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ARTICLE

Carotid artery stenosis-related mortality among older adults (>65 years): a retrospective analytical study

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Abstract

Stroke is a leading cause of death, with carotid artery stenosis (CAS) contributing substantially to ischemic events. Although CAS-related strokes remain common in older adults in the United States, mortality patterns and demographic disparities are not well described. We aimed to evaluate nationwide trends and disparities in CAS-related mortality among US adults aged ≥65 years from 1999 to 2020 using the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. A retrospective analysis of the CDC WONDER database was conducted to investigate CAS-related mortality trends. Using Joinpoint regression analysis, age-adjusted mortality rates (AAMRs) and crude mortality rates (CMRs) per 100,000 individuals, along with annual percent change, were calculated and stratified by year, sex, age, race/ethnicity, and geographic region. Between 1999 and 2020, 44,297 CAS-related deaths occurred among US adults aged ≥65 years. Overall, the AAMR declined from 3.13 in 1999 to 2.27 in 2009, then rose sharply from 3.86 in 2015 to 6.56 in 2020, with an overall average annual percent change of 1.58% (95% CI 0.99-2.16; p<0.001). Mortality was higher in men than women (AAMR 6.52 vs. 3.91) and increased with age, peaking among adults aged ≥85 years (CMR 12.5). Regionally, the Midwest had the highest AAMR (4.55), followed by the West (4.30), South (4.25), and Northeast (4.16). Non-metropolitan and metropolitan areas showed comparable AAMRs. By race/ethnicity, non-Hispanic White individuals had the highest mortality (AAMR 4.6), followed by non-Hispanic Black (3.11) and Hispanic individuals (2.73). At the state level, Vermont had the highest AAMR (7.26), while Utah had the lowest (2.33). After an initial decline, CAS-related mortality among older US adults rose after 2009, reaching its highest levels in 2020. Persistent disparities by sex, age, race/ethnicity, and region highlight the need for targeted interventions in high-risk populations.

Key words: carotid artery stenosis, stroke, mortality, age-adjusted mortality rate.

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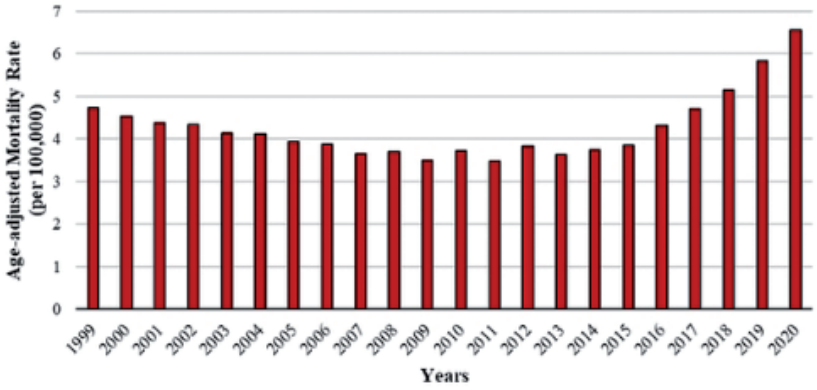
Graphical abstract

Central Illustrations: Carotid Artery Stenosis–Related Mortality Among Older Adults (>65 Years): A Retrospective Analytical Study

Overall Mortality Trends (AAMR per 100,000)



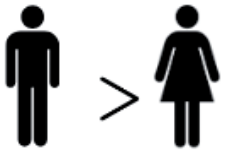
Overall:
1999–2009 (APC: -2.76, 95% CI, -3.33 to -2.19)
2009–2015 (APC: 1.30, 95% CI, -0.36 to 3.00)
2015–2020 (APC: 11.19, 95% CI, 9.77 to 12.64)
AAPC: 1.58 (95% CI, 0.99 to 2.16)

Overall, AAMR due to CAS increased substantially from **3.86** in 2015 to **6.56** in 2020.

Gender and Racial Disparity

NH Whites > NH Blacks > Hispanics or Latino

NH White individuals had the highest overall AAMR for CAS (4.6 per 100,000), followed by NH Black or African American individuals (3.11), while Hispanic or Latino individuals had the lowest AAMR (2.73).



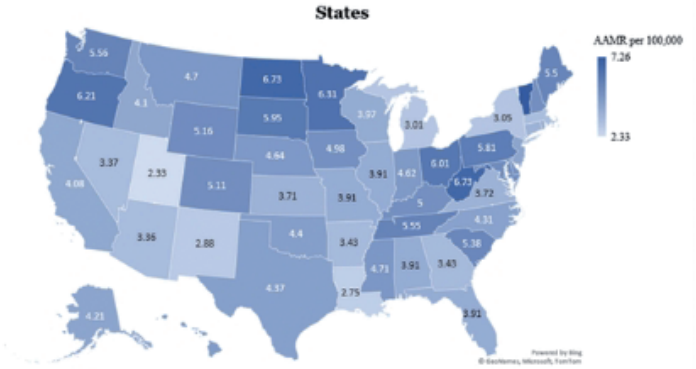
Men > Women

Men exhibited a higher AAMR for CAS than women (6.52 vs. 3.91)

Gender Disparity due to CAS-related Mortality

Vermont (7.26), North Dakota (6.73), West Virginia (6.73), Minnesota (6.31), and Oregon (6.21) were among the high-risk states showing high AAMR due to CAS. While the lowest AAMRs were observed in Utah (2.33), the District of Columbia (2.38), Louisiana (2.75), New Mexico (2.88), and Michigan (3.01).

Similarly, between 1999 and 2020, the AAMR for CAS was highest in the Midwest (4.55), followed by the West (4.30), South (4.25), and Northeast (4.16).



