

Trends and Disparities in Systemic Sclerosis-Related Mortalities in the United States from 1999 to 2023

Nikil Kumar

Liaquat University of Medical and Health Sciences

Muhammad Uzair

Liaquat University of Medical and Health Sciences

Tehreem Rao

Dow University of Health Sciences

Sanya Ashraf Khaskheli

Liaquat University of Medical and Health Sciences

FNU Urooba

CMH Institute of Medical Science, Multan

Najaf Ahmed Rajpar

Bilawal Medical College, LUMHS, Jamshoro

Muddassir Khalid

Nishtar Medical University

Kinza Raza

Bakhtawar Amin Medical & Dental College (BAMDC)

Akash Kumar

Bilawal Medical College, LUMHS, Jamshoro

Saqlain Anwar

PNS Shifa Hospital

Kanwal Asghar

Dow University of Health Sciences

Ammar Alnour

ammaralemam10@gmail.com

Al Mughtaribeen University

Research Article

Keywords:

Posted Date: June 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9624915/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Systemic Sclerosis (SSc) is a chronic, autoimmune fibrosing illness that affects the skin and numerous other organs. Long-term trends in mortality disparities are not well characterized. We analysed demographic and regional inequalities in Systemic sclerosis-related mortality in the US from 1999 to 2023 using CDC WONDER data.

Methodology:

We performed a retrospective analysis of death certificate data for individuals aged 15–85 years, identifying Systemic sclerosis-related deaths (ICD10 M-34). Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated for mortality trends stratified by year, gender, race/ethnicity, census region, urbanization, states, and place of death. Joinpoint regression estimated annual percentage changes (APC) and average APCs (AAPCs) with 95% confidence intervals.

Results

From 1999 to 2023, 44,630 systemic sclerosis-related deaths were recorded. Most occurred in inpatient facilities (52.1%), followed by home (24.58%) and long-term care (10%). The overall age-adjusted mortality rate (AAMR) declined from 0.89 in 1999 to 0.48 in 2023 (AAPC: – 2.57; 95% CI: – 2.80 to – 2.34). AAMR declined from 1.34 in 1999 to 0.74 in 2023 and from 0.35 in 1999 to 0.2 in 2023 in female and male demographics, respectively. All racial groups showed declining AAMRs, with the highest among non-Hispanic Blacks (AAPC: – 3.13). A slight post-2018 rise was noted in non-Hispanic Whites. Regionally, the Midwest and West had the highest AAMRs, while overall, all the regions showed declines. Metropolitan areas had higher AAMRs than non-metropolitan areas. State-level variation was notable, with the highest AAMR in South Dakota (1.11) and the lowest in Nevada (0.39).

Conclusion

Despite the declining overall mortality from Systemic Sclerosis in the US, Significant disparities by gender, race, region and setting of death exist. Targeted patient-centred and structural healthcare reforms are crucial to ensure equitable survival benefits across all groups.

1. INTRODUCTION

Systemic sclerosis (SSc), commonly called scleroderma, is an immune-related disease characterized by vasculopathy and fibrosis of the skin and organs. Despite being rare, SSc significantly increases morbidity and death worldwide because of unintended systemic effects that lead to dreadful

complications, such as interstitial lung disease and pulmonary arterial hypertension. (1,2) Despite having a low prevalence of 276 cases per million in the United States, its chronic and progressive character is also posing a threat to community health. [3, 4] Clinically speaking, SSc is an autoimmune chronic fibrosing illness that affects the skin as well as numerous other organs. It involves early injury to the vascular endothelium, inflammatory infiltration of various cytokines and chemokines, and autoantibodies that form myofibroblasts and deposit a rigid and stiff connective tissue. [5–7].

The clinical picture of advanced disease, characterized by skin hardening at extremities and face, followed by Raynaud's phenomenon and severe digital ulcerations, is easy to diagnose. [8, 9] However, the early stage of the disease, presented by fatigue, hand stiffness, joint pain, and limited hand function, is often overlooked, leading to a higher mortality [10, 11]. These disorders may progress to severe skin complications such as tissue necrosis, telangiectasias, severe pruritus, and widespread calcifications. Multi-organ involvement is manifested by interstitial lung disease and pulmonary arterial hypertension, the leading cause of death in SSc patients. Other complications include cardiac arrhythmias and gastrointestinal symptoms like GERD as well, which also usually remain undiagnosed [12–14]. Multiple environmental risk factors, such as exposure to crystalline silica and organic solvents, and genetic susceptibility, including human leukocyte antigen (HLA) haplotypes and polymorphisms in immune regulatory genes, contribute to the incidence and severity of SSc, underscoring the need for early detection and preventive strategies. [15–17]

Epidemiologically, SSc accounts for a substantial number of hospitalizations and deaths in the United States with higher burdens observed among older adults, Black individuals, women and population with low socioeconomic status or limited access to healthcare [18–20]. Despite advances in diagnostic and therapeutic modalities, disparities in outcomes persist.

