



Article

Rising Burden of Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death in the United States, 1999–2024

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Abstract

Background: Inherited arrhythmic syndromes (IAS) are an important but under-recognized cause of sudden cardiac death (SCD), particularly in younger individuals. Understanding long-term mortality trends is essential to evaluate their public health impact. **Objective:** To assess temporal trends and demographic disparities of IAS-related sudden cardiac death among individuals aged 5–44 years in the United States using CDC WONDER data. **Methods:** This retrospective observational study utilized the CDC WONDER Multiple Cause-of-Death database from 1999 to 2024. Deaths were identified using ICD-10 codes for non-ischemic arrhythmogenic conditions (I42, I44, I45, I47, I49) in combination with sudden cardiac arrest or unexplained death (I46, R96). Ischemic heart disease (I20–I25) was excluded to enhance specificity for inherited causes. Crude and age-adjusted mortality rates (AAMRs) per 1,000,000 population were calculated and stratified by age, sex, race/ethnicity, region, urbanization, and place of death. Joinpoint software helped us calculate the average annual percentage change (AAPC)/annual percent change (APC) in AAMRs and the 95% CIs for these changes. **Results:** A total of 8879 deaths were identified over the study period. The AAMR increased from 1.46 (95% CI: 1.27–1.64) in 1999 to 3.15 (95% CI: 2.89–3.42) in 2024, peaking at 4.54 in 2021, with an overall AAPC of 3.71% ($p < 0.000001$). Mortality was higher in males; however, females demonstrated a greater relative increase over time. Non-Hispanic Black individuals exhibited the highest mortality rates and fastest rise. The 25–44-year age group accounted for most deaths and showed the steepest increase. Regional and urban–rural disparities were observed, with higher mortality rates in the South and rural areas. **Conclusions:** It is concluded that mortality related to inherited arrhythmic syndromes and sudden cardiac death is rising among young individuals in the United States. The findings highlight a growing burden of potentially inherited arrhythmogenic conditions and underscore the need for early detection strategies, including genetic screening and targeted public health interventions, to reduce premature cardiovascular mortality.

Keywords: inherited arrhythmic syndromes; sudden cardiac death; young individuals



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1. Introduction

Sudden cardiac death (SCD) remains a major cause of cardiovascular mortality worldwide and represents a substantial public health burden. In the United States, SCD accounts for an estimated 350,000–450,000 deaths annually and frequently occurs unexpectedly in individuals without previously recognized cardiovascular disease [1]. Although most cases occur in the setting of ischemic heart disease and structural cardiac pathology, a disproportionately high burden of SCD among younger individuals has been associated with non-ischemic arrhythmogenic conditions and cardiac phenotypes compatible with inherited susceptibility [2,3]. These include inherited or potentially inherited cardiomyopathies such as hypertrophic cardiomyopathy and arrhythmogenic cardiomyopathy, as well as primary electrical disorders including long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. In these conditions, ventricular arrhythmias may arise from myocardial structural abnormalities, ion-channel dysfunction, or electrophysiologic instability, predisposing affected individuals to sudden cardiac arrest and premature mortality [3,4].

Over the past decade, increasing attention has been directed toward the epidemiology of SCD in younger populations and toward cardiovascular conditions potentially associated with inherited arrhythmogenic risk. Shah et al. demonstrated persistent mortality attributable to sudden cardiac arrest and highlighted substantial demographic disparities in cardiovascular death patterns across the United States [5]. More recent analyses by Sayed et al. and Maqsood et al. further emphasized the growing contribution of arrhythmia-related and cardiovascular mortality during the post-2019 and COVID-19 eras, including widening racial inequities and shifts in mortality trajectories detectable through CDC WONDER-based analyses [6,7]. Additional contemporary investigations by Zuin et al., Bhagwan et al., and Khan et al. reported increasing national mortality trends related to arrhythmias, heart failure, and sudden cardiac death, while also identifying important regional and sex-based differences in cardiovascular outcomes [8–10]. Collectively, these studies suggest that arrhythmogenic mortality in the United States may be increasing, particularly among younger adults and historically underserved populations.

Despite these important contributions, several limitations remain in the current literature. Prior studies have generally evaluated either overall SCD burden, isolated arrhythmia diagnoses, heart failure-related mortality, or broad cardiovascular mortality trends rather than specifically examining non-ischemic arrhythmogenic conditions occurring concurrently with sudden cardiac arrest in younger populations. Furthermore, many analyses did not specifically exclude ischemic heart disease, making it difficult to distinguish mortality patterns potentially associated with inherited or non-atherosclerotic arrhythmogenic substrates. Existing studies have also provided limited characterization of long-term demographic and geographic disparities among younger individuals at risk for arrhythmogenic sudden death.

Accordingly, the present study aimed to evaluate national mortality trends related to potentially inherited arrhythmogenic syndromes (PIAS) and sudden cardiac death among individuals aged 5–44 years in the United States from 1999 to 2024 using the CDC WONDER Multiple Cause-of-Death database. Importantly, the ICD-10 codes utilized in this analysis were intended as clinical proxies for non-ischemic arrhythmogenic conditions compatible with inherited etiologies rather than confirmed genetic diagnoses. By excluding ischemic heart disease and focusing on younger age groups, this study sought to better characterize temporal trends, demographic disparities, and geographic variation in mortality associated with arrhythmogenic phenotypes that may reflect underlying inherited susceptibility.

2. Materials and Methods

This study is exempt from institutional review board (IRB) approval because of the use of a deidentified government-issued public use database.

2.1. Data Source

We obtained mortality data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause-of-Death Public Use database (Centers for Disease Control and Prevention, Atlanta, GA, USA) for the period 1 January 1999 through 31 December 2024 [11]. We identified death certificates listing arrhythmogenic conditions consistent with inherited etiologies and sudden cardiac arrest as either underlying or contributing causes of death using the International Statistical Classification of Diseases, Tenth Revision (ICD-10 codes). To enhance specificity for non-ischemic cardiomyopathic and arrhythmogenic mortality, we identified decedents aged 5–44 years with any mention of ICD-10 codes I42, I44, I45, I47, or I49 in conjunction with sudden cardiac arrest (I46) or sudden unexplained death (R96) within the Multiple Cause-of-Death record axis (Supplementary Table S1). Atrial Fibrillation (I48) was deliberately excluded as it represents predominantly acquired pathology via hypertension, obesity and structural heart disease rather than primarily inherited arrhythmogenic diseases. The added codes were utilized as clinical proxies for inherited arrhythmogenic etiologies; consequently, ischemic heart disease (I20–I25) was excluded from underlying causes to maximize specificity and reduce confounding from atherosclerotic pathology. However, given the limitations of ICD-10 coding within CDC WONDER, this grouping encompasses arrhythmias, conduction disorders, cardiomyopathies, and congenital anomalies as a heterogeneous composite. Our reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12].

2.2. Data Extraction

Information regarding deaths in patients with concurrent sudden cardiac arrest and inherited arrhythmias, as well as population sizes, years, demographics such as age, sex, ethnicity or racial background, along with census regions, urbanization classifications, states and place of death, was extracted. Race/ethnicity was coded according to the U.S. Office of Management and Budget regulations. It was used as stated on death certificates, with the classifications being as non-Hispanic (NH) White, NH Black, NH American Indian or Alaska Native, NH Asian or Pacific Islander, and Hispanic or Latino [11]. Moreover, regions were defined per U.S. Census 127 Bureau classification as Northeast, Midwest, South, and the West [13]. The National Center for Health Statistics Urban–Rural Classification Scheme was used to categorize the populations. These statistics were based on the 2013 U.S. Census classification. It comprises the urban population that includes large metropolitan areas with a population of ≥ 1 million, medium/small metro areas with a population of 50,000–999,999, and the rural regions with a population of $< 50,000$ [14]. The place of death was categorized based on where the person died, such as in a hospital (inpatient, outpatient, emergency room), at home, in a hospice, nursing home, long-term care facility, or if they were dead on arrival or had an unknown location.