Introduction

Stroke is a leading cause of death and long-term disability in the United States, affecting over 795,000 individuals and resulting in approximately 140,000 deaths annually.[1,2] The majority of strokes, between 80% and 87%, are ischemic in nature, and among these, large-artery atherosclerosis accounts for nearly 25% of cases. Within this etiologic spectrum, carotid artery stenosis (CAS), characterized by progressive atherosclerotic narrowing of the carotid arteries, represents a critical and potentially modifiable contributor.[3] CAS underlies an estimated 10-20% of ischemic strokes, and the risk of cerebrovascular events rises steeply with increasing severity of stenosis.[4] Individuals with high-grade narrowing (≥75%) face a 26% risk of stroke within three years.[5] Even in the absence of overt symptoms, CAS remains clinically significant, as more than one-third of affected individuals are at risk of mortality and approximately 10% may experience a stroke, emphasizing its role as a silent yet formidable driver of cerebrovascular disease.[5]

Since 1968, the epidemiology of stroke has evolved considerably, reflecting both meaningful advances and emerging concerns.[6] Age-adjusted stroke mortality rates declined for many years, largely owing to improved hypertension control, reductions in smoking prevalence, and advances in acute stroke management.[6] However, these gains have not been uniformly distributed across the population.[7] Marked disparities persist along racial, ethnic, socioeconomic, and geographic lines. For example, data from the Northern Manhattan Study demonstrate that Black and Hispanic individuals experience nearly twice the incidence of stroke compared with their White counterparts.[7] Although these observations pertain to stroke broadly, CAS, given its central role in ischemic stroke pathogenesis, likely mirrors similar inequities. Intriguingly, while overall stroke mortality is higher among Black and Hispanic populations, the prevalence of CAS itself appears more common among White individuals, suggesting complex and potentially divergent patterns in disease burden and outcomes.[7,8] Despite this, population-level analyses specifically examining CAS-related mortality trends and disparities remain limited.

Compounding these concerns, recent evidence suggests that the long-standing decline in stroke mortality has plateaued, with rates modestly increasing since 2013.[9] Projections further estimate that by 2030, stroke prevalence will rise by more than 20%, driven in part by demographic shifts and the growing burden of cardiometabolic risk factors.[10] The risk of CAS increases substantially with advancing age and is closely associated with modifiable conditions such as hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking.[11] Aging itself promotes arterial stiffening and atherosclerotic progression, rendering older adults particularly vulnerable. In the context of an expanding elderly population and rising prevalence of these risk factors, CAS-related morbidity and mortality are poised to increase.[11] Accordingly, a detailed understanding of temporal changes and demographic variations in CAS-related outcomes is imperative.

Therefore, we conducted a comprehensive analysis of CAS-related mortality trends among U.S. adults aged 65 years and older. By evaluating longitudinal patterns and assessing differences according to sex, race/ethnicity, age strata, and geographic region, this study aims to clarify evolving epidemiological dynamics, identify vulnerable subgroups, and inform targeted public health strategies to reduce disease burden and address persistent inequities in cerebrovascular outcomes.

Materials and Methods

Study design and source

Our study was a retrospective analysis of mortality data spanning the past two decades. Death certificate data were extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database for the period 1999-2020.[12] We used Multiple Cause-of-Death Public Use records to identify deaths attributed to "cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries" and "aneurysm of the carotid artery," corresponding to International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes I63.2 and I72.0, respectively. These codes were selected based on the higher prevalence of stenosis in the carotid arteries compared with vertebral arteries; however, it should be noted that I63.2 also captures deaths due to stenosis of vertebral arteries. As this study utilized de-identified, publicly available data, it was exempt from institutional review board approval, in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13]

Data extraction

We extracted data regarding population size, year, demographics, and geography from 1999 to 2020. Demographic variables included sex, race/ethnicity, age, and place of death (including medical facilities such as outpatient, emergency room, inpatient, or dead-on arrival; home; hospice; and nursing home/long-term care facilities). Geographical data included urban-rural classifications, census regions, and states. Race/ethnicity was classified as non-Hispanic (NH) White, NH African American, Hispanic or Latino, NH American Indian or Alaska Native, and NH Asian or Pacific Islander. These race/ethnicity categories have previously been used within analyses from the CDC WONDER database, and this information is based on the reported data on death certificates.[12] We categorized age into three groups: 65-74, 75-84, and 85+ years. Using the 2013 National Center for Health Statistics (NCHS) Urban-Rural Classification Scheme, we categorized the population into large central, fringe metropolises, medium/small metropolises (50,000-999,999), non-metro, and non-core.[14] Census regions were divided into the Northeast, Midwest, South, and West.

Statistical analysis

We calculated age-adjusted mortality rates (AAMRs) and crude mortality rates (CMRs) per 100,000 population to identify national trends and disparities. AAMRs were calculated by standardizing condition-related deaths to the year 2000 U.S. standard population, while CMRs were calculated by dividing the number of deaths by the total population for the corresponding year.[15] Trends in AAMRs were analyzed using the Joinpoint Regression Program (Version 5.4.0.0; National Cancer Institute) to estimate annual percent change (APC) with 95% confidence intervals (CIs).[16] This software identifies significant temporal shifts by fitting log-linear regression models. APCs were increasing or decreasing if the slope was significantly different from zero, as determined by two-tailed t-tests. A p-value of <0.05 was considered statistically significant.

Results

Overall trends

Between 1999 and 2020, the U.S. recorded 44,297 adult deaths due to CAS, with an average AAMR of 3.99 per 100,000 population. During this period, the AAMR initially declined significantly from 4.74 in 1999 to 3.49 in 2009, with an APC of –2.76% (95% CI: –3.33 to –2.19), followed by a slight non-significant increase in AAMR to 3.86 in 2015 and an APC of 1.30% (95% CI: –0.36 to 3.00). Following 2015, the death toll increased significantly till 2020 as APC peaked at 11.19% (95% CI: 9.77 to 12.64) with an AAMR of 6.56. Overall, the average annual percent change (AAPC) for the entire 20-year period was 1.58% (95% CI: 0.99 to 2.16; p<0.000001), indicating a statistically significant long-term trend (Figure 1, Table 1, and Supplementary Table 1).

Carotid artery stenosis mortality trends stratified by sex

From 1999 to 2020, men consistently exhibited a higher AAMR for CAS than women (6.52 *vs*. 3.91). The dynamics of both reflected the same trends as observed for the entire population: Among men, the AAMR declined from 5.97 in 1999 to 4.41 in 2009 (APC −3.39%, 95% CI −4.13 to −2.63), followed by a modest increase to 4.86 in 2015 (APC 1.43%, 95% CI −0.70-3.60), and then rose sharply to 8.01 by 2020 (APC 10.78%, 95% CI 8.98-12.61). Overall, the AAPC was 1.21% (95% CI 0.46-1.96; p<0.000001), reflecting a modest but significant upward trend. Among women, the AAMR declined from 3.91 in 1999 to 2.87 in 2009 (APC −2.27%, 95% CI −3.22 to −1.30), followed by a slight, non-significant rise to 3.19 in 2015 (APC 1.03%, 95% CI −1.75-3.88), and then increased significantly to 5.45 by 2020 (APC 11.09%, 95% CI 8.72-13.52). The overall AAPC for women was 1.72% (95% CI 0.74-2.71; p<0.000001), indicating a modest but significant upward trend (Figure 1, Table 1, and Supplementary Table 2).

