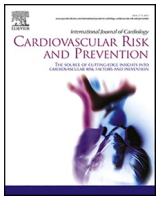
International Journal of Cardiology Cardiovascular Risk and Prevention 25 (2025) 200404

Contents lists available at ScienceDirect

International Journal of Cardiology
Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



# Trends of infective endocarditis mortality in young adult population of US: A concerning rise and its association with substance abuse

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ARTICLE INFO

Handling editor: D Levy

*Keywords:*
Infective endocarditis
Substance abuse
Mortality trends
United States
Disparities

ABSTRACT

*Background:* Substance Abuse (SA) is associated with Infective Endocarditis (IE) morbidity and mortality in the young adult population of the US. However, limited data is available for trends and disparities related to IE mortality and its association with SA in the young adult US population.
*Methods:* Data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research were analyzed from 1999 to 2022 for IE and SA-IE-related mortality in young adults aged 15 to 44 in the US. Age-adjusted mortality rates (AAMR) per 1000,000 people were used to calculate annual percent changes (APC) using Joinpoint regression analysis. Trends were stratified by sex, race/ethnicity, age groups, census region, urbanization classification, and states.
*Results:* IE caused 22,614 deaths in the young adult population of the US between 1999 and 2022. 7235 (32.0 %) of these deaths were associated with SA. AAMR for IE-associated mortality initially decreased from 6.2 in 1999 to 4.7 in 2010. Following that it increased by almost 3 folds to reach 13.5 in 2020 and 2021. SA-IE followed a similar trend, increasing more than 5 folds from an AAMR of 1.0 in 2010 to 5.4 by 2018. Between 1999 and 2009, 15–22 % of all IE deaths were associated with SA annually, which increased to >40 % for 2016–2022. Men had higher AAMR for IE though women witnessed a bigger jump in SA-associated IE mortality. Non-Hispanic American Indian or Alaskan natives, South region, and rural population had a worse increase.
*Conclusions:* IE mortality in the young adult population of the US has increased from 2010 onwards with a concerning rise in SA and IE-associated deaths.

## 1. Introduction

Infective endocarditis (IE) is a life-threatening condition with significant morbidity and mortality. In recent years, its incidence has risen, particularly among younger populations in higher-income countries, largely due to increasing substance abuse (SA) [1]. Historically, IE was primarily associated with older adults and rheumatic fever. However, with advances in antibiotic therapy and healthcare practices, its epidemiology has shifted. Injection drug use (IDU) is now recognized as a leading driver, alongside risk factors such as prosthetic valve replacement, central venous catheters, and implantable cardiac devices [2].

The ongoing opioid crisis in the US has driven a rise in IDU and a 12-fold increase in IDU-associated IE (IDU-IE) hospitalizations from 2007 to 2017. SA patterns have shifted from prescription opioids to heroin, stimulants, and synthetic opioids, with high-risk behaviors like needle sharing facilitating bloodstream infections and bacterial seeding of heart valves [3].

IDU-IE disproportionately affects younger adults and shows notable gender and racial disparities. Women comprise 45–55 % of cases, and American Indians and Alaska Natives (AI/AN) bear a disproportionate burden [1,4]. It is also more common among individuals experiencing homelessness and poverty, underscoring broader healthcare and socio-economic inequities [4].

This study examines the mortality trends from IE in young adults in the US, with a focus on its association with SA trends, demographic and regional disparities, and the impact of the COVID-19 pandemic over the past two decades. By identifying and understanding key trends, we can better shape targeted interventions that address the dual crises of SA and

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https://doi.org/10.1016/j.ijcrp.2025.200404
Received 20 January 2025; Received in revised form 19 March 2025; Accepted 10 April 2025
Available online 15 April 2025

SA-associated IE (SA-IE) [5].

## 2. Methods

### 2.1. Study design and database

This population-based, national observational cohort study analyzed all IE and SA-IE-related deaths among young adults aged 15–44. Data were sourced from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC-WONDER) [6,7]. The International Classification of Diseases (ICD), 10th Revision, Clinical Modification codes were used to extract mortality data (Supplemental Table 1) [8]. The codes B37.6, I33.0, I33.9, and I38 were used to identify IE, consistent with previous studies [5]. SA was defined by the presence of ICD-10 codes T40.0–T40.6, T43.6, T50.9, F11, F13–F16, F19, X42, and B17.1, indicating IDU, psychoactive SA, or acute hepatitis C, following the approach used in a previous study [5]. The study was exempt from institutional review board approval because the CDC WONDER database contains anonymized, publicly available data. All methods adhered to the principles of the Declaration of Helsinki, and the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [9].

### 2.2. Outcome variables

The primary analysis assessed IE as a contributing cause of death. A sub-analysis examined SA-IE-related deaths, where both IE and SA were contributing causes. Sensitivity analysis was conducted using IE as the underlying cause of death; however, sensitivity analysis for SA-IE deaths was limited due to data suppression and unreliability.

Our study evaluated the following outcomes from 1999 to 2022 in both primary and sub-analyses: 1) trends in overall age-adjusted mortality rates (AAMR) for IE and SA-IE; (2) trends in AAMR stratified by sex, race, region, and urbanization status; (3) trends in crude mortality rates (CMR) across different age groups; (4) state-level variations in overall AAMR; (5) trends in proportion of IE deaths associated with SA versus non-SA-related IE deaths (6) trends in percentage of SA-IE deaths among total IE deaths, both overall and stratified by sex, race, age group, urbanization status, and region.

Further analysis was performed to evaluate changes in AAMR and percentage of IE deaths associated with SA across successive three-year periods from 2011 to 2022, focusing on the increasing trend observed in the primary analysis and comparing these changes with the impact of the COVID-19 pandemic. Data were grouped into three-year clusters: 2011–2013, 2014–2016, 2017–2019, and 2020–2022. This approach was selected to maintain equal timeframes for both pre-COVID and COVID subgroups, helping to reduce the effect of year-to-year fluctuations. Percentage changes in state-level AAMR from 2008 to 2022 were analyzed using five-year intervals (2008–2012, 2013–2017, and 2018–2022) to improve data reliability.

### 2.3. Data abstraction

Data extracted for analysis included biological sex, race/ethnicity, 10-year age groups, US census regions, urban-rural classification, states, and place of death. Biological sex included men or women. Race/ethnicity groups were divided into Hispanic or Latino, non-Hispanic (NH) White, NH Black or African American, NH Asian or Pacific Islander, and NH-AI/AN. 10-year age groups were divided into 15–24, 25–34 and 35–44. For urban-rural classification, the National Center for Health Statistics Urban-Rural Classification Scheme was used to divide the population into large metropolitan (population $\geq$1 million), medium/small metropolitan (population 50,000 to 999,999), and rural/non-metropolitan (population <50,000) per the 2013 United States census classification [10]. Regions were classified into Northeast, Midwest, South, and West according to the Census Bureau definitions. Places of death were categorized as medical facilities (outpatient/emergency room or inpatient), home, hospice, nursing home/long-term care facilities, or other locations.

### 2.4. Statistical analysis

IE and SA-IE-related crude number of deaths, CMR, and AAMR per 1,000,000 were calculated. AAMR were standardized to the 2000 US population [11]. We used the Joinpoint Regression Program (Joinpoint version 5.2.0.0 available from National Cancer Institute, Bethesda, Maryland) to determine trends in mortality within the study period [12]. This program identifies significant changes in annual mortality proportions/percentage trends over time through Joinpoint regression, which fits models of linear segments where significant temporal variation occurred. Annual percentage change (APC) with 95 % confidence intervals (CIs) for the percentages of mortality were calculated for the line segments linking a Joinpoint using the Monte Carlo permutation test. The weighted average of the APCs was calculated and reported as AAPCs and corresponding 95 % CIs to summarize the reported mortality trend for the entire study period. APC and AAPCs were considered to increase or decrease if the slope describing the change in mortality over the time interval significantly differed from zero using a 2-tailed *t*-test. Statistical significance was set at $p \leq 0.05$ (represented by an asterisk '*' in results and figures) [13].