Most existing studies have examined single conditions or short timeframes, often lacking disaggregated data across population subgroups. This study provides a comprehensive national assessment of disparities and mortality trends associated with systemic sclerosis (SSc) in the United States from 1999 to 2023 using CDC WONDER data, examining demographic and geographic patterns to identify evolving disparities and guide targeted public health interventions.

2. METHODOLOGY

2.1. Study setting and Population

The International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) code M-34 was used to analyse death certificate data from 1999 to 2023 for systemic sclerosis-related mortality in patients aged 15–85 and older [21]. The data were taken from the CDC WONDER (Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research) database [22]. In the past, systemic sclerosis was identified in administrative databases using the same ICD code. Numerous research studies have previously used this data collection, which includes cause of

death information from death certificates for all 50 states and the District of Columbia, to evaluate trends in the mortality of individuals with systemic sclerosis.

The Multiple Cause-of-Death Public Use records were examined to identify deaths related to systemic sclerosis illnesses that were noted anywhere on the death certificate as either an underlying cause or a contributing factor. Those who were 85 years of age or older at the time of death were considered elderly adults, were observed to be on greater risk. Due to the use of de-identified government-issued public use data sets and adherence to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting requirements [23], this study was exempt from local institutional review board approval.

2.2. Data Abstraction

Abstracted data included demographics, 2013 urbanisation, states, year, population size, and place of death. The demographics included sex (male, female), state of residence, and race/ethnicity. Non-Hispanic (NH) White, NH Black or African American, Hispanic or Latino, NH American Indian or Alaska Native, and NH Asian or Pacific Islander were the categories for race and ethnicity. The urbanisation, according to the 2013 NCHS classification included large central metro, large fringe metro, medium metro, small metro, micropolitan, and noncore. According to the 2013 U.S. census, the population was classified as urban (large metropolitan area [population of \$1 million], medium/small metropolitan area [population 50,000-999,999]), and rural (population < 50,000) counties using the National Center for Health Statistics Urban-Rural Classification Scheme. According to the U.S. Census Bureau's classifications, the regions were divided into the Northeast, Midwest, South, and West [24]. The place of death included hospital, home, nursing, and home/long-term care.

2.3. Statistical Analysis

In order to analyze national trends in associated mortality, we computed the crude and age-adjusted mortality rates (AAMRs) per 100,000 population by year, sex, race/ethnicity, state, and 2013 urbanisation with 95% confidence intervals (CIs) between 1999 and 2023. Mortality rates were calculated and presented with decimal precision up to two places. By dividing the number of fatalities from SSc by the corresponding U.S. population for that year, crude mortality rates were calculated. AAMRs were computed by normalising fatalities from SSc to the U.S. population in 2000. The Joinpoint Regression Program (Joinpoint V 5.4.0.0, National Cancer Institute) was utilised to calculate the annual percent change (APC) within AAMR to measure national annual trends in SSc-related mortality [25].

This approach uses log-linear regression models to fit temporal variation and find significant changes in AAMR across time. If, using two-tailed t-testing, the slope characterising the change in mortality was statistically different from zero, APCs were deemed to be rising or falling. P less than 0.05 was regarded as statistically significant.

3. RESULTS

A total of 44,630 deaths occurred from SSc during the last two decades. Over half of all deaths (52.1%) occurred in inpatient medical facilities, making them the most common setting. Decedents' home (24.58%) was the second most frequent place of death, followed by Nursing homes and long-term care facilities (10%), outpatient clinics and emergency rooms (5.67%), Hospice facilities (3.87%), deaths on arrival (0.39%), and cases where the place of death remained unknown (0.26%). The latter likely reflects gaps in death certificate record-keeping or unique logistic circumstance. Most deaths happen in medical facilities, but a significant number also occur at home or in long-term care. (Supplementary Tables 1 and 2)

The overall AAMR for SSc-related deaths decreased from 0.89 in 1999 to 0.48 in 2023, exhibiting an AAPC value of -2.57 (95% CI: -2.80 to -2.34; p-value:<0.000005). A uniform and continuous decline in the trend was observed during the past two decades. (Fig. 1.) (Supplementary Tables 1 and 2)