2.3. Statistical Analysis

To analyze national trends in patients with concurrent sudden cardiac arrest and inherited arrhythmias, we calculated crude mortality rates (CMRs) and age-adjusted mortality rates (AAMRs) per 1,000,000 population from 1999 to 2024. Rates were stratified by age

groups, year, sex, race/ethnicity, census regions, states, urban–rural classification, and place of death. We calculated the rates using 95% confidence intervals (CIs) to show the range in which the true values likely fall. To find the CMRs, we divided the number of deaths caused by the total U.S. population for that year. For AAMRs, we adjusted the death counts based on the age distribution of the population in the year 2000 [15]. To analyze how these rates changed over time, we used the Joinpoint Regression Program (version 5.2.0) from the National Cancer Institute, Bethesda, MD, USA [16]. This software helped us calculate the annual percent change (APC) in AAMRs and the 95% CIs for these changes. The program uses log-linear regression models to identify when significant shifts occurred in the trend. We used a statistical method called the Weighted BIC test to find the APCs for each time segment between these change points (joinpoints). To reduce the pandemic dataset-driven understanding of the trends, custom ranges were specified within Joinpoint to evaluate period-specific trends corresponding to two decades of pre-pandemic (1999–2009 and 2010–2019), followed by pandemic (2020–2022) and post-pandemic phases (2023–2024) (Supplementary Table S10). To decide if the changes in mortality were increasing or decreasing, we applied a two-tailed *t*-test. A *p*-value of 0.05 or less was considered statistically significant, meaning the change was unlikely to have occurred by chance.

3. Results

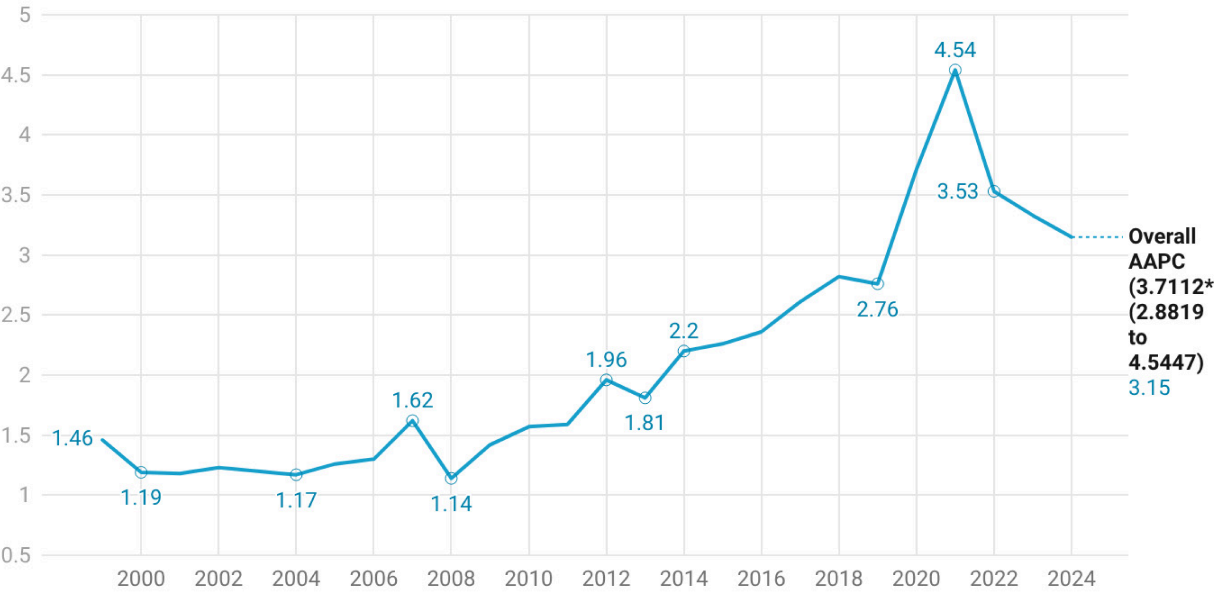
3.1. Overall

A total of 8879 deaths were related to arrhythmogenic phenotypes suggestive of inherited syndromes and sudden cardiac death between 1999 and 2024. The age-adjusted mortality rates (AAMR) per million increased from 1.46 (95% CI 1.27–1.64) in 1999 to 3.15 (95% CI 2.89–3.42) in 2024, peaking in 2021 with an AAMR of 4.54 (95% CI 4.22–4.88) (Figure 1, Supplementary Table S2). With an average annual percentage change (AAPC) of 3.71* (95% CI 2.88–4.54, $p < 0.000001$), mortality rates demonstrated an upward trend over the study period. An APC of 9.39%* (95% CI 7.87–14.10, $p < 0.000001$) demonstrated the greatest rise between 2010 (1.57) and 2019 (2.76). APC of $-7.59\%^*$ (95% CI -18.13 – -0.57 , $p = 0.036$) showed a significant fall from 2023 (3.33) to 2024 (3.15). Non-significant APCs were observed between 1999 and 2009 (APC = 0.70 (95% CI -0.96 – 3.33 , $p = 0.32$)) and 2020 and 2022 (APC = 0.54 (95% CI -0.61 – 9.51 , $p = 0.81$)).

3.2. Sex

Males exhibited slightly higher AAMRs compared to females. From 1999 to 2024, males accounted for 5174 deaths, while females accounted for 3704 deaths (Figure 2, Supplementary Table S2). Between 1999 and 2024, males showed an overall increase, with an AAPC of 2.64* (95% CI 1.85–3.61, $p < 0.000001$), with their AAMR increasing from 1.78 to 3.53. In the same period, the female AAMR increased from 1.16 to 2.73 with an AAPC of 3.95* (95% CI 2.80–5.10, $p < 0.000001$). Both their AAMRs peaked in 2021 at 5.10 vs. 3.93. Looking at a time period with significant trends, between 2010 and 2019, both males 6.77* (95% CI 6.19–8.33, $p < 0.000001$) and females 10.17* (95% CI 8.44–12.83, $p < 0.000001$) exhibited steeply rising AAPCs. Additionally, males showed a significant decline in trend between 2023 and 2024 with an AAPC of $-11.83\%^*$ (95% CI -18.67 – -6.76 , $p < 0.000001$). For these same two years, females did not exhibit a significant AAPC (-6.65 (95% CI -20.5 – 2.46 , $p = 0.118376$)).