## 3. Results

Fig. 1 provides a central illustration of our study's IE mortality summary. Detailed results of the study are shown in Figs. 1–5, Supplemental Tables 1–10, and Supplemental Figs. 6–18.

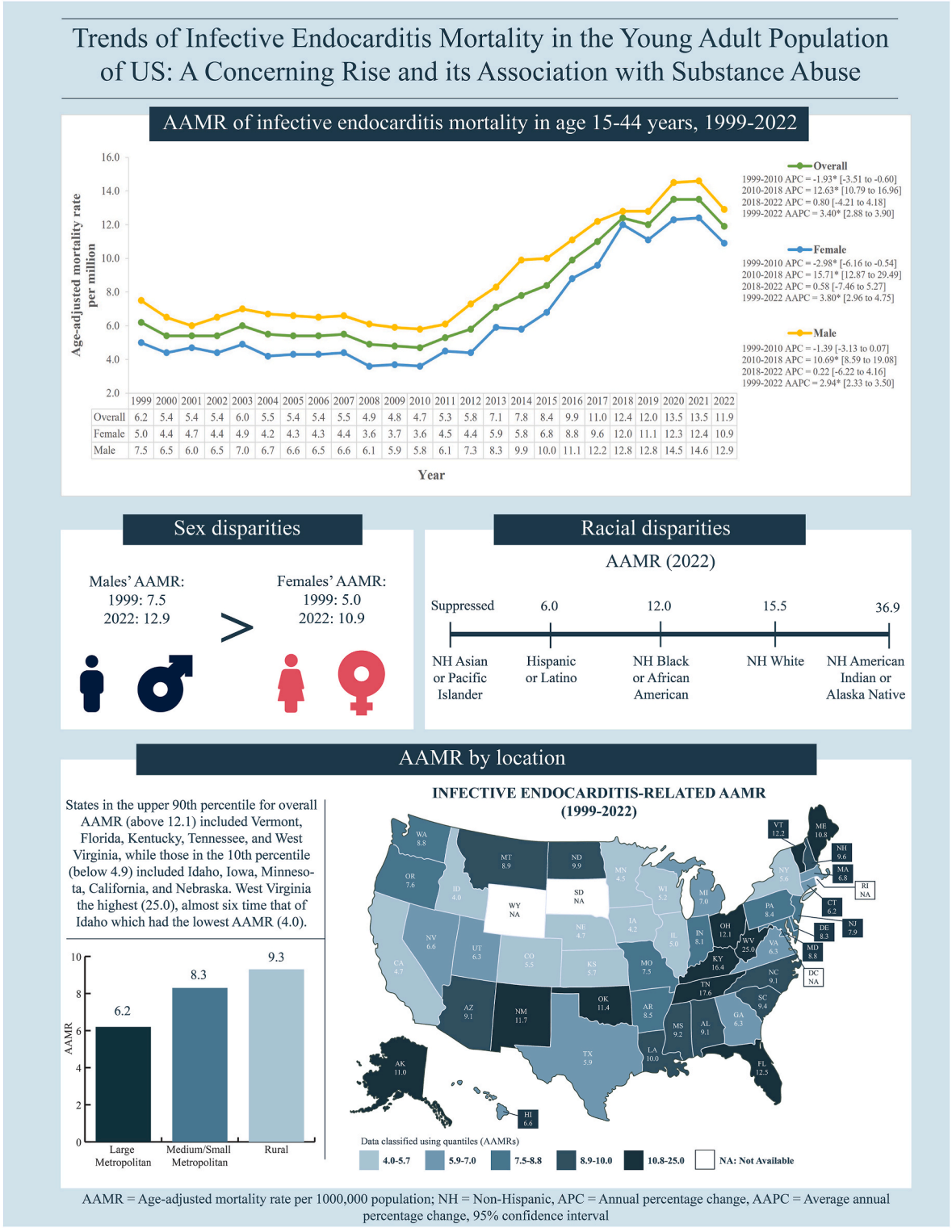
### 3.1. Overall

IE has caused a total of 22,614 deaths in the young adult population of the US between 1999 and 2022. 7235 (32.0 %) of these deaths were associated with SA-IE (Table 1). For overall IE mortality, AAMR increased from 6.2 in 1999 to 11.9 in 2022 (AAPC = 3.40*, CI: 2.88 to 3.90). The AAMR initially declined from 6.2 in 1999 to 4.7 in 2010 (APC = −1.93*, CI: −3.51 to −0.60) but increased by almost 3 times from 4.7 in 2010 to 12.4 by 2018 (APC = 12.63*, CI: 10.79 to 16.96). The AAMR of IE peaked at 13.5 in 2020 and 2021 (APC 2018 to 2022: 0.80, CI -4.21 to 4.18) (Fig. 2). SA-IE followed a similar trend, increasing more than 5 folds from an AAMR of 1.0 in 2010 to 5.4 by 2018 (APC = 25.63*, CI: 22.65 to 30.18) (Fig. 2). Between 1999 and 2009, 15–22 % of all IE deaths were associated with SA-IE annually, which increased to >40 % for 2016–2022 (Supplemental Fig. 10). Sensitivity analysis of IE deaths had a similar increasing trend and is presented in Supplemental Figs. 16–18 and Tables 10 and 11.

Most deaths occurred in medical facilities (81.6 %), followed by homes (9.9 %), hospice facilities (2.8 %), and nursing home/long-term care facilities (1.1 %). Other locations accounted for 4.5 % of deaths (Supplemental Table 8).

### 3.2. Sex stratified

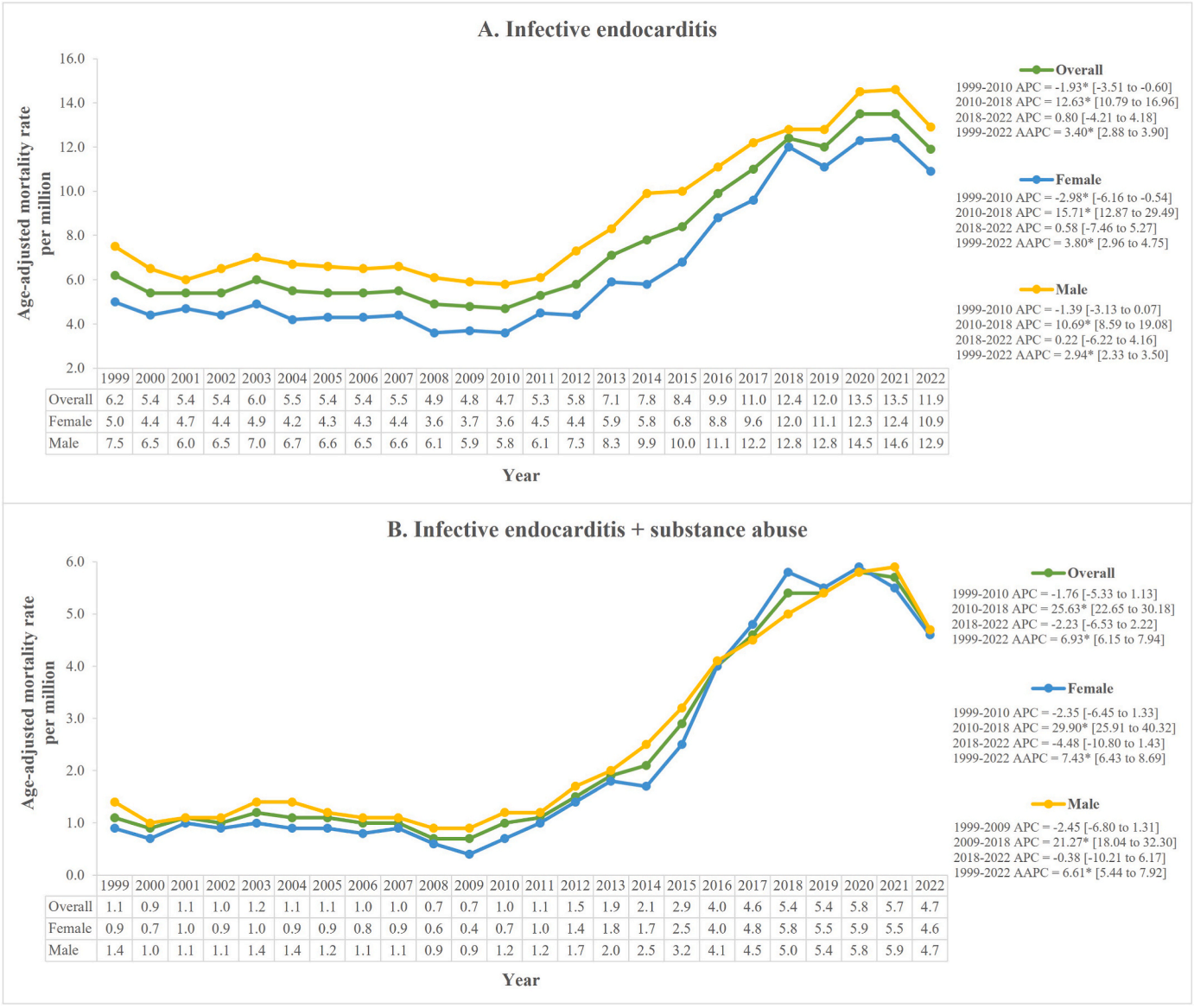
Of the total IE deaths, 12,917 (57.1 %) were men, with consistently higher AAMR than women from 1999 to 2022. Women experienced a decline in AAMR until 2010 from 5.0 to 3.6 (APC = −2.98*, CI: −6.16 to




| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 6.2 | 5.4 | 5.4 | 5.4 | 6.0 | 5.5 | 5.4 | 5.4 | 5.5 | 4.9 | 4.8 | 4.7 | 5.3 | 5.8 | 7.1 | 7.8 | 8.4 | 9.9 | 11.0 | 12.4 | 12.0 | 13.5 | 13.5 | 11.9 |
| Female | 5.0 | 4.4 | 4.7 | 4.4 | 4.9 | 4.2 | 4.3 | 4.3 | 4.4 | 3.6 | 3.7 | 3.6 | 4.5 | 4.4 | 5.9 | 5.8 | 6.8 | 8.8 | 9.6 | 12.0 | 11.1 | 12.3 | 12.4 | 10.9 |
| Male | 7.5 | 6.5 | 6.0 | 6.5 | 7.0 | 6.7 | 6.6 | 6.5 | 6.6 | 6.1 | 5.9 | 5.8 | 6.1 | 7.3 | 8.3 | 9.9 | 10.0 | 11.1 | 12.2 | 12.8 | 12.8 | 14.5 | 14.6 | 12.9 |

AAMR = Age-adjusted mortality rate per 1000,000 population; NH = Non-Hispanic, APC = Annual percentage change, AAPC = Average annual percentage change, 95% confidence interval

**Fig. 1.** Central illustration summarizing key findings of the results.




| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 6.2 | 5.4 | 5.4 | 5.4 | 6.0 | 5.5 | 5.4 | 5.4 | 5.5 | 4.9 | 4.8 | 4.7 | 5.3 | 5.8 | 7.1 | 7.8 | 8.4 | 9.9 | 11.0 | 12.4 | 12.0 | 13.5 | 13.5 | 11.9 |
| Female | 5.0 | 4.4 | 4.7 | 4.4 | 4.9 | 4.2 | 4.3 | 4.3 | 4.4 | 3.6 | 3.7 | 3.6 | 4.5 | 4.4 | 5.9 | 5.8 | 6.8 | 8.8 | 9.6 | 12.0 | 11.1 | 12.3 | 12.4 | 10.9 |
| Male | 7.5 | 6.5 | 6.0 | 6.5 | 7.0 | 6.7 | 6.6 | 6.5 | 6.6 | 6.1 | 5.9 | 5.8 | 6.1 | 7.3 | 8.3 | 9.9 | 10.0 | 11.1 | 12.2 | 12.8 | 12.8 | 14.5 | 14.6 | 12.9 |

| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1.1 | 0.9 | 1.1 | 1.0 | 1.2 | 1.1 | 1.1 | 1.0 | 1.0 | 0.7 | 0.7 | 1.0 | 1.1 | 1.5 | 1.9 | 2.1 | 2.9 | 4.0 | 4.6 | 5.4 | 5.4 | 5.8 | 5.7 | 4.7 |
| Female | 0.9 | 0.7 | 1.0 | 0.9 | 1.0 | 0.9 | 0.9 | 0.8 | 0.9 | 0.6 | 0.4 | 0.7 | 1.0 | 1.4 | 1.8 | 1.7 | 2.5 | 4.0 | 4.8 | 5.8 | 5.5 | 5.9 | 5.5 | 4.6 |
| Male | 1.4 | 1.0 | 1.1 | 1.1 | 1.4 | 1.4 | 1.2 | 1.1 | 1.1 | 0.9 | 0.9 | 1.2 | 1.2 | 1.7 | 2.0 | 2.5 | 3.2 | 4.1 | 4.5 | 5.0 | 5.4 | 5.8 | 5.9 | 4.7 |

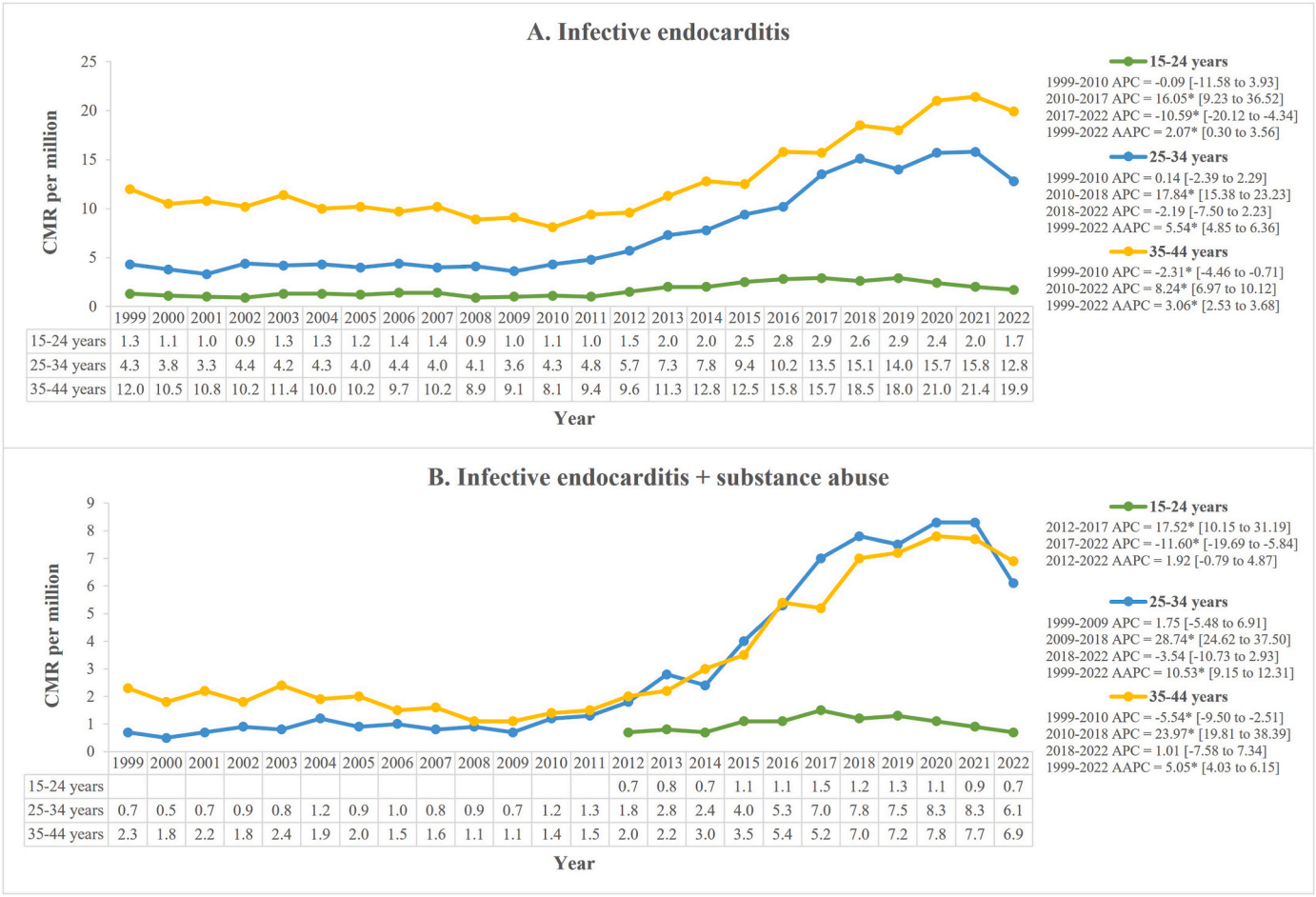
**Fig. 2.** IE and SA-IE-related AAMR in the United States, 1999 to 2022, Overall and stratified by sex.