3.1 Systemic Sclerosis -Related AAMR by Gender

AAMR-related disparities were observed across genders. The AAMR was disproportionately higher among females than males throughout the study period. However, the number of deaths recorded was higher among males (40,444) than among females (36,035). The overall AAMR decreased among females from 1.34 in 1999 to 0.74 in 2023, exhibiting an AAPC value of -2.27 (95% CI: -2.66 to -1.87; p-value:<0.000001). Similarly, it decreased among males from 0.35 in 1999 to 0.2 in 2023, exhibiting an AAPC value of -3.06 (95% -3.56 to -2.56; p-value:<0.000001). In females, a significant decrease in AAMR was observed from 1.34 in 1999 to 0.78 in 2018 (APC: -2.67; 95% CI: -2.89 to -2.45), which continued to decrease until 2023 (APC: -0.73; 95% CI: -2.60 to -1.16), reaching an AAMR of 0.74. Among males, there was a uniform decline in AAMR between 1999 and 2023, reaching an AAMR of 0.2. (Fig. 1.) (Supplementary Tables 1 and 3)

3.2 AAMR by Age Group

While observing the mortality trends among various age groups, the age group that experienced the highest burden of SSc-related deaths was the 65 to 85 years age group, with a cumulative total of 25,605 deaths over the study period, followed by 17,859 deaths in the 45 to 64 years age group, and 3,303 deaths in the 25 to 44 years age group. The number of deaths consistently increased with advancing age. The AAMR was notably highest among the 65 to 85 years group (AAMR:2.5), compared to 45 to 64 (AAMR: 0.75), and 25 to 44 (AAMR: 0.15) years age group.

3.3 Systemic Sclerosis -Related AAMR by Race

For race and ethnicity, variations were also observed for the AAMR. The AAMR was highest among NH Black African American individuals (AAPC: -3.13; 95% CI: -3.51 to -2.76; p-value:<0.000001), followed by Hispanic or Latino individuals (AAPC: -2.61; 95% CI: -3.22 to -2.00; p-value:<0.000001), NH White individuals (AAPC: -2.36; 95% CI: -2.86 to -1.85; p-value:<0.000001) and NH Asian or Pacific Islander individuals (AAPC: -2.08; 95% CI: -2.82 to -1.34; p-value:0.000007). Among NH Asian or Pacific Islander

individuals, there was a significant decrease in AAMR from 0.48 in 1999 to 0.3 in 2023 (APC: -2.08; 95% CI: -2.82 to -1.34). Similarly, among NH Black African American individuals, there was a notable decline in AAMR from 1.27 in 1999 to 0.63 in 2023 (APC: -3.13; 95% CI: -3.51 to -2.76). In NH White individuals, a significant initial decrease was observed in AAMR from 0.86 in 1999 to 0.48 in 2018 (APC: -3.06; 95% CI: -3.40 to -2.72), followed by an increase until 2023, reaching an AAMR of 0.47. For Hispanic individuals, there was a uniform decline in trend with AAMR at 1.00 in 1999 to 0.54 in 2023 (APC: -2.61; 95% CI: -3.22 to -2.00). Overall, AAMR showed a consistent decline across all racial and ethnic groups; however, a slight increase in AAMR was exhibited by NH White individuals after 2018. (Fig. 2.) (Supplementary Tables 1 and 4)

3.4 Systemic sclerosis -Related AAMR by Census Regions

In terms of census region, the AAMR-related differences were found across various regions. The overall AAMR was highest in the Midwest region at 0.719 (AAPC: -2.33; 95% CI: -2.66 to -2.00; p-value: <0.000001) followed closely by the Northeast region at 0.72 (AAPC: -2.41; 95% CI: -2.78 to -2.04; p-value: <0.000001), the West region at 0.70 (AAPC: -1.98; 95% CI: -2.47 to -1.47; p-value: <0.000001) and the South region at 0.69 (AAPC: -2.86; 95% CI: -3.48 to -2.23; p-value: <0.000001). In the South region, a significant decline was observed from 0.95 in 1999 to 0.5 in 2016 (APC: -3.62; 95% CI: -4.08 to -3.15), which continued to decrease until 2023 (APC: -0.99; 95% CI: -2.98 to 1.03), reaching an AAMR of 0.45. In the Northeast region, the AAMR decreased from 0.9 in 1999 to 0.54 in 2023 (APC: -1.98; 95% CI: -2.47 to -1.47). A similar decreasing trend was observed in the Midwest region and West region for AAMR, which decreased from 0.84 in 1999 to 0.48 in 2023 (APC: -2.33; 95% CI: -2.66 to -2.00) and from 0.89 in 1999 to 0.48 in 2023 (APC: -2.41; 95% CI: -2.78 to -2.04), respectively. A continuous declining trend was observed in all regions during the last two decades. (Fig. 3.) (Supplementary Tables 5)