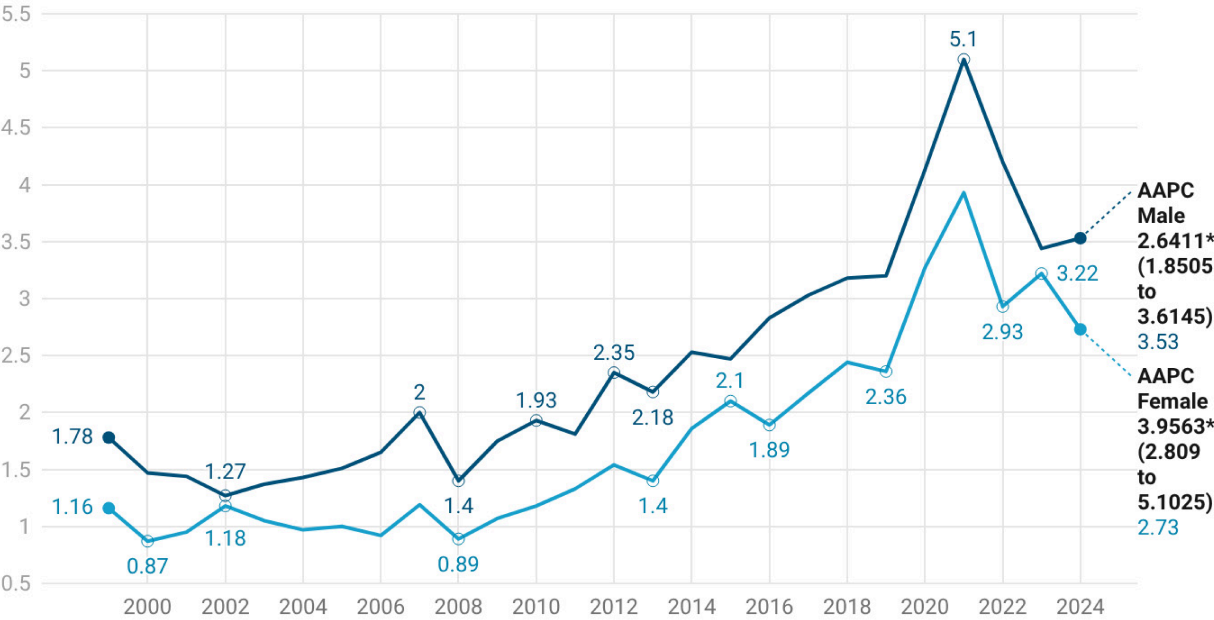
Overall AAMR



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Figure 1. Overall potentially inherited arrhythmic syndromes and sudden cardiac death-related AAMR per 1,000,000 in the United States, 1999 to 2024. * Denotes statistically significant annual percent change (APC) or average annual percent change (AAPC) at $p < 0.05$, as determined by two-tailed t -test using Joinpoint Regression Analysis.

Sex Stratified AAMR



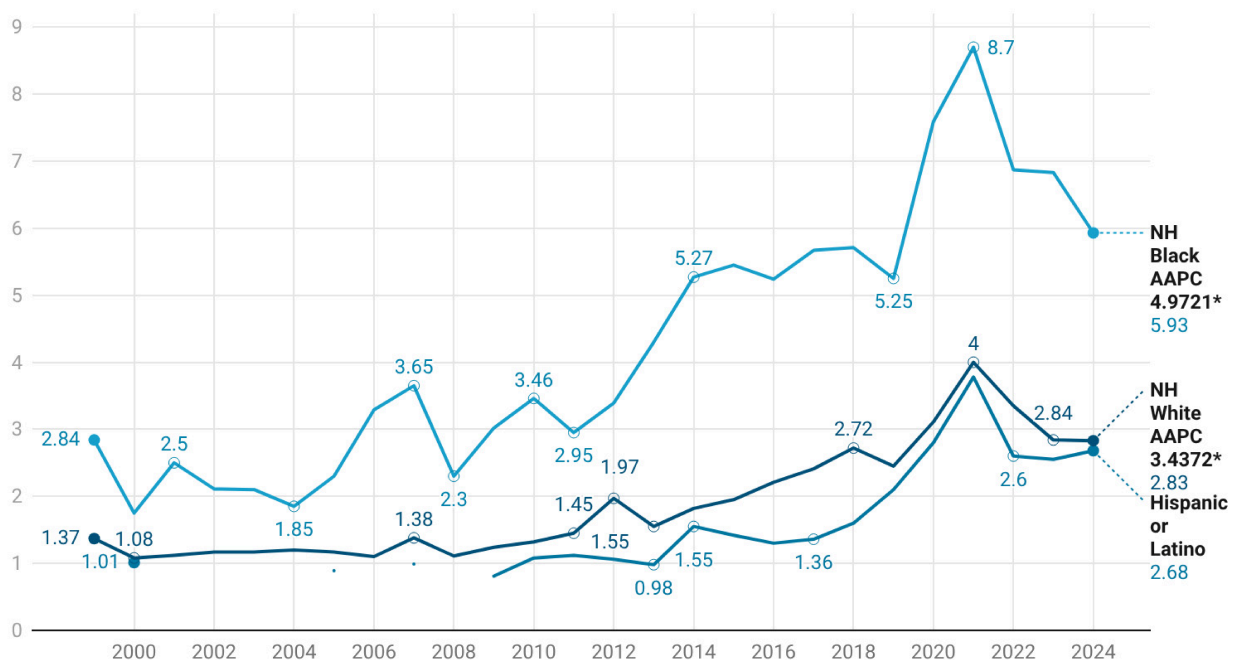
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Figure 2. Sex-stratified potentially inherited arrhythmic syndromes and sudden cardiac death-related AAMRs per 1,000,000 in the United States, 1999 to 2024. * Denotes statistically significant annual percent change (APC) or average annual percent change (AAPC) at $p < 0.05$, as determined by two-tailed t -test using Joinpoint Regression Analysis.

3.3. Race/Ethnicity

The database for the races was divided into two main categories: HISPANIC or LATINO and NON-HISPANIC ORIGIN, which included four races (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White). Between 1999 and 2024, among non-Hispanic groups, the significant AAPCs were observed among Black or African Americans 4.97* (95% CI 3.39–8.02, $p < 0.000001$) and Whites 3.43* (95% CI 2.63–4.25, $p < 0.000001$), both peaking in 2022 (8.70 vs. 4.00) (Figure 3). Between the two races, Black or African American showed considerably higher AAMRs compared to Whites between 1999 (2.84 vs. 1.37) and 2024 (5.93 vs. 2.83). Black or African American populations showed significant rise between 1999 and 2009 (APC = 6.58% (95% CI 5.14–12.83, $p < 0.000001$)) and 2010 and 2019 (APC = 6.58% (95% CI 4.45–8.21, $p < 0.000001$)), while the White population showed their significant change between 2010 and 2019 (APC = 9.34% (95% CI 7.81–11.37, $p < 0.000001$)) and 2023 and 2024 (APC = −7.60% (95% CI −17.83–0.29, $p = 0.044$)) (Supplementary Table S3). The Non-Hispanic, American Indian or Alaska Native, Asian or Pacific Islander and the Hispanic or Latino races showed suppressed results.

Race Stratified AAMR



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Figure 3. Race/ethnicity stratified potentially inherited arrhythmic syndromes and sudden cardiac death-related AAMR per 1,000,000 deaths in the United States, 1999 to 2024. * Denotes statistically significant annual percent change (APC) or average annual percent change (AAPC) at $p < 0.05$, as determined by two-tailed t -test using Joinpoint Regression Analysis.