Carotid artery stenosis-related mortality trends stratified by age

From 1999 to 2020, adults aged ≥85 years had the highest CMR for CAS (12.5), followed by those aged 75-84 years (5.16), and 65-74 years (1.82). Among adults aged 65-74 years, the CMR declined from 2.27 in 1999 to 1.46 in 2009 (APC −4.31%, 95% CI −5.31 to −3.29), followed by a slight, non-significant increase to 1.52 in 2015 (APC 1.23%, 95% CI −1.75 to 4.29). A subse-

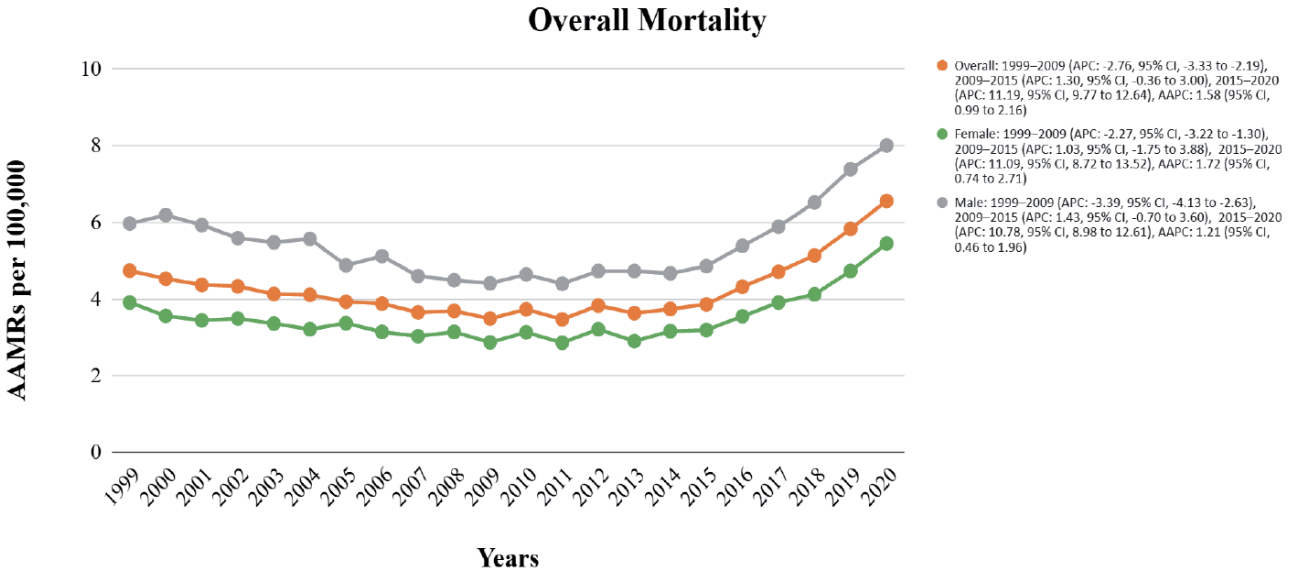


Figure 1. Age-adjusted mortality rates per 100,000 population, stratified by sex and overall, from 1999 to 2020.

quent rise occurred through 2020, reaching 2.48 (APC 9.60%, 95% CI 7.06-12.19), resulting in an overall, non-significant AAPC of 0.43% (95% CI −0.60-1.48; p=0.41). In the 75-84-year age group, the CMR decreased significantly from 5.88 in 1999 to 4.60 in 2006 (APC −3.76%, 95% CI −4.54 to −2.97), followed by a non-significant gradual decline to 4.21 in 2014 (APC −0.51%, 95% CI −1.37 to 0.36). From 2014 to 2020, the rate rose sharply to 7.27 (APC 8.75%, 95% CI 7.78-9.73), with an overall AAPC of 0.93% (95% CI 0.47-1.39; p<0.0001), indicating a significant upward trend. Among adults aged ≥85 years, the CMR decreased slightly from 11.8 in 1999 to 9.26 in 2009 (APC −1.37%, 95% CI −2.51 to −0.22), followed by a slight rise to 10.9 in 2015 (APC −1.37%, 95% CI −2.51 to −0.22; p=0.3) before a steep increase to 21.67 by 2020 (APC 13.67%, 95% CI 11.10-16.30), resulting in an overall AAPC of 2.88% (95% CI 1.81-3.97; p<0.0001), representing the largest and most significant rise across all age groups (Figure 2, Table 1, and Supplementary Table 3).

Carotid artery stenosis mortality trends stratified by census region

Between 1999 and 2020, the AAMR for CAS was highest in the Midwest (4.55), followed by the West (4.30), South (4.25), and Northeast (4.16). Trends in all regions followed the similar dynamics as described for the entire population: West showed the highest overall increase in AAMR from 4.08 in 1999 to 6.77 in 2020 (AAPC 2.90%, 95% CI 1.91-3.91; p<0.000001). Similarly, in the South, AAMR rose from 4.48 in 1999 to 6.50 in 2020 (AAPC 1.95%, 95% CI 1.30-2.60; p<0.000001). In the same way, Midwest showed a significant upward trend from 5.33 in 1999 to 6.71 in 2020 (AAPC 0.93%, 95% CI 0.12-1.74; p=0.024). Finally, Northeast showed an apparent rise in AAMR over the study period, from 5.01 in 1999 to 6.16 in 2020, although the trend was not significant (AAPC 0.75%, 95% CI −0.38-1.90; p=0.192) (Figure 3, Table 1, and Supplementary Table 4).