−0.54). This was followed by an almost three-fold increase to 12.0 in 2018 (APC = 15.71*, CI: 12.87 to 29.49). For men, AAMR more than doubled from 5.8 in 2010 to 12.8 in 2018 (APC = 10.69*, CI: 8.59 to 19.08). For SA-IE, women had a higher percentage of SA-IE deaths than men (35.7 % vs. 29.2 %). Gender-specific trends in SA-IE mirrored those in IE, with women experiencing an almost eight-fold increase in AAMR from 2010 to 2018 (APC = 29.90*, CI: 25.91 to 40.32), while men had a five-fold increase from 2009 to 2018 (APC = 21.27*, CI: 18.04 to 32.30). AAPC was higher for women (IE: 3.80*, CI: 2.96 to 4.75; SA-IE: 7.43*, CI: 6.43 to 8.69) compared to men (IE: 2.94*, CI: 2.33 to 3.50; SA-IE: 6.61*, CI: 5.44 to 7.92) (Fig. 2). From 1999 to 2022, the proportion of IE deaths associated with SA increased in both sexes, peaking at 50.9 % for women in 2017 and 42.7 % for men in 2019 (Supplemental Fig. 10).

### 3.3. Age stratified

The age-stratified analysis of IE reveals a significant upward trend across all age groups, particularly from 2010 to 2018. The 25–34 age group, however, demonstrated the most pronounced change, with AAMR rising from 4.3 in 1999 to 12.8 in 2022 (AAPC = 5.54*, CI: 4.85 to 6.36) (Fig. 3) and the highest proportion of SA-IE deaths (41.1 %) (Table 1). This group underwent a 3.5-fold increase in AAMR from 4.3 in 2010 to 15.1 in 2018 (APC = 17.84*, CI: 15.38 to 23.23).

The 15–24 age group had lower IE AAMR overall, with a peak of 2.9 in 2017 and 2019, yet showed a higher percentage of SA-IE deaths (34.7 %) compared to the 35–44 age group (26.1 %). This younger group experienced a significant rise in AAMR from 2010 to 2017 (APC = 16.05*, CI: 9.23 to 36.52), followed by a decline through 2022 (APC = −10.59*, CI: −20.12 to −4.34). The 35–44 age group consistently had




| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15-24 years | 1.3 | 1.1 | 1.0 | 0.9 | 1.3 | 1.3 | 1.2 | 1.4 | 1.4 | 0.9 | 1.0 | 1.1 | 1.0 | 1.5 | 2.0 | 2.0 | 2.5 | 2.8 | 2.9 | 2.6 | 2.9 | 2.4 | 2.0 | 1.7 |
| 25-34 years | 4.3 | 3.8 | 3.3 | 4.4 | 4.2 | 4.3 | 4.0 | 4.4 | 4.0 | 4.1 | 3.6 | 4.3 | 4.8 | 5.7 | 7.3 | 7.8 | 9.4 | 10.2 | 13.5 | 15.1 | 14.0 | 15.7 | 15.8 | 12.8 |
| 35-44 years | 12.0 | 10.5 | 10.8 | 10.2 | 11.4 | 10.0 | 10.2 | 9.7 | 10.2 | 8.9 | 9.1 | 8.1 | 9.4 | 9.6 | 11.3 | 12.8 | 12.5 | 15.8 | 15.7 | 18.5 | 18.0 | 21.0 | 21.4 | 19.9 |

| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15-24 years | | | | | | | | | | | | | | 0.7 | 0.8 | 0.7 | 1.1 | 1.1 | 1.5 | 1.2 | 1.3 | 1.1 | 0.9 | 0.7 |
| 25-34 years | 0.7 | 0.5 | 0.7 | 0.9 | 0.8 | 1.2 | 0.9 | 1.0 | 0.8 | 0.9 | 0.7 | 1.2 | 1.3 | 1.8 | 2.8 | 2.4 | 4.0 | 5.3 | 7.0 | 7.8 | 7.5 | 8.3 | 8.3 | 6.1 |
| 35-44 years | 2.3 | 1.8 | 2.2 | 1.8 | 2.4 | 1.9 | 2.0 | 1.5 | 1.6 | 1.1 | 1.1 | 1.4 | 1.5 | 2.0 | 2.2 | 3.0 | 3.5 | 5.4 | 5.2 | 7.0 | 7.2 | 7.8 | 7.7 | 6.9 |

**Fig. 3.** IE and SA-IE-related crude mortality rates (CMR) in the United States, 1999 to 2022, stratified by age groups.

the highest IE AAMR, peaking at 21.4 in 2021. In this age group, AAMR initially fell by one-third from 12.0 in 1999 to 8.1 in 2010 (APC = −2.31*, CI: −4.46 to −0.71) and then nearly doubled by 2022 (APC = 8.24*, CI: 6.97 to 10.12), culminating in an overall increase to 19.9 (AAPC = 3.06*, CI: 2.53 to 3.68). SA-IE trends mirrored these patterns, except between 2017 and 2021 when the 25–34 age group exceeded the 35–44 age group in AAMR values (Fig. 3).

### 3.4. Race stratified

NH-AI/AN had the highest IE AAMR, nearly double or more compared to other races, with an increase from 26.8 in 2015 to 36.9 in 2022 (AAPC = 8.67*, CI: 0.24 to 19.62). NH Whites were the only other group with a significant overall increase in IE AAMR, rising from 4.7 in 1999 to 17.9 in 2021 (AAPC = 5.79*, CI: 5.12 to 6.44). In 1999, NH Whites had an AAMR of 4.7, about one-third of NH Blacks (16.4). From 2009, NH White AAMR rose nearly four-fold, reaching 16.4 by 2018 (APC = 15.42*, CI: 13.66–19.35), surpassing NH Black rates in 2015. NH Blacks and Hispanics saw initial declines in AAMR from 1999 to 2012 (NH Black: APC = −5.00*, CI: −6.32 to −3.96; Hispanics: APC = −3.74*, CI: −13.05 to −0.29), followed by significant increases through 2022 (NH Black: APC = 3.90*, CI: 2.27 to 6.38; Hispanics: APC = 7.54*, CI: 3.27 to 25.62). NH Black individuals were the only group with a significant overall decrease in AAMR (AAPC = −1.23*, CI: −1.75 to −0.71). In contrast, Hispanics experienced an overall stable AAMR (AAPC = 1.01, CI: −0.58 to 2.87). SA-associated IE AAMR followed a similar pattern, with SA-IE AAMR for NH whites increasing more than 10 times between 2009 and 2021. Supplemental Fig. 7 illustrates these race-stratified trends in AAMR for IE and SA-IE from 1999 to 2022.