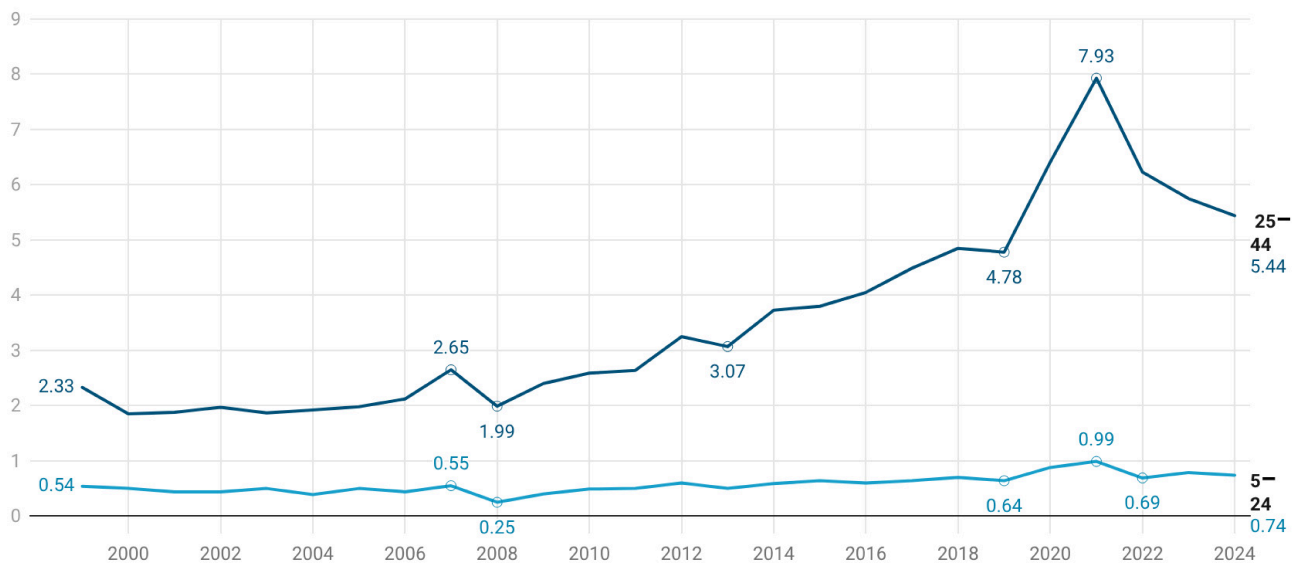
3.4. Age Groups

The mortality trends were divided into two age groups: 5–24 years and 25–44 years. The trends revealed that the 25–44 years age group (AAPC: 3.67% (95% CI 2.89–4.54, $p < 0.000001$)) showed a greater increase in mortality rates compared to the 5–24 years age group (AAPC: 2.32% (95% CI 1.15–3.72, $p < 0.000001$)).

For the 5–24 years group, 1277 deaths were recorded between 1999 and 2024. The age group showed a non-significant fall from 1999 to 2009 with an APC of −0.87% and a

significant rise from 2010 to 2024 with a consistent APC ($4.52\% < 0.000001$). The AAMR increased from 0.54 to 0.74 between 1999 and 2024 (Figure 4).

Age-Adjusted Mortality Stratified by Age (5–24 vs 25–44 Years)



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Figure 4. Age-stratified potentially inherited arrhythmic syndromes and sudden cardiac death-related AAMR per 1,000,000 deaths in the United States, 1999 to 2024.

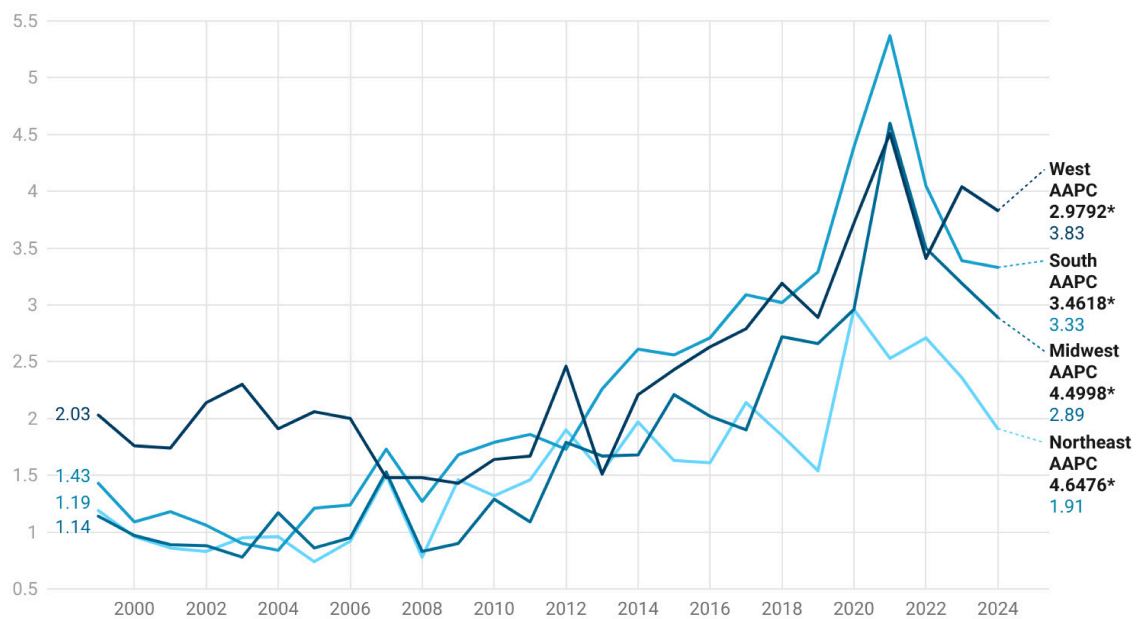
The 25–44 years age group experienced 7602 deaths. The group showed a mild rise between 1999 and 2009 (APC = 1.83^* (95% CI 0.21–3.67, $p < 0.000001$)) followed by a steep incline from 2010 to 2019 (APC = 7.95^* (95% CI 7.26–9.60, $p < 0.000001$)). A significant decline was seen between 2023 and 2024 (APC = -11.22^* (95% CI -17.68 – -6.79 , $p < 0.000001$)). The AAMR rose from 2.33 to 5.44 from 1999 to 2024 (Supplementary Table S4).

3.5. Geographical Regions (Census and States)

Among the four regions, the highest number of deaths was reported in the South (3628 deaths), followed by the West (2508 deaths), the Midwest (1593 deaths) and the Northeast (1150 deaths) from 1999 to 2024 (Figure 5). All the regions experienced an increase in mortality trends from 1999 to 2024, with the Northeast showing the greatest rise (AAPC 4.64% (95% CI 3.40–6.27, $p < 0.000001$), followed by Midwest (AAPC 4.49% (95% CI 2.77–6.15, $p < 0.000001$), South (AAPC 3.46% (95% CI 2.16–4.84, $p < 0.000001$)) and West (AAPC 2.97% (95% CI 1.80–4.39, $p < 0.000001$)) (Supplementary Table S5).

Both the Midwest and South showed the same fluctuations. From 1999 to 2009, they showed a slight rise, although not statistically significant (APC = 0.79 (95% CI -2.48 – 5.70 , $p = 0.55$) vs. (APC = 1.42 (95% CI -1.49 – 4.43 , $p = 0.27$)). The 2010-to-2019-time frame showed a steady and significant increase for both regions (APC = 11.28^* (95% CI 8.12–14.88, $p < 0.000001$) vs. (APC = 9.26^* (95% CI 8.33–11.29, $p < 0.000001$)). From 2020 to 2022, there was a mild increase for the Midwest (APC = 0.99 (95% CI -9.09 – 12.62 , $p = 0.81$)) and a mild decrease for the South (APC = -1.45 (95% CI -8.60 – 9.40 , $p = 0.35$)). Both regions experienced steep declines from 2023 to 2024, but only the value for South was significant (APC = -8.33 (95% CI -25.37 – 4.64 , $p = 0.20$) vs. (APC = -11.12^* (95% CI -22.52 – 2.99 , $p = 0.007$)). Period-specific trends for the Northeast were insignificant.