Carotid artery stenosis mortality trends stratified by urbanization

Between 1999 and 2020, heterogeneity was observed across urbanization strata in AAMR trends for CAS. In large central metropolitan areas, the AAMR declined from 3.98 in 1999 to 2.75 in 2013 (APC −1.85%, 95% CI −2.54 to −1.16), followed by an increase to 4.90 in 2020 (APC 7.19%, 95% CI 5.39-9.01), resulting in an overall AAPC of 1.07% (95% CI 0.39-1.76; p<0.000001). In large fringe metropolitan areas, the AAMR decreased from 4.93 in 1999 to 3.37 in 2006 (APC −5.00%, 95% CI −6.83 to −3.13), followed by a non-significant change to 3.59 in 2014 (APC 0.24%, 95% CI −1.71 to 2.22), and then increased to 5.44 in 2020 (APC 7.75%, 95% CI 5.66-9.88), with an overall AAPC of 0.52% (95% CI −0.52-1.56; p=0.31). In medium metropolitan areas, the AAMR declined from 4.99 in 1999 to 4.00 in 2014 (APC −1.58%, 95% CI −2.17 to −0.98), followed by a marked increase to 7.24 in 2020 (APC 11.73%, 95% CI 9.64-13.86), resulting in an overall AAPC of 2.06% (95% CI 1.40-2.71; p<0.000001). In small metropolitan areas, the AAMR declined from 5.73 in 1999 to 3.76 in 2008 (APC −3.73%, 95% CI −5.45 to −1.98), followed by an increase to 5.29 in 2016 (APC 3.35%, 95% CI 0.77-5.99), and then a sharp rise to 9.14 in 2020 (APC 16.04%, 95% CI 11.16-21.13), with an overall AAPC of 2.49% (95% CI 1.11-3.89; p<0.000001). Among non-metropolitan areas, micropolitan regions exhibited a decline from 5.40 in 1999 to 4.04 in 2015 (APC −1.80%, 95% CI −2.86 to −0.72), followed by a steep increase to 8.92 in 2020 (APC 16.23%, 95% CI 10.47-22.29), resulting in an overall AAPC

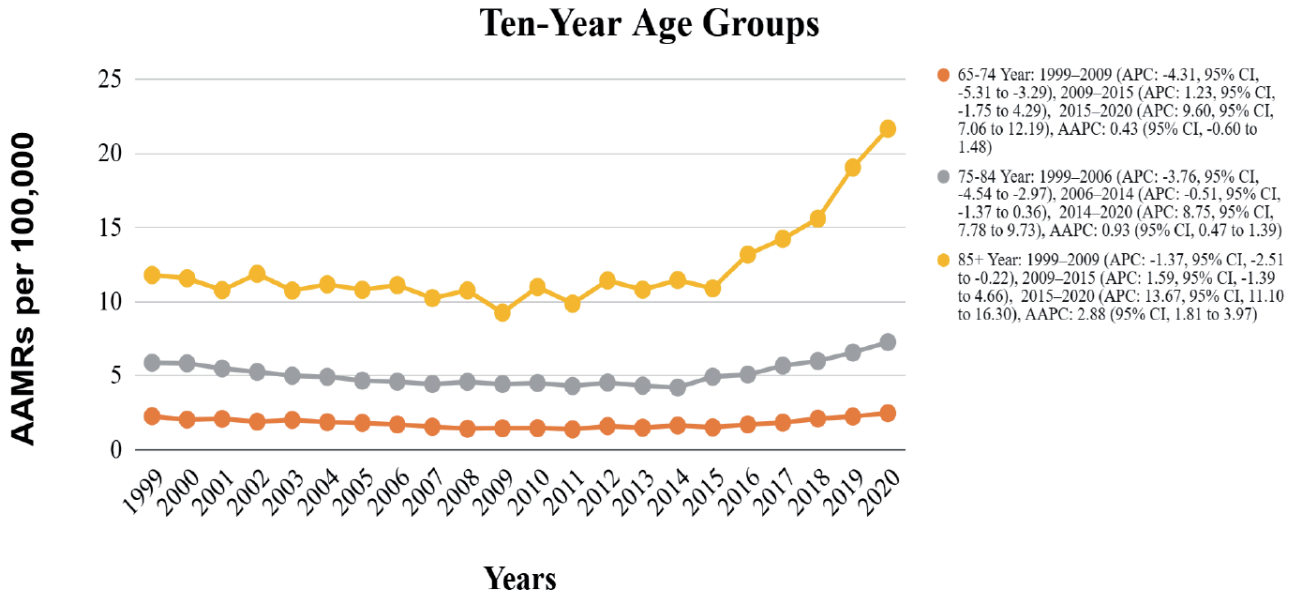


Figure 2. Crude mortality rate per 100,000 among ten-year age groups from 1999-2020.

of 2.22% (95% CI 0.84-3.63; p<0.000001). Similarly, noncore regions showed a decline from 4.13 in 1999 to 3.81 in 2014 (APC −1.51%, 95% CI −2.47 to −0.54), followed by an increase to 7.71 in 2020 (APC 12.41%, 95% CI 8.84-16.11), with an overall AAPC of 2.28% (95% CI 1.19-3.39; p<0.000001) (Figure 4, Table 1, and Supplementary Table 5).