Among racial groups, NH-AI/AN had the highest percentage of IE deaths associated with SA deaths (39.1 %), closely followed by NH Whites (37.8 %) (Table 1). In 2022, the percentage of SA-IE deaths among NH Whites was nearly triple that of NH Blacks (44.6 % vs. 16.5 %) and had more than doubled for NH White Americans from 18.5 % in 1999. NH Black and Hispanic groups also saw increases, though to a lesser extent (Supplemental Fig. 10).

### 3.5. Region stratified

All four US census regions saw an increase in IE mortality. AAMR for IE increased in the west from 4.6 in 2000 to 10.0 in 2022 (AAPC = 2.49*, CI: 1.25 to 4.03). AAMR nearly doubled in the Northeast (AAPC = 4.11*, CI: 3.44 to 4.90), Midwest (AAPC = 4.07*, CI: 3.10 to 5.01), and South (AAPC = 3.49*, CI: 2.73 to 4.27), with the South maintaining the highest

rates and peaking at 16.6 in 2021. The Northeast was the only region with a significant initial AAMR decline, from 6.0 in 1999 to 4.0 in 2011 (APC = −1.98*, CI: −4.41 to −0.10) (Supplemental Fig. 8). A similar trend was seen for SA-IE (Supplemental Fig. 8). The West had the highest proportion of IE deaths associated with SA (36.2 %) and witnessed a peak of 52.8 % of IE deaths related to SA in 2019 (Table 1, Supplemental Fig. 11).

### 3.6. Urbanization stratified

Initially, all three urbanization categories had similar AAMR until 2008. Afterward, a gap emerged, with rural areas peaking at double the AAMR of large metropolitan areas in 2020 (20.3 vs. 10.0). Rural AAMR showed the largest increase, rising from 4.0 in 2000 to 20.3 in 2020 (AAPC = 7.44*, CI: 6.79–8.14), with the steepest increase from 2011 to 2014 (APC = 25.42*, CI: 15.27–30.97). Medium/small metropolitan AAMR nearly tripled from 4.9 in 2008 to 17.5 in 2020 (AAPC = 5.66*, CI: 4.85–6.77), while large metropolitan areas saw a smaller rise from 6.7 to 10.0 (AAPC = 2.17*, CI: 1.53–2.95) (Supplemental Fig. 9). SA-IE followed similar trends (Supplemental Fig. 9). Each of the 3 groups saw an increase in the percentage of SA-IE-associated deaths (Supplemental Fig. 11).

### 3.7. States stratified

From 1999 to 2022, states in the upper 90th percentile for overall AAMR (above 12.1) included Vermont, Florida, Kentucky, Tennessee, and West Virginia, while those in the 10th percentile (below 4.9) included Idaho, Iowa, Minnesota, California, and Nebraska. Idaho had the lowest AAMR (4.0), and West Virginia had the highest (25.0) (Fig. 4). Over the last decade, all states showed increasing trends in AAMR, with West Virginia showing the most significant percentage increase (462.5 %) from 12.0 in 2008–2013 to 67.5 in 2018–2022 (Supplemental Table 9 and Supplemental Fig. 13). Within this timeframe, Tennessee showed the highest AAMR increase for IE from 8.7 to 27.4 (214.9 %) between 2008–2012 and 2013–2017 (Supplemental Fig. 14). Between 2013–2017 and 2018–2022, Colorado had the highest AAMR increase for IE, rising from 4.7 to 10.0 (112.8 %) (Supplemental Fig. 15), while South Carolina showed the largest increase for SA-IE, tripling from 2.2 to 6.6 (200.0 %) (Supplemental Fig. 15). Hawaii, Idaho, and Montana were the only states to report a decrease in IE AAMR during this period. Georgia recorded the lowest AAMR (1.0) for SA-IE, and West Virginia the highest (12.6) (Supplemental Fig. 12).

### 3.8. Changes from 2011 to 2022 and the impact of the pandemic

The increasing trend in our study is notable from 2010 onwards (Supplemental Fig. 6). In 2010, IE was associated with 561 deaths; only 131 (20.7 %) of these were associated with SA. By 2021, the number of IE-associated deaths increased to 1734, with 750 (43.3 %) of those associated with SA (Supplemental Fig. 6). When focused on this increasing trend, most subgroups have experienced a rising trend in IE AAMR through the COVID-19 pandemic years (2020–2022), while the SA-IE plateaued at higher AAMR. Subsequently, the percentage of IE deaths associated with SA stayed stable or decreased across most subgroups during the COVID-19 years (2020–2022) compared to the pre-pandemic period (2017–2019). Table 2 and Fig. 5 summarize this trend when seen in groups of successive 3-year from 2011 to 2022