Region Stratified AAMR



Created with Datawrapper

Figure 5. Potentially inherited arrhythmic syndromes and sudden cardiac death-related AAMR per 1,000,000 stratified by regions in the United States, 1999 to 2024. * Denotes statistically significant annual percent change (APC) or average annual percent change (AAPC) at $p < 0.05$, as determined by two-tailed t -test using Joinpoint Regression Analysis.

From 1999 to 2024, the highest number of deaths related to the conditions were reported in California with 1082, while the lowest were seen in North Dakota with 38. Idaho demonstrated the highest AAMR at 8.66 per million, representing a statistical outlier more than double the next highest state, while several neighboring states are excluded from state-level analysis due to falling below the CDC WONDER reporting threshold for suppressed data. New York had the lowest AAMR amongst all states at 1.52 per million (Supplementary Tables S6 and S7).

3.6. Urbanization

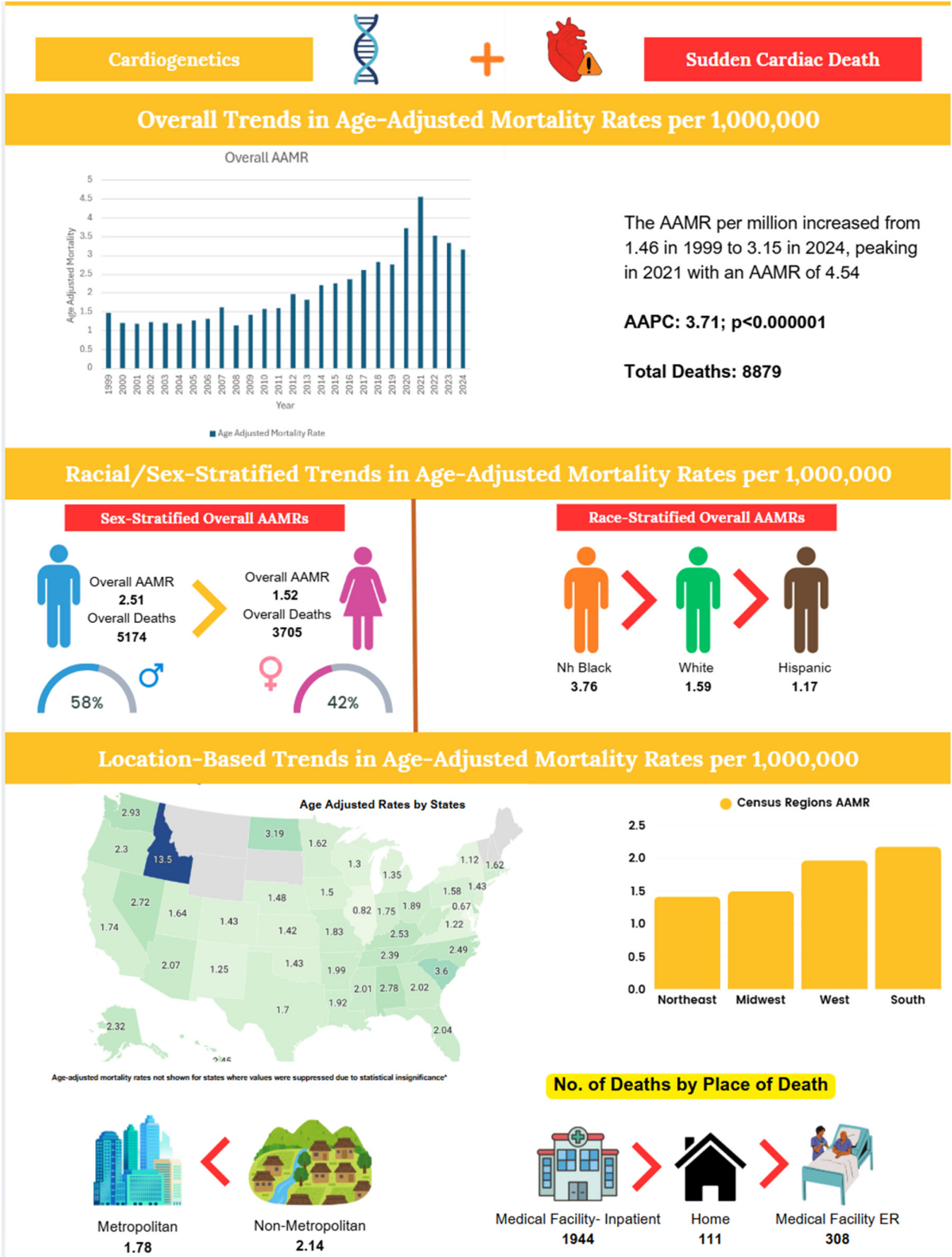
In the years 1999–2020, rural areas (2.14) had a higher average AAMR compared to urban areas (1.78), with both peaking in 2020 with AAMRs of 4.55 and 3.56. The APC between 1999 and 2009 was insignificant for both rural (APC = 2.66 (95% CI −1.22–6.37, $p = 0.166$) and urban areas (APC = 0.95 (95% CI −0.70–3.15, $p = 0.284$). Significant APCs were observed for rural (APC = 9.71* (95% CI 6.42–12.56, $p < 0.000001$) and urban areas (APC = 7.99* (95% CI 6.48–9.77, $p < 0.000001$) between 2010 and 2019. Both rural and urban areas had an overall increase in mortality trends from 1999 to 2020 with AAPCs of 5.96% (95% CI 3.94–8.01, $p < 0.000001$) and 4.58% (95% CI 3.73–5.60, $p < 0.000001$) respectively. Urban areas experienced more deaths (5392) than rural areas (1029) (Supplementary Table S8).

3.7. Place of Death

Database trends from 1999 to 2024 showed that Medical Facility—inpatient had a total of 6260 deaths, with the highest number of deaths in 2020 (468) and the lowest in 2001 (38). It was followed by Medical Facility—outpatient or ER (1564 deaths) and decedent's home (629 deaths). Categories like nursing home/long-term care, Medical Facility—dead on arrival, Medical Facility—status unknown, hospice facility, other and

place of death unknown reported suppressed data or negligible deaths across the years. (Supplementary Table S9).

The central illustration showing overall AAMR trends from 1999 to 2024 is shown in Figure 6.