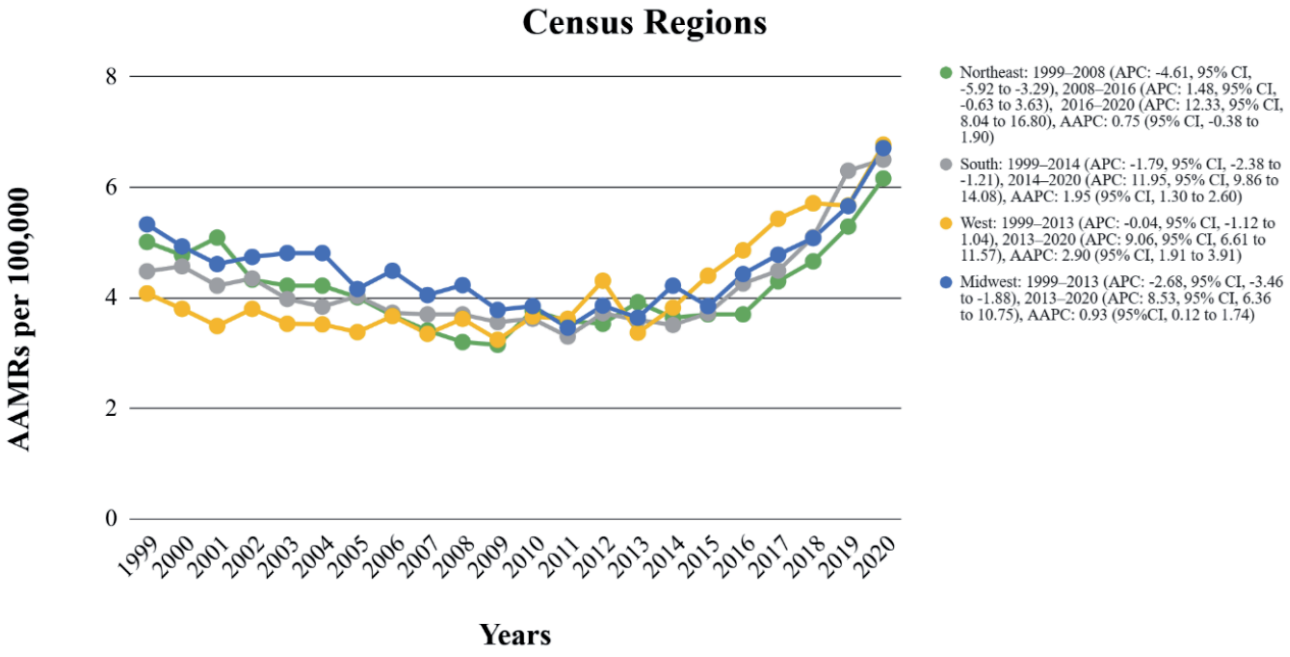


Figure 3. Age-adjusted mortality rate per 100,000 in the census regions from 1999-2020.

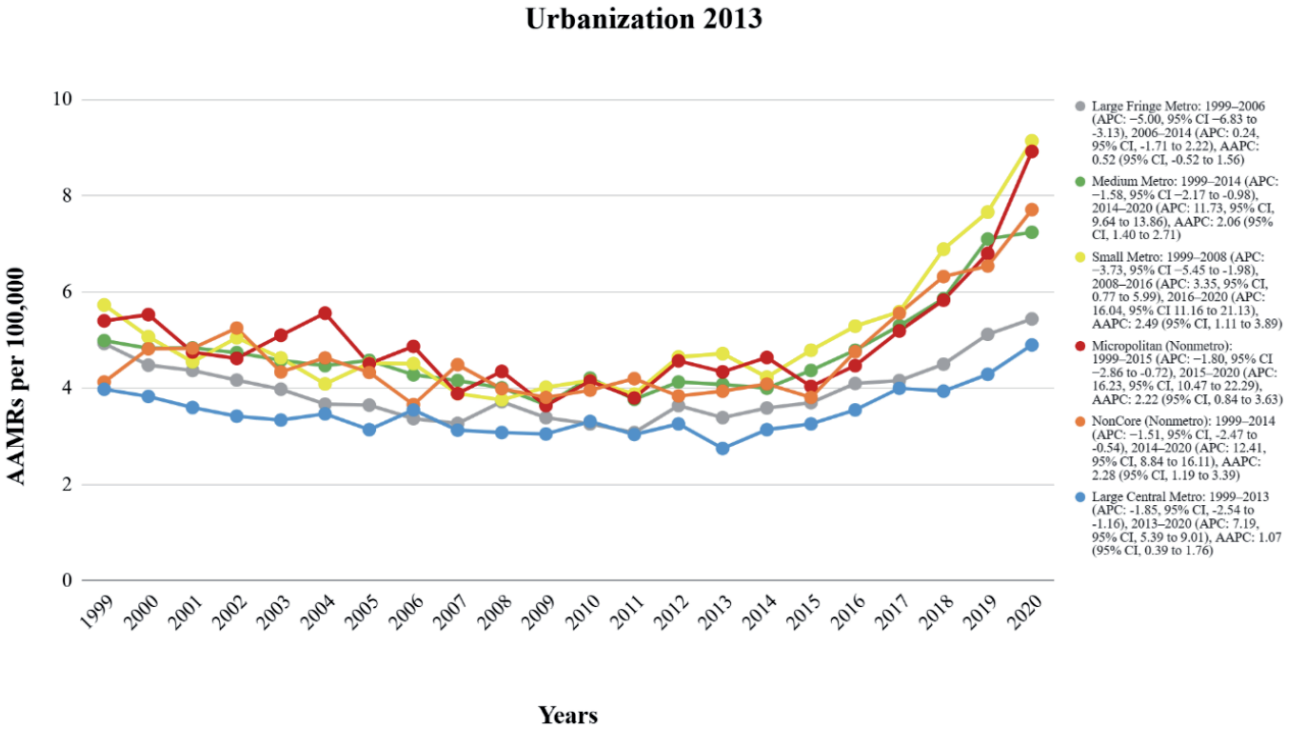


Figure 4. Age-adjusted mortality rate per 100,000 among rural and urban areas from 1999-2020.

Carotid artery stenosis mortality trends stratified by race/ethnicity

Across the study period, NH White individuals had the highest overall AAMR for CAS (4.6 per 100,000), followed by NH Black or African American individuals (3.11), while Hispanic or Latino individuals had the lowest AAMR (2.73). Data for NH American Indian and Alaska Native individuals were considered unreliable. Among NH White individuals, the AAMR declined significantly from 5.07 in 1999 to 3.71 in 2009 (APC −2.65%, 95% CI −3.16 to −2.13), followed by a slight, non-significant rise to 4.20 in 2015 (APC 1.64%, 95% CI 0.06-3.26). Thereafter, a sharp increase was observed, reaching 7.12 in 2020 (APC 11.33%, 95% CI 10.01-12.66), resulting in an overall significant AAPC of 1.76% (95% CI 1.21-2.31; p<0.000001). In NH Black or African American individuals, the AAMR decreased from 2.98 in 1999 to 2.39 in 2014 (APC −1.91%, 95% CI −3.75 to −0.04), followed by a significant increase through 2020, reaching 5.04 (APC 12.30%, 95% CI 6.23-18.72). The overall AAPC was 1.95% (95% CI −0.00 to 3.95; p=0.05), indicating a borderline non-significant trend. Among Hispanic or Latino individuals, the AAMR showed a non-significant decline from 2.01 in 1999 to 2.18 in 2013 (APC −0.07%, 95% CI −2.05 to 1.95), followed by a significant increase to 4.13 in 2020 (APC 7.86%, 95% CI 4.11-11.74). The overall AAPC was 2.51% (95% CI 0.82-4.22; p=0.003), reflecting a significant upward trend. (Figure 5, Table 1, and Supplementary Table 6).