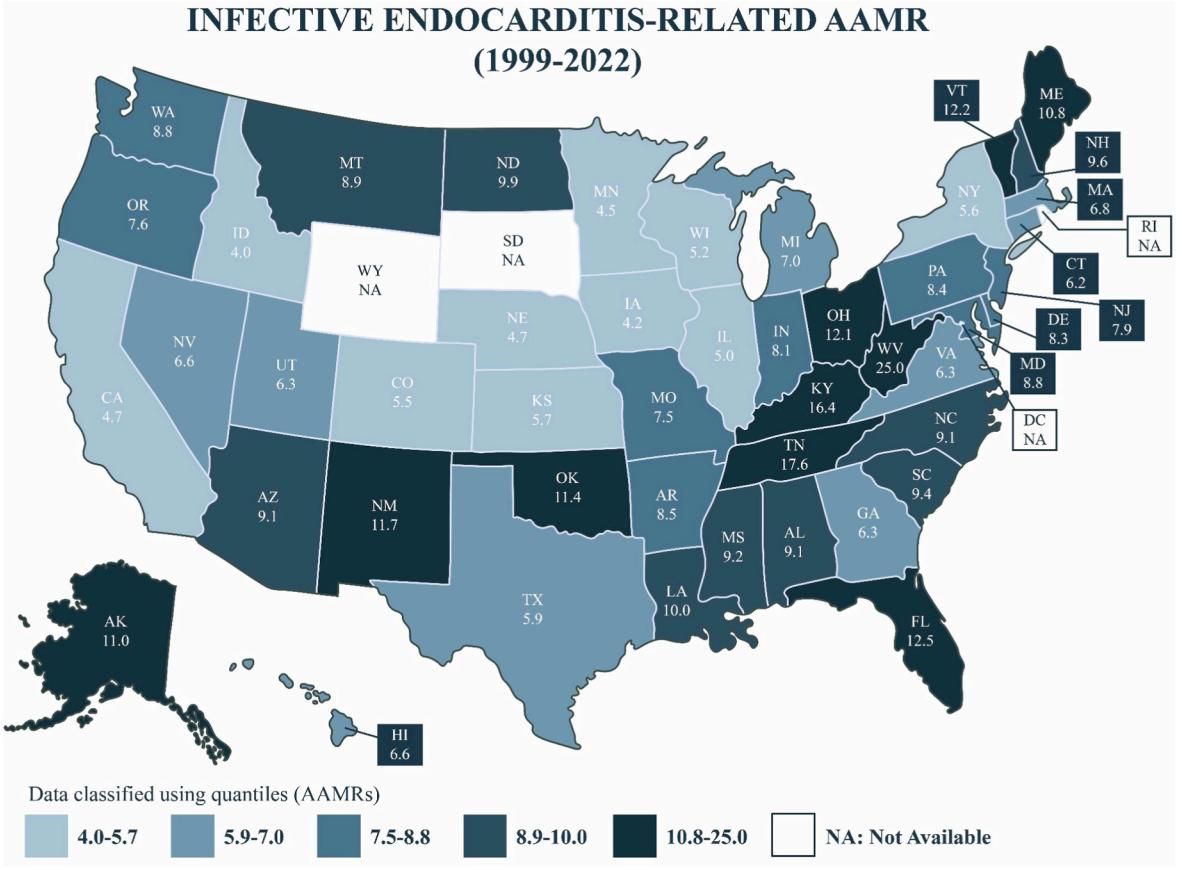



**Fig. 4.** State-level IE-related AAMR in the United States, 1999 to 2022.

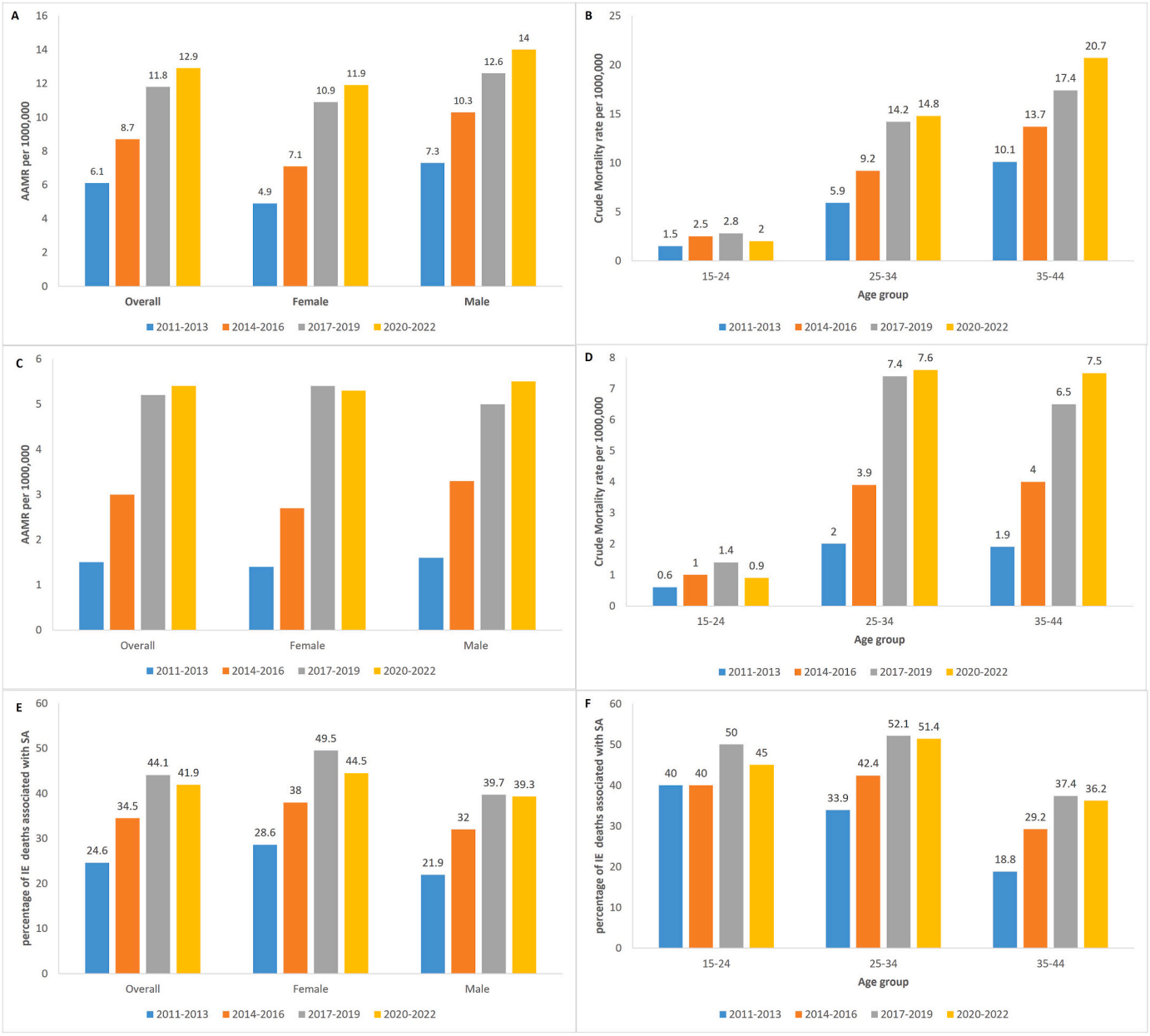



**Fig. 5.** Change in IE and SA-IE mortality in successive 3-year time periods with a focus on years with an increasing trend (2011–2022): IE-related mortality rate **a)** overall AAMR and stratified by sex **b)** Stratified by age groups SA-IE-related mortality rate **c)** overall AAMR and stratified by sex **d)** Stratified by age groups Percentage of IE deaths associated with SA **e)** overall and stratified by sex **f)** Stratified by age groups.

## 4. Discussion

Our analysis highlights a concerning increase in IE mortality in the young population in the US. This increase is associated with an increase in SA-IE mortality. While IE mortalities continued to increase through the COVID-19 pandemic, SA-IE plateaued at a high AAMR. We also found significant disparities with men having higher mortality rates, though women experienced a proportionally greater increase; NH-AI/AN had the worst increase in AAMR of all races, followed by NH White Americans. Geographically, the South experienced the most increase, and rural areas were disproportionally impacted during the later years of the study.

Comparing IE mortality with other Organization for Economic Cooperation and Development (OECD) countries reveals similar challenges. Between 2009 and 2019, many other countries also saw an increase in IE mortality such as France, Belgium, and Canada, but Greece and Italy saw the most dramatic rise – up to 250 %. Notably, Austria and Finland saw a gradual decline over the last 30 years, highlighting potential success in prevention and management strategies [14]. Globally shared challenges that increase the overall IE burden include the continued rise in IDU, changing microbiological trends towards more aggressive species, and the increasing use of implantable cardiac devices and valve replacements [14].

### 4.1. Substance abuse as a driver of IE

SA, especially IDU, increases the risk of IE by allowing bacteria to enter the bloodstream through contaminated injection equipment. This most commonly affects the tricuspid valve, followed by the aortic and mitral valves. From 2011 to 2018, the number of people who inject drugs (PWID) increased five-fold, mirroring the escalation of overdose deaths from 6 in 100,000 to 22 in 100,000. The surge in IE among

**Table 1**
Crude Number of IE and IE + SA associated deaths with percentage of IE death associated with SA in young adult population of US from 1999 to 2022.

| | Infective endocarditis deaths | Infective endocarditis + substance abuse deaths | Percentage of IE deaths associated with substance abuse (%) |
|---|---|---|---|
| **Overall** | 22614 | 7235 | 32.0 |
| **Sex** | | | |
| Female | 9697 | 3463 | 35.7 |
| Male | 12917 | 3772 | 29.2 |
| **Age groups** | | | |
| 15–24 | 1731 | 600 | 34.7 |
| 25–34 | 7864 | 3236 | 41.1 |
| 35–44 | 13019 | 3399 | 26.1 |
| **Race** | | | |
| NH White | 15186 | 5739 | 37.8 |
| NH Black or African American | 4062 | 530 | 13.0 |
| NH Asian or Pacific Islander | 384 | 47 | 12.2 |
| NH American Indian or Alaska native | 427 | 167 | 39.1 |
| Hispanic | 2448 | 704 | 28.8 |
| **Region** | | | |
| Northeast | 3643 | 1190 | 32.7 |
| Midwest | 4343 | 1328 | 30.6 |
| South | 10338 | 3165 | 30.6 |
| West | 4290 | 1552 | 36.2 |
| **Urbanization** | | | |
| Large Metropolitan | 10983 | 3345 | 30.5 |
| Medium/Small Metropolitan | 7649 | 2592 | 33.9 |
| Rural | 3982 | 1298 | 32.6 |

younger patients appears to be closely linked with the continued rise in SA in the younger patient population, which has been exacerbated by the ongoing and evolving opioid crisis toward injectable drugs [1]. Notably, half of all PWID were within the younger age group of 18–39 years old, despite this age range only comprising around 40 % of the general population [3].

While SA is a prominent driver of IE mortality among younger patients, other factors also contribute to fatalities. Advancements in medical care have enabled more patients with congenital heart disease to survive into adulthood, creating a growing population at risk for IE [14].

