
1999.0-2003.0 APC = 3.04
2003.0-2008.0 APC = -1.65
2008.0-2014.0 APC = 1.45
2014.0-2018.0 APC = 7.60*
2018.0-2020.0 APC = 13.52*


Multiple Joinpoint Models
All - 4 Joinpoints
1999.0-2002.0 APC = 1.97
2002.0-2012.0 APC = -0.62*
2012.0-2018.0 APC = 4.65*
2018.0-2021.0 APC = 10.44*
2021.0-2024.0 APC = 0.86
Age Adjusted Rate
Year
10
9
8
7
6
5
4
3
1998
2001
2004
2007
2010
2013
2016
2019
2022
2025

"Neuro-Cardiac Collapse in Cerebral Infarction: A 25-Year CDC WONDER Mortality Analysis of Hypertensive Disease, Cardiomyopathy, and Tachyarrhythmias (1999–2024)"

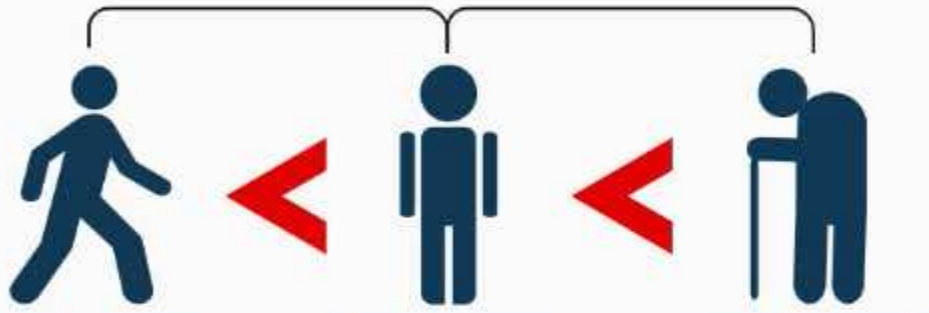
GENDER DISPARITIES



MALE
1999 **AAMR** = *4.75*
2024 **AAMR** = 9.42

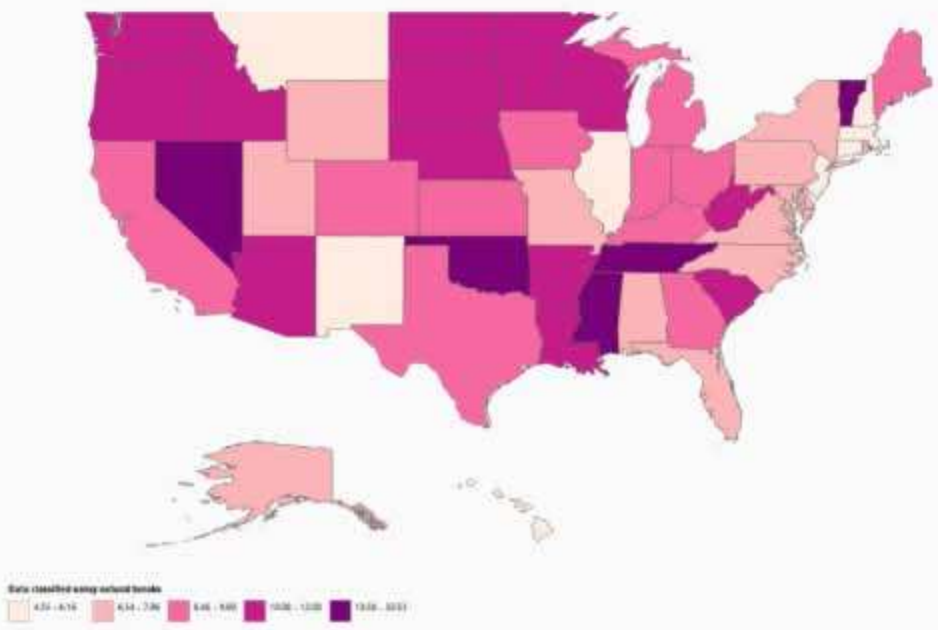
FEMALE
1999 **AAMR** = *4.74*
2024 **AAMR** = *8.16*