Carotid artery stenosis mortality trends stratified by states

Between 1999 and 2020, Vermont had the highest AAMR for CAS (7.26 per 100,000), followed closely by North Dakota (6.73), West Virginia (6.73), Minnesota (6.31), and Oregon (6.21). In contrast, the lowest AAMRs were observed in Utah (2.33), the District of Columbia (2.38), Louisiana (2.75), New Mexico (2.88), and Michigan (3.01) (Supplementary Figure 2, Table 1, and Supplementary Table 7).

Carotid artery stenosis mortality trends stratified by place of death

Most CAS-related deaths occurred in inpatient medical facilities (42.68%). An additional 5.33% occurred in outpatient or emergency departments, and 0.49% were pronounced dead on arrival, while 0.07% had unspecified medical facility status. Deaths at home accounted for 24.83%, followed by nursing homes or long-term care facilities (18.27%) and hospice settings (4.62%). A smaller proportion occurred in other locations (3.51%), and 0.18% had an unknown place of death (Supplementary Figure 1, Table 1, and Supplementary Table 8).

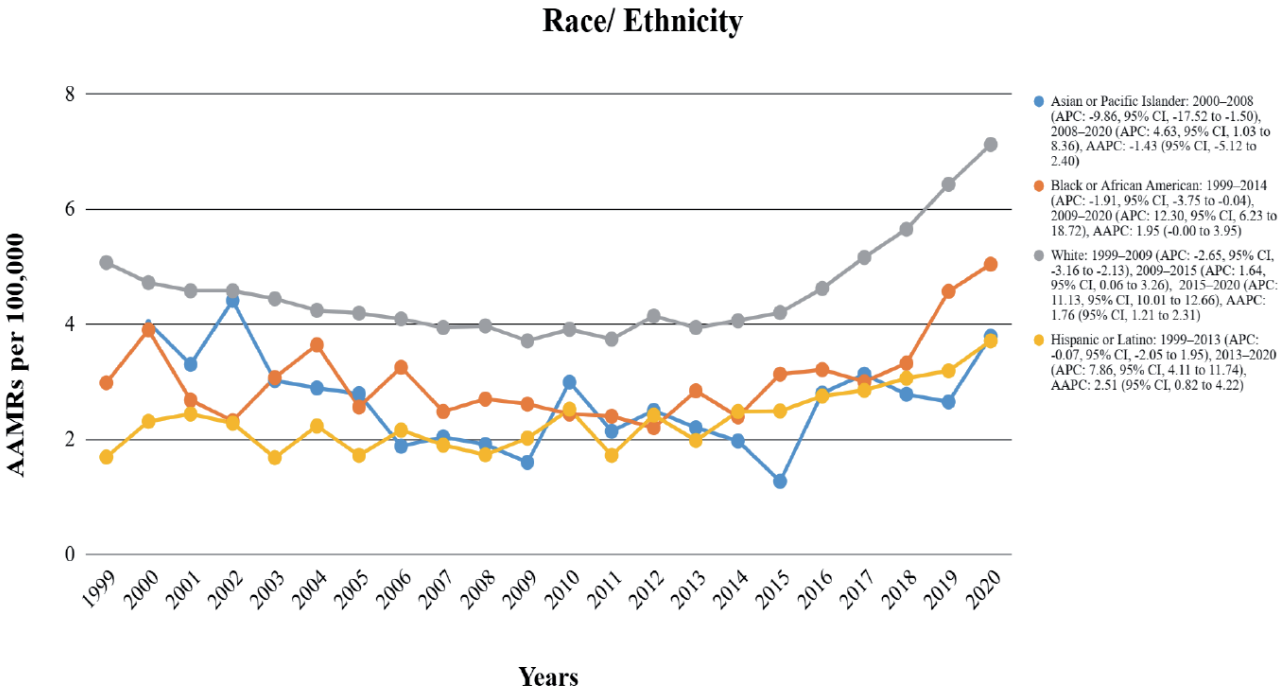


Figure 5. Age-adjusted mortality rate per 100,000 of race/ethnicity from 1999-2020.

Table 1. Annual and average annual percent changes in mortality by demographic and geographic subgroups (1999-2020).

Cohort	Lower endpoint	Upper endpoint	APC (95% CI)	AAPC (95% CI)
Overall	1999	2009	−2.76 (−3.33 to −2.19)	
	2009	2015	1.30 (−0.36 to 3.00)	1.58 (0.99 to 2.16)
	2015	2020	11.19 (9.77 to 12.64)	
Gender				
Female	1999	2009	−2.27 (−3.22 to −1.30)	
	2009	2015	1.03 (−1.75 to 3.88)	1.72 (0.74 to 2.71)
	2015	2020	11.09 (8.72 to 13.52)	
Male	1999	2009	−3.39 (−4.13 to −2.63)	
	2009	2015	1.43 (−0.70 to 3.60)	1.21 (0.46 to 1.96)
	2015	2020	10.78 (8.98 to 12.61)	
Ten-year age groups				
65-74 years	1999	2009	−4.31 (−5.31 to −3.29)	
	2009	2015	1.23 (−1.75 to 4.29)	0.43 (−0.60 to 1.48)
	2015	2020	9.60 (7.06 to 12.19)	
75-84 years	1999	2006	−3.76 (−4.54 to −2.97)	
	2006	2014	−0.51 (−1.37 to 0.36)	0.93 (0.47 to 1.39)
	2014	2020	8.75 (7.78 to 9.73)	
85+ years	1999	2009	−1.37 (−2.51 to −0.22)	
	2009	2015	1.59 (−1.39 to 4.66)	2.88 (1.81 to 3.97)
	2015	2020	13.67 (11.10 to 16.30)	
Race/ethnicity				
White	1999	2009	−2.65 (−3.16 to −2.13)	
	2009	2015	1.64 (0.06 to 3.26)	1.76 (1.21 to 2.31)
	2015	2020	11.33 (10.01 to 12.66)	
Black or African American	1999	2014	−1.91 (−3.75 to −0.04)	1.95 (−0.00 to 3.95)
	2014	2020	12.30 (6.23 to 18.72)	
Hispanic or Latino	1999	2013	−0.07 (−2.05 to 1.95)	2.51 (0.82 to 4.22)
	2013	2020	7.86 (4.11 to 11.74)	
Asian or pacific islander	2000	2008	−9.86 (−17.52 to −1.50)	−1.43 (−5.12 to 2.40)
	2008	2020	4.63 (1.03 to 8.36)	
Census regions				
Northeast	1999	2008	−4.61 (−5.92 to −3.29)	
	2008	2016	1.48 (−0.63 to 3.63)	0.75 (−0.38 to 1.90)
	2016	2020	12.33 (8.04 to 16.80)	
Midwest	1999	2013	−2.68 (−3.46 to −1.88)	0.93 (0.12 to 1.74)
	2013	2020	8.53 (6.36 to 10.75)	
South	1999	2014	−1.79 (−2.38 to −1.21)	1.95 (1.30 to 2.60)
	2014	2020	11.95 (9.86 to 14.08)	
West	1999	2013	−0.04 (−1.12 to 1.04)	2.90 (1.91 to 3.91)
	2013	2020	9.06 (6.61 to 11.57)	
Urbanization 2013				
Metropolitan (large central)	1999	2013	−1.85 (−2.54 to −1.16)	1.07 (0.39 to 1.76)
	2013	2020	7.19 (5.39 to 9.01)	
Metropolitan (large fringe)	1999	2006	−5.00 (−6.83 to −3.13)	
	2006	2014	0.24 (−1.71 to 2.22)	0.52 (−0.52 to 1.56)
	2014	2020	7.75 (5.66 to 9.88)	
Medium metro	1999	2014	−1.58 (−2.17 to −0.98)	2.06 (1.40 to 2.71)
	2014	2020	11.73 (9.64 to 13.86)	
Small metro	1999	2008	−3.73 (−5.45 to −1.98)	
	2008	2016	3.35 (0.77 to 5.99)	2.49 (1.11 to 3.89)
	2016	2020	16.04 (11.16 to 21.13)	
Nonmetropolitan (micropolitan)	1999	2015	−1.80 (−2.86 to −0.72)	2.22 (0.84 to 3.63)
	2015	2020	16.23 (10.47 to 22.29)	
Nonmetropolitan (noncore)	1999	2014	−1.51 (−2.47 to −0.54)	2.28 (1.19 to 3.39)
	2014	2020	12.41 (8.84 to 16.11)	