4. Discussion

This nationwide analysis demonstrates a significant and sustained rise in mortality associated with non-ischemic arrhythmogenic conditions compatible with potentially inherited aetiologies and sudden cardiac death (SCD) in the United States from 1999 to 2024. The age-adjusted mortality rate increased more than twofold throughout the study period, but a sharp increase was registered after 2009, and a maximum was experienced in 2021. One of the most obvious overrepresentations of deaths is of young adults (ages 25 to 44). Not only did this group comprise most of the death rates, but it also showed the sharpest rise in the mortality rates. The problems associated with SCD in the old population are mainly due to ischemic heart disease, while in the young population, they are more frequently linked to primary electrical disorders and genetic cardiomyopathies [10]. Hereditary arrhythmogenic disorders have always been reported as a leading cause of sudden death of healthy normal hearts and are typically the first manifestation. Furthermore, national mortality rates have suggested a growing problem among younger adults, suggesting our finding of an increasing trend in premature cardiovascular mortality [2]. One of the most significant factors is the mortality spike seen in the 2020–2022 period that coincided with the COVID-19 pandemic. This increase was very clear visually, but the join point analysis revealed a non-significant short-term APC during this time period, possibly because of the short time interval, or because of the annual variability or because of limited statistical power to confirm the stable trend for this short time period. However, the temporal association must be interpreted with caution. SARS-CoV-2 infection can cause direct myocardial injury, myocarditis, myocardial inflammation, autonomic dysfunction, and electrophysiological instability, which can raise the risk of malignant ventricular arrhythmias and sudden cardiac death. Viral and post-viral myocarditis is an accepted cause of ventricular arrhythmogenesis, especially in children, and this may be especially so in patients with congenital arrhythmic substrates (channelopathies and arrhythmogenic cardiomyopathies), where inflammatory myocardial stress could reduce arrhythmogenic thresholds and trigger fatal arrhythmic events. Acute COVID-19 myocarditis has been reported as an important complication with a severe cardiac prognosis, such as sudden death [17]. COVID-19 thus could have both been a competing cause of sudden death and interacted with underlying inherited arrhythmogenic susceptibility to cause sudden death. The nationwide mortality study revealed rising rates of deaths attributed to non-ischaemic arrhythmogenic conditions compatible with potentially inherited aetiologies and sudden cardiac death in the United States during the period 1999 to 2024 in people aged 5–44 years. This rise was not consistent over the entire time period of the study. The overall AAMR rose from 1.46 per million in 1999 to 3.15 per million in 2024, with the period from 2010 to 2019 reflecting the greatest increase, and the period from 2020 to 2022 reflecting a visually great but statistically non-significant change, with a decline during 2023–2024 [18]. This pattern does not necessarily reflect an increase in the number of genetically diagnosed inherited arrhythmic syndrome-related deaths but is rather a result of increasing mortality records from arrhythmogenic and sudden cardiac death-related causes.

An important interpretative problem is whether the apparent increase is a genuine increase in epidemiology or ascertainment. The relatively flat trend seen for most cohorts in the 1999–2009 period might be due to under-recognition and non-specific coding prior to the widespread clinical application of genetic testing, inherited cardiac disease clinics, family cascade screening and improved arrhythmia phenotyping. However, the sharp increase between 2010 and 2019 may, to some extent, be due to better awareness and coding of non-ischaemic arrhythmogenic death. Yet, better ascertainment alone does not fully account for the results since the arrhythmic thresholds may be reduced further in susceptible persons by worsening cardiometabolic risk factors, stimulant use, psychosocial

stress, sleep disturbance, and environmental factors. Thus, the most optimal interpretation is that the trend most likely is due to increased recognition as well as actual increased arrhythmogenic susceptibility [4,19].

The racial results make a simple ascertainment-based explanation more complicated. The overall AAMRs of non-Hispanic Black individuals were higher than those of White individuals, and there was an increasing trend for NHB individuals in the period 1999–2009, when most other groups had relatively stable trends [2]. This indicates that there may be some structural differences, access to specialist cardiac services, reduced availability of preventive screening, variation in emergency response and cardiovascular risk burden contributing to excess mortality that predates the full account of the rise by modern coding and genetic testing. Thus, it is important to recognize that this racial difference in the current study is not merely a coding effect but a significant public health warning [20].

Patterns of mortality may also have been affected by disruption in the healthcare system during the pandemic. Emergency response delays, not going to the hospital, decreased outpatient cardiac access, not completing diagnostic workups, and missed family screening may have contributed to the likelihood of sudden death outside of a hospital. Studies during the pandemic showed higher rates of OOHCA and higher odds of OOHCA occurring at home, lending credence to the idea that the impact of healthcare access disruption increased mortality risk during this timeframe [21].

This is especially relevant to the age-specific findings. Most deaths occurred between the ages of 25 and 44 years, and between 2010 and 2019, there was a sharp increase in deaths in this age group, but a slight decrease from 2023 to 2024. The 5- to 24-year group, however, experienced a more sustained recovery following 2010 that did not see the same decline in year-over-year gains. This pattern is of concern as younger children, adolescents and young adults may be at risk of having undiagnosed arrhythmogenic substrates that can present catastrophically. Signs and symptoms of syncope, exertional palpitations, seizure-like episodes, and family history of sudden death are often not recognized or investigated in children. This trend reinforces the need for a higher level of awareness of warning signs and symptoms in children, assessing family history, targeted ECG screening and strengthened referrals for the evaluation of inherited cardiac disease [22].

There were absolute increases in mortality among males and relative increases over time among females. This discovery should be interpreted with caution and not as evidence for sex-specific genetic risk, but rather as a clue to the fact that the risk for arrhythmogenic mortality may differ for women and men due to changing cardiovascular risk factors, diagnostic recognition, hormonal effects, and health care inequities. The female trend needs to be further evaluated; female patients with arrhythmic symptoms might either be underdiagnosed or diagnosed late, and associated with an increased risk of referral and risk stratification [23]. In the post-pandemic period, males demonstrated a significant decline in AAMR between 2023 and 2024 (APC -11.84% , $p < 0.000001$), while females showed a non-significant decline (APC -6.65% , $p = 0.12$); however, given that this observation spans only two years, these diverging trajectories should be interpreted with caution and are insufficient to draw conclusions about long-term sex-specific trend direction.

There was some geographic variation, too. The highest number of deaths occurred in the South, and the relative increase in deaths was the greatest in the Northeast. The mean proportion of AAMR was found to be higher in the rural areas as compared to the urban areas, although the absolute numbers of deaths were higher in the urban areas. The results indicate that geography and healthcare access are vital modifiers of mortality. Emergency response may be delayed, electrophysiology services may not be available, fewer inherited cardiac disease clinics may exist, and there may be a lack of genetic counseling in rural areas. These geographic differences reinforce the need for targeted

prevention and emergency response efforts on a regional level [24]. This could be due to the growing importance of the use of wearables for rhythm surveillance, and this explanation should be taken with a pinch of salt. In 2019, about 21% of U.S. adults used a smartwatch or fitness tracker regularly, according to Pew Research Center. A study of the JAMA Network Open revealed that wearable use was present in 29% of the general population, 18% of adults with cardiovascular disease, and 26% of adults with risk for cardiovascular disease. Lower uptake was also observed among older age, low-income, and low-educational-level groups. These demographic gradients imply that wearables could have a greater effect on increasing ascertainment in certain groups but not fully account for differences in ascertainment, such as between Black Americans and White Americans, or between urban and rural communities, in which the use of digital health tools is limited, or even in some cases, lessened [25].

These results should be interpreted with caution because the ICD-10 classification was heterogeneous. The arrhythmias, conduction disorders, cardiomyopathic conditions, and congenital cardiac abnormalities covered by the codes used in this analysis are likely to be quite broad. This approach enhances sensitivity for the detection of mechanisms for sudden cardiac death in younger individuals without ischemic heart disease, but also amalgamates heterogeneous disorders of different biology, causal factors, risk factors, prognosis, and prevention. Thus, the present results should not be interpreted as trends specific to individual arrhythmogenic conditions, such as long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, or even any specific cardiomyopathy [19].

Considering the overall picture of the literature with the six recent studies incorporated, the present analysis corroborates the overall literature review, indicating increased awareness of premature sudden cardiac death, arrhythmogenic mortality, and the importance of genetic and digital risk stratification. But this study makes some unique contributions. It applied a unique combination strategy; it limited the age range of participants to 5–44 years; it excluded ischemic heart disease to minimize atherosclerotic disease as a potential confounder; it examined four time periods instead of just overall trends; and it emphasized disparities by race, geography, urban versus rural residence, and pediatric age group. Specifically, the sustained increase in Black Americans and persistent increase in those aged 5–24 years builds on previous work by identifying priority populations that could benefit from surveillance and prevention efforts that are targeted [8].