### 4.2. Disparities in gender and race

Our findings underscore significant gender and racial disparities in IE mortality. While males exhibit the highest overall mortality rates, likely due to the higher number of overdose deaths and cardiac device implantation [3,15], there was a marked three-fold increase in overall IE mortality rates among females. This may be because women are more likely to have immunosuppressive conditions, more advanced symptoms at presentation, and are less likely to undergo valve surgery. Those who do undergo cardiac surgery also have worse outcomes compared to their male counterparts. A study in Spain had even reported the female sex as an independent predictor of IE in-hospital mortality [16]. These disparities may reflect the systemic gender inequities in healthcare delivery [15].

In addition to the significant rise in mortality among females, it was noted that females had a greater percentage attributed to SA-IE. Previous studies suggested that women experience a steeper increase in SA-IE hospitalizations compared to men, our results have shown that women also have higher SA-IE mortality rates [1]. This phenomenon may be attributed to systemic inequities, such as reduced access to housing, harm-reduction resources, employment, and needle exchange services for women [17]. Additionally, women are more likely to engage in high-risk behaviors, such as sharing needles and other injection drug equipment, often due to social dynamics in IDU settings. This is thought to be due to women frequently initiating IDU with others, and the power imbalances in these relationships, particularly romantic or sexual, may increase the likelihood of needle sharing [17].

Racial disparities in IE mortality are also concerning. NH-AI/AN race has the highest AAMR and the largest increase over time. This could be due to this population having the highest rate of diabetes among all ethnic groups, which is associated with double the likelihood of in-hospital death in patients with IE. Additionally, limited access to healthcare services and inadequate federal funding for the Indian Health Service (IHS), which primarily serves tribal lands, may further contribute to these disparities [18,19]. Among all racial groups, AI/AN also have the highest proportional percentage of IE deaths associated with SA. This likely is due to the higher rates of SA among AI/AN adolescents, particularly those living on reservations or dropped out of high school [20]. These disparities contribute to their susceptibility to SA-IE.

NH White individuals also saw a significant increase in IE AAMR. The AAMR quadrupled over the study period, now surpassing NH Black to become the racial group with the second-highest IE AAMR. This could be attributed to the rise in SA and IDU noted among this population. NH White individuals were documented to have the highest rate of fatal and non-fatal drug overdose events in 2018 [3].

While NH White individuals continue to see a rise in IE mortality, NH Black and Hispanic individuals initially noted a decrease in mortality through 2012 but has now started to increase again. However, both racial groups were less impacted by SA-IE, as their increase in mortality rates attributed to SA-IE was less dramatic as compared to NH White individuals. These findings highlight the complex interplay of socioeconomic factors, access to healthcare, and SA patterns that shape the burden of IE among different communities.

### 4.3. Geographical disparities

We also noted in our results that there were geographical disparities among IE mortality rates. There was a significant increase in mortality rates among the Southern states and rural areas. This may be due to the high rates of overdose deaths noted in the South, consistent with prior studies that observed a prominent rise in the states of Kentucky, Tennessee, and West Virginia [3,5].

The rise in mortality in rural communities is also observed. This disparity may be due to the difference in healthcare access. Rural regions may lack access to specialty care, and hospitals located in rural areas are less likely to have the advanced imaging and/or surgical potential to diagnose and manage complex IE cases compared to more urban areas [21].

### 4.4. Impact of COVID-19 pandemic

An intriguing aspect of our findings is the plateau in SA-IE mortality rates during the COVID-19 pandemic. This trend is likely multifactorial. Public health restrictions during the pandemic reduced social interactions, subsequently limiting access to alcohol, tobacco, and other substances [22]. Additionally, disruptions in the drug supply chain led to adaptations in SA patterns, inadvertently reducing high-risk behaviors. For example, data from San Francisco (2018–2020) documented a shift from injecting heroin to smoking fentanyl due to changes in opioid availability [23]. However, SA-IE-related deaths during the pandemic, particularly in its early phase, may have been underreported. Many deaths may have been attributed solely to COVID-19, overlooking IE as a contributing factor, especially given the more rigorous diagnostic criteria required for IE. Furthermore, out-of-hospital deaths due to severe acute COVID-19 may have contributed to the underestimation of IE-related mortality [24].

**Table 2**
AAMR for IE, IE + SA and percentage of IE deaths related to SA out of all IE deaths stratified by age groups, sex, race, regions and urbanization status for successive clusters of 3 consecutive years from 2011 to 2022.

| | 2011–2013 | | | 2014–2016 | | | 2017–2019 | | | 2020–2022 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IE | IE + SA | Percentage of IE deaths associated with SA (%) | IE | IE + SA | Percentage of IE deaths associated with SA (%) | IE | IE + SA | Percentage of IE deaths associated with SA (%) | IE | IE + SA | Percentage of IE deaths associated with SA (%) |
| **Overall [AAMR]** | 6.1 [5.8–6.3] | 1.5 [1.4–1.6] | 24.6 [24.1–25.4] | 8.7 [8.4–9.1] | 3.0 [2.8–3.2] | 34.5 [33.3–35.2] | 11.8 [11.4–12.1] | 5.2 [4.9–5.4] | 44.1 [43.0–44.6] | 12.9 [12.6–13.3] | 5.4 [5.2–5.7] | 41.9 [41.3–42.9] |
| **Age groups [Crude Mortality Rates]** | | | | | | | | | | | | |
| 15–24 | 1.5 [1.3–1.7] | 0.6 [0.5–0.7] | 40.0 [38.5–41.2] | 2.5 [2.2–2.7] | 1.0 [0.8–1.1] | 40.0 [36.4–40.7] | 2.8 [2.5–3.1] | 1.4 [1.2–1.6] | 50.0 [48.0–51.6] | 2.0 [1.8–2.3] | 0.9 [0.7–1.0] | 45.0 [38.9–43.5] |
| 25–34 | 5.9 [5.5–6.4] | 2.0 [1.7–2.2] | 33.9 [30.9–34.4] | 9.2 [8.6–9.7] | 3.9 [3.6–4.2] | 42.4 [41.9–43.3] | 14.2 [13.5–14.8] | 7.4 [7.0–7.9] | 52.1 [51.9–53.4] | 14.8 [14.1–15.4] | 7.6 [7.1–8.0] | 51.4 [50.4–51.9] |
| 35–44 | 10.1 [9.6–10.7] | 1.9 [1.6–2.1] | 18.8 [16.7–19.6] | 13.7 [13.1–14.4] | 4.0 [3.6–4.3] | 29.2 [27.5–29.9] | 17.4 [16.6–18.1] | 6.5 [6.1–7.0] | 37.4 [36.7–38.7] | 20.7 [20.0–21.5] | 7.5 [7.0–7.9] | 36.2 [35.0–36.7] |
| **Sex [AAMR]** | | | | | | | | | | | | |
| Female | 4.9 [4.6–5.2] | 1.4 [1.2–1.6] | 28.6 [26.1–30.8] | 7.1 [6.8–7.5] | 2.7 [2.5–2.9] | 38.0 [36.8–38.7] | 10.9 [10.4–11.4] | 5.4 [5.1–5.7] | 49.5 [49.0–50.0] | 11.9 [11.4–12.4] | 5.3 [5.0–5.6] | 44.5 [43.9–45.2] |
| Male | 7.3 [6.9–7.7] | 1.6 [1.4–1.8] | 21.9 [20.3–23.4] | 10.3 [9.9–10.8] | 3.3 [3.0–3.5] | 32.0 [30.3–32.4] | 12.6 [12.1–13.1] | 5.0 [4.6–5.3] | 39.7 [38.0–40.5] | 14.0 [13.5–14.5] | 5.5 [5.2–5.8] | 39.3 [38.5–40.0] |
| **Race[a] [AAMR]** | | | | | | | | | | | | |
| NH White | 6.8 [6.5–7.2] | 2.1 [1.9–2.3] | 30.9 [29.2–31.9] | 11.1 [10.6–11.5] | 4.5 [4.2–4.8] | 40.5 [39.6–41.7] | 15.4 [14.9–15.9] | 7.5 [7.2–7.9] | 48.7 [48.3–49.7] | 17.0 [16.4–17.5] | 8.0 [7.6–8.3] | 47.1 [46.3–47.4] |
| NH Black or African American | 8.4 [7.6–9.3] | – | – | 8.7 [7.8–9.5] | 1.1 [0.8–1.4] | 12.6 [10.3–14.7] | 10.2 [9.3–11.1] | 2.0 [1.6–2.4] | 19.6 [17.2–21.6] | 11.5 [10.6–12.5] | 1.9 [1.5–2.3] | 16.5 [14.2–18.4] |
| NH American Indian or Alaska native | 14.6 [10.5–19.6] | – | – | 21.3 [16.3–27.2] | 6.3 [3.9–9.8] | 29.6 [23.9–36.0] | 28.3 [22.8–34.7] | 16.4 [12.3–21.4] | 58.0 [53.9–61.7] | 42.7 [35.1–50.3] | 19.3 [14.6–25.1] | 45.2 [41.6–49.9] |
| Hispanic | 3.4 [2.9–3.8] | 0.7 [0.5–0.9] | 20.6 [17.2–23.7] | 3.8 [3.4–4.3] | 0.9 [0.7–1.1] | 23.7 [20.6–25.6] | 5.4 [4.9–5.9] | 1.9 [1.6–2.3] | 35.2 [32.7–39.0] | 6.5 [6.0–7.1] | 2.3 [2.0–2.6] | 35.4 [33.3–36.6] |
| **Region [AAMR]** | | | | | | | | | | | | |
| Northeast | 4.9 [4.4–5.5] | 1.4 [1.1–1.7] | 28.6 [25.0–30.9] | 6.7 [6.1–7.4] | 2.6 [2.2–3.1] | 38.8 [36.1–41.9] | 10.4 [9.6–11.2] | 4.7 [4.2–5.3] | 45.2 [43.8–47.3] | 13.1 [12.2–14.0] | 5.3 [4.8–5.9] | 40.5 [39.3–42.1] |
| Midwest | 5.7 [5.1–6.2] | 1.4 [1.1–1.6] | 24.6 [21.6–25.8] | 7.8 [7.2–8.4] | 2.4 [2.1–2.8] | 30.8 [29.2–33.3] | 11.9 [11.1–12.7] | 5.1 [4.6–5.6] | 42.9 [41.4–44.1] | 12.7 [11.9–13.5] | 5.3 [4.7–5.8] | 41.7 [39.5–43.0] |
| South | 7.6 [7.1–8.1] | 1.6 [1.4–1.8] | 21.1 [19.7–22.2] | 11.6 [11.0–12.2] | 3.7 [3.4–4.0] | 31.9 [30.9–32.8] | 14.7 [14.1–15.3] | 6.2 [5.8–6.6] | 42.2 [41.1–43.1] | 15.6 [14.9–16.2] | 6.5 [6.1–6.9] | 41.7 [40.9–42.6] |
| West | 5.0 [4.5–5.5] | 1.6 [1.3–1.8] | 32.0 [28.9–32.7] | 6.5 [6.0–7.0] | 2.7 [2.3–3.0] | 41.5 [38.3–42.9] | 8.2 [7.6–8.8] | 4.0 [3.6–4.4] | 48.8 [47.4–50.0] | 9.0 [8.4–9.6] | 3.9 [3.5–4.3] | 43.3 [41.7–44.8] |