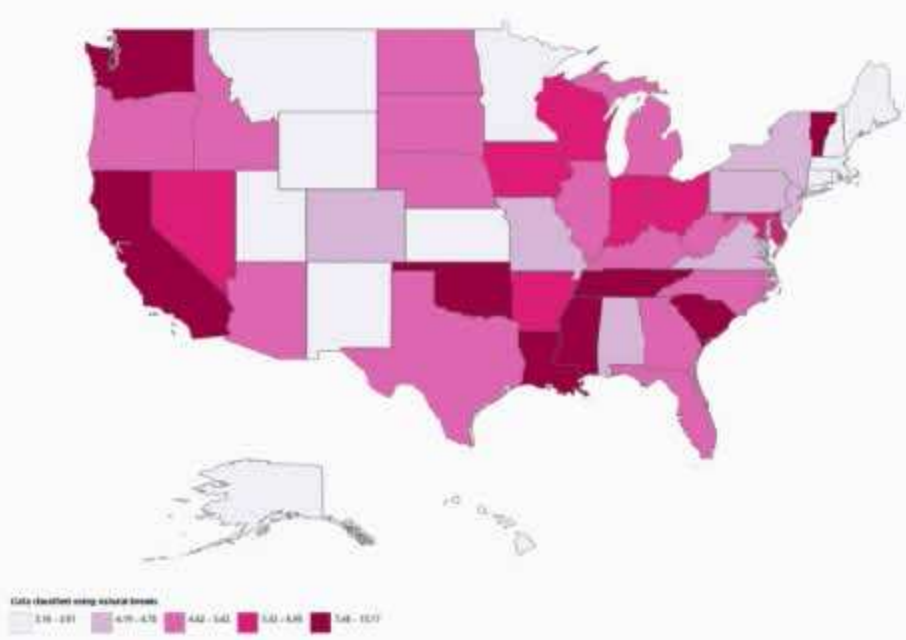
AGE DISPARITIES



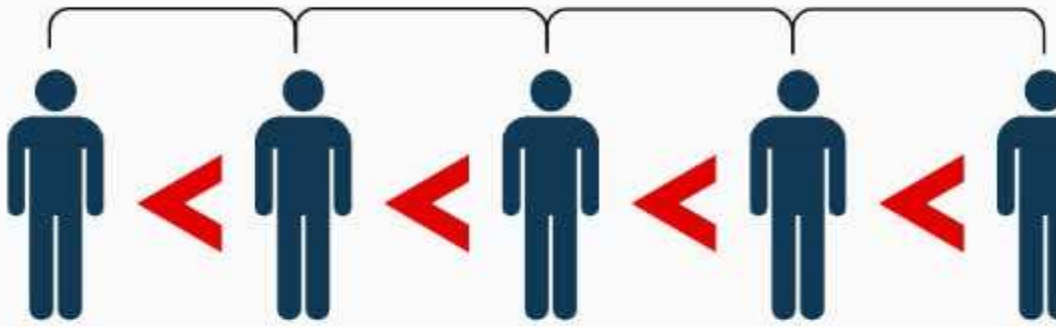
25-44 YEARS	45-64 YEARS	65-85+ YEARS
AAMR	AAMR	AAMR
1999 **0.26**	1999 **1.87**	1999 **20.89**
2024 **0.42**	2024 **2.58**	2024 **39.69**