APC, annual percent change; AAPC, average annual percent change; CI, confidence interval.

Discussion

Our study shows a remarkable trend reversal of CAS-related mortality in the U.S. with a decline in mortality in the first decade but a sharp increase in mortality from mid-2010 years resulting in a meaningful overall increase from 1999 to 2020. This trend including the sharp acceleration from 2015 was consistent across all subgroups including both genders, age ethnicity, geographic region, and urbanization. The sharp upward trend was most pronounced among older adults, particularly those aged ≥85 years, underscoring the disproportionate burden in advanced age. Geographic disparities were also evident, with higher mortality in non-metropolitan areas and in regions such as the Midwest and South, alongside marked state-level variation. Racial and ethnic differences persisted, with the highest mortality burden among NH-White individuals and notable recent increases among Hispanic populations. Most deaths occurred in inpatient medical settings, followed by long-term care facilities and decedents' homes.

Consistent with prior epidemiological studies of stroke mortality, our findings demonstrate that CAS-related mortality among U.S. adults aged ≥65 years declined steadily from 1999 to 2009, reflecting major advances in cerebrovascular prevention and acute treatment.[10] The late 1990s marked a pivotal shift with the widespread adoption of intravenous thrombolysis as a cornerstone of ischemic stroke management, followed by the establishment of endovascular thrombectomy as standard care for large-vessel occlusions, both of which substantially improved outcomes when delivered within evidence-based time periods.[10,17] In tandem, advances in secondary prevention, including intensive lipid-lowering strategies demonstrated in landmark trials such as Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), further reduced recurrent cerebrovascular risk.[18] However, this favorable trajectory attenuated after 2009, with a more evident rise in CAS-related mortality emerging in the mid-2010s and persisting through 2020. Although the underlying causes of this reversal are likely multifactorial, the escalating prevalence of cardiometabolic risk factors, including obesity, diabetes mellitus, hypertension, and substance use disorders, provides a plausible explanatory framework.[6] These conditions accelerate atherosclerotic progression and may have offset gains achieved through advances in acute intervention and secondary prevention. The rising burden of modifiable risk factors underscores the need for earlier, sustained, and multidisciplinary preventive strategies beginning in primary care settings.[19] Additionally, improved survival among patients with head and neck malignancies may represent an underrecognized contributor, as radiation-induced vascular injury is increasingly linked to accelerated carotid atherosclerosis and subsequent cerebrovascular events.[20] This evolving survivorship-related risk further highlights the importance of coordinated long-term surveillance among oncology, vascular, and neurology specialists.

Although the rise in mortality attributable to CAS is concerning, this burden is not evenly distributed across demographic groups, with our findings demonstrating persistently higher rates of CAS-related mortality among men compared with women. This sex disparity is partially explained by the greater prevalence of classical vascular risk factors in men, such as smoking, hypertension, and diabetes, which accelerate atherosclerotic progression and increase the likelihood of clinically significant carotid disease.[21-23] Beyond these established contributors, accumulating evidence highlights intrinsic sex-specific differences in vascular biology and plaque composition as additional modulators of risk.[24] Men tend to develop atherosclerosis at an earlier age and exhibit a higher proportion of unstable plaque phenotypes, both of which confer heightened susceptibility to cerebrovascular events.[24] Supporting this, histopathological analyses of carotid endarterectomy specimens show that plaques in women are less inflammatory, with lower macrophage infiltration, reduced interleukin-8 expression, and greater smooth muscle and collagen content, characteristics consistent with more stable vascular structures.[25] Complementing these molecular and cellular distinctions, sex-based variations in carotid bifurcation geometry and local hemodynamics appear to influence plaque distribution and rupture propensity, providing a biomechanical basis for the observed mortality gradient.[25] These findings underscore the need for clinical trials and preventive strategies that are adequately powered for sex-stratified analyses and incorporate the biological, structural, and hemodynamic factors that contribute to elevated CAS risk in men.