The clinical implications of the findings suggest a need to consider earlier diagnosis of young children at risk for non-ischaemic arrhythmogenic conditions that have inherited causes. This includes a careful assessment of syncope, exertional symptoms, seizure-like episodes, family history of sudden death and unexplained cardiac arrest in family members. In high-risk settings, ECG screening, referral to inherited cardiac disease services, genetic counseling (if applicable), and access to electrophysiology services may be beneficial. These recommendations, however, should be presented with caution, as the current study is not able to validate a genetic diagnosis for any patient [3].

4.1. Clinical Heterogeneity of ICD-10 Case Definition

One crucial interpretation point is that the ICD-10 case definition for this analysis is clinically heterogeneous. A wide range of non-ischaemic arrhythmogenic disease types included in the mortality grouping encompassed arrhythmic disorders, conduction abnormalities, cardiomyopathic processes, and selected congenital cardiac conditions, which are all potentially inherited diseases. An advantage of this composite approach was that it would allow for more sensitivity to capture mechanisms of sudden cardiac death in the younger population, but it necessarily includes clinically distinct entities, which have

differing mechanisms, genetic architectures, age distributions and prognostic trajectories. Primary channelopathies, inherited cardiomyopathies, congenital conduction disorders and congenital structural abnormalities, for instance, can all play different roles in the mortality patterns and may require different diagnostic and preventive measures. Thus, the results should be viewed as a reflection of the mortality pattern of the population as a whole or a group of arrhythmogenic conditions of heterogeneous nature, rather than of a given inherited syndrome. Conclusions should not be too general, e.g., long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, or individual cardiomyopathies without condition-specific validation.

4.2. Age 5–24 Years: Distinct and Concerning Mortality Pattern

One of the most concerning observations in this analysis was the distinct mortality trajectory among individuals aged 5–24 years, which differed from nearly all other demographic subgroups. Unlike the 25–44-year cohort, which demonstrated a post-pandemic decline between 2023 and 2024, the younger group showed a persistent and continuous rise in mortality following 2010 without a comparable corrective trend. This suggests that the underlying drivers in younger children, adolescents, and young adults may differ from those influencing older cohorts. Several explanations are plausible. Younger individuals with silent arrhythmogenic substrates may remain undiagnosed until catastrophic presentation because symptoms such as syncope, palpitations, exertional intolerance, or seizure-like episodes are under-recognized in pediatric populations. Pandemic-related healthcare disruption may also have contributed through delayed cardiology referrals, deferred evaluation of concerning symptoms, interrupted school-based health surveillance, and reduced access to specialist diagnostic services. Environmental and behavioral triggers, including stimulant exposure, psychosocial stress, sleep disruption, viral myocarditis, post-viral autonomic dysfunction, and changing cardiometabolic risk even in younger populations, may also have lowered arrhythmic thresholds in vulnerable individuals. The absence of a post-pandemic correction raises concern that this may not represent a transient phenomenon alone but potentially an ongoing public health issue. These findings reinforce the importance of earlier identification strategies in younger populations, including improved recognition of warning symptoms, targeted family history assessment, paediatric ECG evaluation in selected high-risk contexts, and strengthened pathways for inherited cardiac disease referral and preventive screening.

5. Limitations

This study has several limitations that should be considered when interpreting the findings. First, the analysis was based on death certificate data obtained from the CDC WONDER database, which is subject to misclassification and underreporting. The accuracy of cause-of-death coding depends on physician documentation, and inherited arrhythmic syndromes are often underdiagnosed or not explicitly recorded, potentially leading to underestimation of the true burden. Second, the use of ICD-10 codes limits the ability to precisely identify specific inherited arrhythmic syndromes. Many primary electrical disorders, such as long QT syndrome or Brugada syndrome, may be coded under broader arrhythmia categories, reducing diagnostic specificity and potentially introducing classification bias. Third, the study lacked individual-level clinical data, including genetic testing results, family history, comorbid conditions, medication use, and treatment interventions such as implantable cardioverter-defibrillator (ICD) placement. This restricts the ability to confirm genetic etiology, assess causal relationships, or evaluate the impact of clinical management on outcomes. Fourth, temporal changes in coding practices, diagnostic awareness, and reporting standards over the study period may have influenced observed

trends. Increased recognition of arrhythmic conditions and improved documentation may partially explain the rising mortality rates, independent of a true increase in incidence. Fifth, although ischemic heart disease was excluded and the analysis was restricted to individuals aged 5–44 years to enhance specificity for inherited causes, residual confounding from non-genetic etiologies cannot be eliminated. Conditions such as myocarditis, substance use, or undiagnosed structural heart disease may still contribute to sudden cardiac death in this population. Sixth, suppression of small cell counts in the CDC WONDER database limited detailed analysis for certain racial/ethnic groups and geographic regions, potentially affecting the completeness of subgroup comparisons. The findings reflect population-level associations and trends rather than individual-level risk and therefore should be interpreted within the context of observational epidemiology.

6. Conclusions

This nationwide analysis demonstrated an increase in mortality records coded as non-ischaemic arrhythmogenic conditions compatible with potentially inherited aetiologies and sudden cardiac death among individuals aged 5–44 years in the United States from 1999 to 2024. The increase was not a simple linear trend; it was most pronounced during 2010–2019, followed by pandemic-era fluctuation and a decline from 2023 to 2024. Because the study relied on ICD-10-coded death certificate data, the findings should not be interpreted as confirmed inherited arrhythmic syndrome deaths, but rather as a population-level signal of rising recorded mortality in a young, non-ischemic arrhythmogenic category. The higher burden among Black Americans and the persistent increase among individuals aged 5–24 years identify important priority groups for further investigation and prevention. If these patterns reflect a combination of improved ascertainment, structural disparities, and true increases in arrhythmogenic risk, then targeted public health strategies, earlier recognition of warning symptoms, family-based assessment, selected cardiology referral, and equitable access to genetic evaluation may help reduce preventable sudden cardiac deaths.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cardiogenetics16030014/s1>, Table S1: Number of Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death Related Deaths, Stratified by Sex and Race in Adults in the United States 1999–2024; Table S2: Overall and Sex-Stratified Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death-related Age-Adjusted Mortality Rates per 1,000,000 in Adults in the United States 1999–2024; Table S3: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death related Age-Adjusted Mortality Rates per 1,000,000, Stratified by Race in Adults in the United States 1999–2024; Table S4: Annual Percent Change (APC) and Average Annual Percent Change (AAPC) of Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death Related Age-Adjusted Mortality Rates per 1,000,000 in Adults in the United States 1999–2024; Table S5: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death-related Age-Adjusted Mortality Rate per 1,000,000 Stratified by Census Region in Adults in the United States 1999–2024; Table S6: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death and related Age-Adjusted Mortality Rates per 1,000,000, Stratified by States in Adults in the United States 1999–2020; Table S7: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death-related Age-Adjusted Mortality Rates per 1,000,000, Stratified by States in Adults in the United States 1999–2020 ranked according to Percentiles; Table S8: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death-related Age-Adjusted Mortality Rates per 1,000,000 in the Metropolitan and Non-metropolitan areas in Adults in the United States 1999–2020; Table S9: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death-related Mortality, Stratified by Place of Death in Adults in the United States 1999–2024. Table S10: Potentially Inherited Arrhythmic Syndromes and Sudden Cardiac Death-related Annual-Average-Percentage Change, Stratified by Time Frame in Adults in the United States 1999–2024.

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Informed Consent Statement: Not applicable. The study did not include individual patient data.

Data Availability Statement: All data used in this study are publicly available through the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. Data were accessed in accordance with the CDC's data use guidelines.