[a] NH Asian or Pacific Islander had suppressed/unreliable data throughout the time period. "-" represents suppressed/unreliable data.

Despite the plateau of SA-IE, there was a continued rise in overall IE mortality during the COVID-19 pandemic. This trend is likely due to the significant impact that COVID-19 had on healthcare systems. The restrictions delayed primary care, diagnostics, and overall access to care. This delay in diagnosis led to patients who present with higher comorbidity burdens, increased disease severity and consequently more complications, longer stays in the intensive care unit and increased in-hospital mortality [25].

### 4.5. Public health and clinical implications

These findings have significant implications for public health and clinical practice. SA-IE imposes a large financial burden on healthcare systems, as many patients tend to be of lower socioeconomic status and rely on publicly funded medical insurance [1]. From a clinical perspective, patients with SA and IE also face unique challenges. While short-term outcomes are overall favorable, long-term prognoses are often poor due to high rates of recidivism [1]. The standard of care includes a prolonged course of antibiotics and is often associated with surgical valve replacement in those who meet the criteria. However, valve surgery in this patient population brings controversy due to the concern of postoperative relapse and subsequent prosthetic valve infection [26], leading to worse outcomes for these patients compared to non-SA-IE patients who underwent surgery [4]. However, emerging minimally invasive techniques, such as percutaneous aspiration devices may offer a promising alternative for managing patients who are not surgical candidates [4].

### 4.6. Mitigation strategies

IE, especially SA-IE, represents a growing public health challenge among young individuals aged 15–44 in the United States. Addressing the root causes of SA through expanded access to addiction treatment services, including medication-assisted therapy, is critical in mitigating the long-term impacts of the opioid epidemic and its overall role in SA. Additionally, harm reduction strategies, such as needle exchange programs and supervised injection facilities, should be considered to decrease the high-risk behaviors that put patients at risk of blood-borne infections. A multicenter, prospective, cohort study completed in Spain demonstrated promising results of their implemented SA programs, as there is now a very low proportion of IE associated with IDU [27].

While the COVID-19 pandemic appeared to briefly plateau mortality rates for SA-IE, the persistent increase in IE suggests that the disruption to harm reduction services and healthcare access may have exacerbated existing vulnerabilities that may have been masked during the lockdown. It will be interesting to see how this trend evolves in coming years – whether it stays plateaued in the post-pandemic world, starts to trend downwards, or resumes the upward trend. Future efforts should focus on implementing comprehensive harm reduction strategies, addiction management, and addressing systemic inequities, so we can alleviate the disease burden and improve outcomes for vulnerable populations.

### 4.7. Limitations

Given the retrospective nature of the study, the analysis is limited by the quality and completeness of the existing datasets. CDC WONDER database is compiled of death certificates that rely on ICD codes for the identification of disease thus adding a potential for misclassification bias. Variability in data reporting, coding errors, or underreporting of SA and associated infections could introduce bias or inaccuracies. The aggregate nature of the database allows us to show an association with the increasing trends in both SA and IE but precludes establishing a cause-effect relationship. While the dataset does provide information through the COVID-19 pandemic, we cannot fully account for any variability that could have occurred with the enacted restrictions and the disrupted healthcare access during the lockdown. The rural-urban stratified analysis was conducted for the period 1999 to 2020, as the database does not report population data for rural and urban areas or mortality rates beyond 2020. CDC suppresses the counts of fewer than 10 in CDC WONDER data to protect confidentiality, and death rates are marked unreliable for a count less than 20. Our data did have suppressed or unreliable data for subgroups with lower counts. This limitation was more common for state-level data and sensitivity analysis and has been indicated with "-" in the tables and dotted lines in the figures.

## 5. Conclusion

IE-related mortality in the young adult population of the US has increased from 2010 onwards, with a concerning rise in SA and IE-associated deaths. Pronounced disparities have emerged, including a greater proportional increase among women and the highest mortality rates observed among the NH-AI/AN race.

## CRediT authorship contribution statement

**Ali Bin Abdul Jabbar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Daniyal Ali Khan:** Visualization, Writing – review & editing. **May Li-Jedras:** Writing – review & editing, Writing – original draft. **Amjad Kabach:** Writing – review & editing. **Ahmed Aboeata:** Supervision.

## Statement of ethics

Study approval statement: Our study was exempt from institutional review board approval because the CDC WONDER database contains anonymized, publicly available data.

Consent to participate statement: No patient consent was needed for this study, as CDC WONDER contains anonymized, publicly available data.

## Data availability statement

Data was extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) website and was used for this study. https://wonder.cdc.gov/. Data is provided within the manuscript and the supplemental files.

## Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2025.200404.

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