LOCATION WISE AAMR PER 100,000 PEOPLE



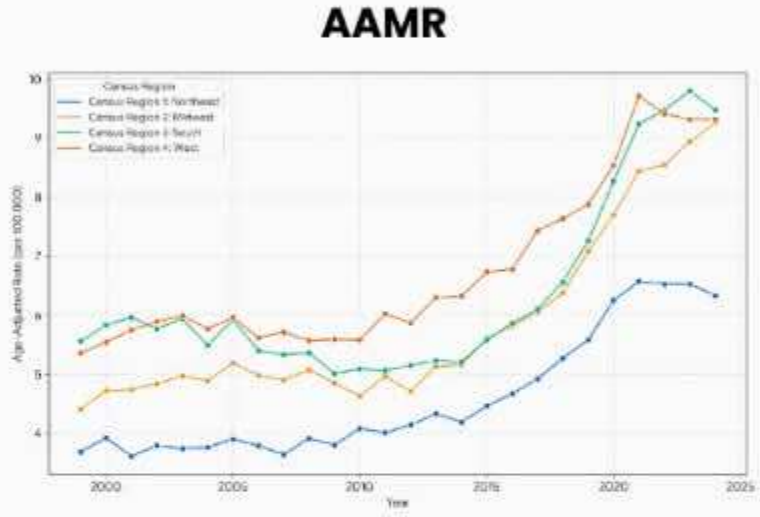


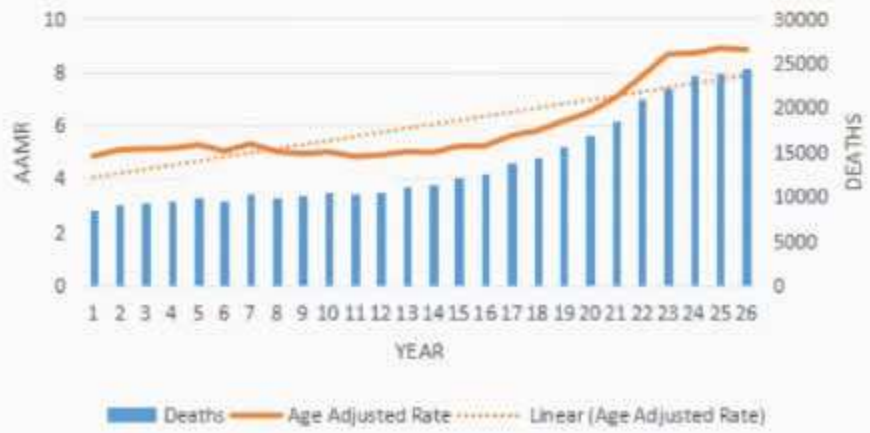
RACIAL DISPARITIES



ASIAN	AMERICAN INDIAN	WHITE	HISPANIC	BLACK
AAMR	AAMR	AAMR	AAMR	AAMR
1999 4.28	1999 3.56	1999 4.12	1999 4.02	1999 12.5
2024 4.03	2024 5.15	2024 8.92	2024 5.34	2024 10.63

CENSUS REGION AAMR





OVERALL AAMR

Over the 26-year study period, both absolute crude deaths and the overall Age-Adjusted Mortality Rate (AAMR) demonstrated a significant upward trajectory, as illustrated by the linear trendline. The AAMR remained relatively stable in the initial phase (Years 1–15) before exhibiting a sharp accelerated increase from Year 16 onward, peaking above 8 per 100,000 population.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Race1analysisTrend.png
- censusregion1trends.png
- ageAnalysisTrend.png
- Race2analysisTrend.png
- censusregion2anaysisTrens.png
- sexanalysisTrend.png
- YearanalysisTrends.png
- urbanizationanalysisTrend.png
- censusANALYSISSFILEFINAL.xlsx
- CensusGRAPHFILEFINAL.xlsx
- yearanalysisfile.xlsx
- Urbanisationanalysisfile.xlsx
- AGEANALYSISFILE.xlsx
- URBANISATIONTABLEFILE.xlsx
- YEARTABLEFILE.xlsx
- RACETABLEFILE.xlsx
- censusTABLEFILEE.xlsx
- PODTABLE.xls
- raceanalysisfile.xlsx
- urbanisationgraphfile.xlsx
- AGEETABLEEFILEE.xlsx
- sexgraphfile.xlsx
- SEXANALYSISTABLEFILE.xlsx
- YEargraphfile.xlsx
- statetablefile20202024.xlsx
- sextablefile.xlsx
- statetablefile19992020.xlsx
- racegraphfile.xlsx