Another group disproportionately affected by the burden of CAS in our study was NH-White individuals. This finding aligns with prior evidence from a large study at Los Angeles County General Hospital, where 21.5% of Caucasian patients exhibited >59% stenosis, compared with substantially lower rates among Hispanic (10.1%), Black (8.7%), and Asian (10.7%) individuals (7). Although traditional cardiovascular risk factors might intuitively explain such disparities, this attribution proves inadequate as Black individuals typically exhibit a higher prevalence of obesity, hypertension, and dyslipidemia than their White counterparts, yet manifest lower rates of severe CAS.[26] Converging lines of evidence from vascular imaging underscore race-specific differences in plaque location and morphology.[26] For instance, Watase et al. demonstrated that White individuals more frequently harbor plaques featuring luminal surface disruption and other high-risk plaque characteristics, features linked to plaque instability and heightened cerebrovascular event risk.[27] Additionally, data from the Multi-Ethnic Study of Atherosclerosis (MESA) further reveals a stronger association between sleep apnea and carotid plaque burden in White participants relative to other racial/ethnic groups, potentially mediated by recurrent nocturnal hypoxia and sympathetic activation that promote plaque formation and vulnerability in genetically or environmentally susceptible populations.[28] Clarifying the biological and environmental drivers of these differences will be critical for developing more precise, population-informed strategies to reduce disparities in carotid atherosclerosis and its downstream consequences.

Furthermore, advancing age was strongly associated with higher mortality in our analysis, reflecting the cumulative structural and biological changes that predispose older individuals to CAS. Aging is characterized by progressive remodeling of the carotid vasculature, including increases in vessel

diameter, arterial tortuosity, and alterations in the geometry of the common and internal carotid arteries.[29] These age-related morphological adaptations extend to widening of the carotid bifurcation and internal carotid artery angles, as well as a more cephalad anatomical positioning of the internal carotid artery in older adults.[29] Such geometric modifications induce hemodynamic perturbations, particularly at the carotid bifurcation, a well-recognized predilection site for atherosclerotic plaque formation due to its inherently complex flow patterns.[29] These structural changes occur alongside the lifelong accrual of atherosclerotic risk factors. Prolonged exposure to hypertension, dyslipidemia, diabetes, smoking, and obesity promotes cumulative endothelial injury, chronic inflammation, and progressive plaque development over decades.[30] The interaction between age-related vascular remodeling and sustained risk factor burden provides a plausible explanation for the sharp rise in CAS-related mortality with advancing age, highlighting the importance of early risk factor control and age-tailored screening strategies.

Our analysis also uncovered marked geographic disparities in CAS-related mortality, with the Midwest and non-metropolitan regions shouldering a disproportionately heavy burden. Rural populations face entrenched structural impediments to optimal vascular care, including restricted access to specialized stroke and neurovascular services, chronic shortages of vascular specialists and multidisciplinary teams, and substantial travel distances to comprehensive or tertiary centers, factors that collectively delay CAS detection, narrow therapeutic windows for intervention, and undermine adherence to guideline-directed preventive therapies.[6,31] These infrastructural limitations intersect with pervasive socioeconomic disadvantages in rural counties, encompassing lower educational attainment, reduced median household incomes, elevated poverty levels, and food insecurity.[32] Such determinants constrain effective risk factor control and timely diagnostic evaluation through interconnected pathways, including chronic psychosocial stress, limited health literacy, and reduced engagement with preventive services.[32] The combined effect of geographic isolation, healthcare resource scarcity, and socioeconomic vulnerability likely underlies the steep geographical gradient in CAS-related mortality observed in our study. Addressing these entrenched inequities requires multifaceted, regionally tailored strategies, most notably the scalable deployment of telestroke and telehealth networks to facilitate earlier specialist consultation and CAS management, alongside upstream public health interventions aimed at mitigating socioeconomic disparities and strengthening preventive care in underserved rural communities.[33]

Our study has several limitations that should be considered when interpreting the findings. First, the reliance on death certificate data introduces the potential for misclassification due to inaccuracies in ICD coding or human error in cause-of-death documentation. Second, the CDC WONDER database lacks granular clinical information, preventing adjustment for important variables such as lipid profiles, hematologic indices, or disease severity. Third, because the dataset captures only decedents, we could not assess the underlying prevalence of CAS in the living population. Finally, methodological constraints of Joinpoint regression include reduced statistical power with small event counts, the assumption of log-linear trends that may oversimplify complex temporal patterns, sensitivity to the number of join points selected, and an inability to adjust for individual-level confounders, which limits causal inference.

Conclusions

CAS-related mortality in the US has sharply risen from the mid-2010 years following an earlier period of decline, with the increase disproportionately affecting older adults, men, non-metropolitan populations, and residents of certain high-burden regions, particularly in the Midwest. Persistent racial and geographic disparities further underscore the uneven distribution of disease burden. These findings signal a concerning reversal in progress and emphasize the need for focused prevention strategies, improved risk factor control, and strengthened healthcare delivery in vulnerable populations. Targeted public health and policy-driven interventions aimed at high-risk demographic and regional groups may be critical to mitigating rising mortality and advancing health equity.

Ethical approval

Our study included de-identified publicly available data. Thus, institutional review board approval was not required.

Availability of data and material

The data supporting the findings of this study are available from the corresponding author upon reasonable request

Conflict of interests

The authors declare no potential conflict of interest.

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Authors' contributions

AHBG, AAC, and HN contributed to the study conception, design, data acquisition, and drafting of the manuscript. SSJ contributed to data analysis, interpretation of results, and critical revision of the manuscript. WD, HA, and MSK contributed to study supervision, methodological guidance, and critical revision of the manuscript for important intellectual content. All authors contributed to manuscript writing, approved the final version, and agree to be accountable for all aspects of the work.

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Online supplementary material:

Supplementary Figure S1. Distribution of deaths by place of occurrence from 1999-2020.

Supplementary Figure S2. Age-adjusted mortality rate per 100,000 population by U.S. state, 1999–2020.

Supplementary Table S1. Overall CAS-related age-adjusted mortality rate per 100,000.

Supplementary Table S2. CAS-related age-adjusted mortality rate per 100,000 stratified by sex.

Supplementary Table S3. CAS-related age-adjusted mortality rate per 100,000 based on ten-year age groups.

Supplementary Table S4. Census regions with CAS-related age-adjusted mortality rate per 100,000.

Supplementary Table S5. CAS-related age-adjusted mortality rate per 100,000 as per urbanization.

Supplementary Table S6. Race/ ethnicity based CAS-related age-adjusted mortality rate per 100,000.

Supplementary Table S7. CAS-related age-adjusted mortality rate per 100,000 at state-level.

Supplementary Table S8. CAS-related age-adjusted mortality rate per 100,000 stratified by place of death.