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References

1. Chugh, S.S.; Havmoeller, R.; Narayanan, K.; Singh, D.; Rienstra, M.; Benjamin, E.J.; Gillum, R.F.; Kim, Y.H.; McAnulty, J.H., Jr.; Zheng, Z.J.; et al. Worldwide epidemiology of sudden cardiac death: A global burden of disease study. *Circulation* **2014**, *129*, 837–847. [PubMed]
2. Hayashi, M.; Shimizu, W.; Albert, C.M. The spectrum of epidemiology underlying sudden cardiac death. *Circ. Res.* **2015**, *116*, 1887–1906. [CrossRef] [PubMed]
3. Ackerman, M.J.; Priori, S.G.; Willems, S.; Berul, C.; Brugada, R.; Calkins, H.; Camm, A.J.; Ellinor, P.T.; Gollob, M.; Hamilton, R.; et al. HRS/EHRA expert consensus statement on the state of genetic testing for channelopathies and cardiomyopathies. *Heart Rhythm*. **2011**, *8*, 1308–1339. [CrossRef] [PubMed]
4. Deo, R.; Albert, C.M. Epidemiology and genetics of sudden cardiac death. *Circulation* **2012**, *125*, 620–637. [CrossRef] [PubMed]
5. Shah, N.S.; Molsberry, R.; Rana, J.S.; Sidney, S.; Capewell, S.; O'Flaherty, M.; Carnethon, M.; Lloyd-Jones, D.M.; Khan, S.S. Heterogeneous trends in burden of heart disease mortality by subtypes in the United States, 1999–2018: Observational analysis of vital statistics. *BMJ* **2020**, *370*, m2688. [CrossRef] [PubMed]
6. Sayed, A.; Abramov, D.; Fonarow, G.C.; Mamas, M.A.; Kobo, O.; Butler, J.; Fudim, M. Reversals in the Decline of Heart Failure Mortality in the US, 1999 to 2021. *JAMA Cardiol.* **2024**, *9*, 585–589. [CrossRef] [PubMed]
7. Maqsood, M.H.; Talha, K.M.; Minhas, A.M.K.; Fudim, M.; Khan, S.S.; Butler, J.; Khan, M.S. CDC-WONDER Database Analysis of COVID-19 and Cardiovascular Disease-Related Mortality. *J. Am. Coll. Cardiol.* **2023**, *81*, 1743–1745. [CrossRef] [PubMed]
8. Zuin, M.; Mohanty, S.; Aggarwal, R.; Bertini, M.; Bickdeli, B.; Hamade, N.; Leyva, H.; Natale, A.; Boriani, G.; Piazza, G. Trends in Sudden Cardiac Death Among Adults Aged 25 to 44 Years in the United States: An Analysis of 2 Large US Databases. *J. Am. Heart Assoc.* **2025**, *14*, e035722. [CrossRef] [PubMed]
9. Bhagwan, R.; Nabi, R.; Rath, S.; Chaudhry, S.A.A.; Meghwar, S.; Rath, D.; Kumar, S.P.; Das, N.B.; Collins, P.; Ahmad, H.; et al. Trends in Sudden Cardiac Death Related Mortality in Adults in the United States: A CDC WONDER Database Analysis, 1999–2020. *Clin. Cardiol.* **2025**, *48*, e70180. [CrossRef] [PubMed]
10. Khan, S.A.; Assad, A.A.; Qadri, M.; Abbasi, S.U.A.M.; Saleem, H.; Saeed, M.; Rahman, S.U.; Nawaz, T.; Saleh, A.; Ashraf, H. National trends in arrhythmias and heart failure-related mortality in the United States from 1999 to 2023: A CDC WONDER analysis. *J. Arrhythm.* **2025**, *41*, e70222. [PubMed]
11. Centers for Disease Control and Prevention. Multiple Cause of Death Data on CDC Wonder. Available online: <https://wonder.cdc.gov/mcd.html> (accessed on 25 February 2026).

12. STROBE Statement—Strengthening the Reporting of Observational Studies in Epidemiology. Available online: <https://www.strobe-statement.org/> (accessed on 25 February 2026).
13. US Census Bureau. Census Regions and Divisions of the United States. Available online: http://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf (accessed on 10 October 2025).
14. Ingram, D.D.; Franco, S.J. NCHS urban–rural classification scheme for counties. *Vital. Health Stat. 2* **2014**, *166*, 1–65.
15. Anderson, R.N.; Rosenberg, H.M. Age standardization of death rates: Implementation of the year 2000 standard. *Natl. Vital. Stat. Rep.* **1998**, *47*, 1–16. [[PubMed](#)]
16. Joinpoint Regression Program. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute. Available online: <https://surveillance.cancer.gov/joinpoint/> (accessed on 10 October 2025).
17. Manolis, A.S.; Manolis, A.A.; Manolis, T.A.; Apostolopoulos, E.J.; Papatheou, D.; Melita, H. COVID-19 infection and cardiac arrhythmias. *Trends Cardiovasc. Med.* **2020**, *30*, 451–460. [[CrossRef](#)] [[PubMed](#)]
18. Zheng, Z.J.; Croft, J.B.; Giles, W.H.; Mensah, G.A. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* **2001**, *104*, 2158–2163. [[CrossRef](#)] [[PubMed](#)]
19. Behr, E.R.; Dalageorgou, C.; Christiansen, M.; Syrris, P.; Hughes, S.; Tome Esteban, M.T.; Rowland, E.; Jeffery, S.; McKenna, W.J. Sudden arrhythmic death syndrome: Familial evaluation identifies inheritable heart disease in the majority of families. *Eur. Heart J.* **2008**, *29*, 1670–1680. [[CrossRef](#)] [[PubMed](#)]
20. Bagnall, R.D.; Weintraub, R.G.; Ingles, J.; Duflou, J.; Yeates, L.; Lam, L.; Davis, A.M.; Thompson, T.; Connell, V.; Wallace, J.; et al. A prospective study of sudden cardiac death among children and young adults. *N. Engl. J. Med.* **2016**, *374*, 2441–2452. [[CrossRef](#)] [[PubMed](#)]
21. Virani, S.S.; Alonso, A.; Aparicio, H.J.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Cheng, S.; Delling, F.N.; et al. Heart disease and stroke statistics—2023 update: A report from the American Heart Association. *Circulation* **2023**, *147*, e93–e621. [[CrossRef](#)]
22. Tsao, C.W.; Aday, A.W.; Almarzooq, Z.I.; Alonso, A.; Beaton, A.Z.; Bittencourt, M.S.; Buxton, A.E.; Commodore-Mensah, Y.; Anderson, C.A.; Avery, C.L.; et al. Heart disease and stroke statistics—2024 update: A report from the American Heart Association. *Circulation* **2024**, *149*, e347–e913.
23. Adabag, A.S.; Luepker, R.V.; Roger, V.L.; Gersh, B.J. Sudden cardiac death: Epidemiology and risk factors. *Nat. Rev. Cardiol.* **2010**, *7*, 216–225. [[CrossRef](#)] [[PubMed](#)]
24. Noseworthy, P.A.; Newton-Cheh, C. Genetic determinants of sudden cardiac death. *Circulation* **2008**, *118*, 1854–1863. [[CrossRef](#)] [[PubMed](#)]
25. Winkel, B.G.; Holst, A.G.; Theilade, J.; Kristensen, I.B.; Thomsen, J.L.; Ottesen, G.L.; Bundgaard, H.; Svendsen, J.H.; Haunsø, S.; Tfelt-Hansen, J. Nationwide study of sudden cardiac death in persons aged 1–35 years. *Eur. Heart J.* **2011**, *32*, 983–990. [[PubMed](#)]

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