3.5 Systemic Sclerosis -Related AAMR by Urbanization

The disparities were also observed across different urbanizations during the study. The overall AAMR was higher in metropolitan areas (AAPC: -3.01; 95% CI: -3.25 to -2.77; p-value: <0.000001) than in non-metropolitan areas (AAPC: -2.56; 95% CI: -2.96 to -2.16; p-value: <0.000001). For metropolitan areas, there was a significant decrease in AAMR from 0.92 in 1999 to 0.54 in 2023 (APC: -3.01; 95% CI: -3.25 to -2.77). A similar trend was also observed in non-metropolitan areas, where it decreased from 0.85 in 1999 to 0.52 in 2023 (APC: -2.56; 95% CI: -2.96 to -2.16). (Fig. 4.) (Supplementary Tables 6)

3.6 Systemic Sclerosis -Related AAMR by States

While stratifying the data by state, variations across different states were also found. The highest AAMR was observed in South Dakota (AAMR: 1.11). Conversely, the state with the lowest AAMR is Nevada (0.39). The states that fall within the 90th percentile for AAMR include South Dakota, Montana, and Nebraska; on the other hand, states in the lowest 10th percentile include Nevada, Kentucky, Alabama, and Arkansas. (Fig. 5.) (Supplementary Tables 7)

4. DISCUSSION

The findings demonstrate a notable and consistent decline in SSc-related mortality nationally. The significant negative average annual percent change reflects substantial progress, which can be attributed to multiple converging advancements in the management of SSc. Improvements in early detection strategies, such as the application of novel technologies like Near Infrared Spectroscopy (NIRS), which enables non-invasive vascular assessment in SSc patients, have enhanced clinical sensitivity for disease onset, particularly for microvascular dysfunction. [26] These diagnostic advancements, alongside the increasing incorporation of machine learning to optimize biomarker wavelength selection, have played a pivotal role in identifying disease earlier and more accurately.

Simultaneously, significant developments in pharmacological therapies, including immunomodulators and antifibrotic agents, have expanded treatment options, enabling better control of disease progression and organ-specific complications. Tailored pharmaceutical approaches, as well as multidisciplinary supportive care models, have contributed to improved survival outcomes and quality of life, especially for lung, gastrointestinal, and skin involvement, the most commonly affected systems in SSc. Despite its relatively low prevalence, systemic sclerosis bears the highest mortality among rheumatic diseases, further highlighting the importance of these therapeutic milestones [27]. Collectively, these advancements in early diagnosis, targeted treatment, and comprehensive care are likely contributors to the observed national mortality decline, underlining the critical need for continued innovation and equitable access to specialized rheumatologic services.

Despite an overall decline in AAMRs for both sexes, persistent sex-based disparities were evident. Females consistently exhibited higher AAMRs than males throughout the study period, aligning with the markedly higher prevalence of SSc among women, with female-to-male ratios exceeding 4:1 in most cohorts [28]. This female predominance is multifactorial, attributed to complex hormonal influences, epigenetic patterns, and incomplete X-chromosome inactivation, which results in overexpression of immune-related genes such as TLR7 and BTK, thereby predisposing women to heightened immune reactivity [28, 29]. Moreover, autoimmune diseases broadly affect approximately 8% of the population, with nearly 78% of affected individuals being women, underscoring a systemic biological vulnerability [30]. Interestingly, while women had higher SSc-related mortality rates, the absolute number of deaths was greater among men. This paradox may reflect a severity or diagnostic delay bias, with men more likely to present with rapidly progressive diffuse cutaneous SSc (dcSSc), accompanied by more severe organ involvement such as interstitial lung disease and cardiac complications [28, 29]. Occupational and environmental exposures, including silica and solvent contact, which are more prevalent among men, may further exacerbate disease progression [28]. Supporting this, men demonstrated a slightly steeper decline in AAMRs compared to females, potentially reflecting differences in comorbidities, earlier therapeutic escalation, or sex-specific treatment responses. This study clearly demonstrated the disproportionate burden of SSc observed among elderly individuals aged 65 to 85 years. This group accounted for over 25,000 deaths during the study period, reflecting the highest age-adjusted mortality rate compared to younger cohorts. Several factors may contribute to the increased mortality among

older adults with SSc. Advancing age is associated with compromised physiological reserve and immune senescence (31), both of which may worsen the disease course and can lead to complications like pulmonary arterial hypertension (32), interstitial lung disease (33), or scleroderma renal crisis (34). Moreover, the presence of multiple age-related comorbidities complicates disease management and elevates the risk of adverse outcomes. Lastly, diagnostic delays and differences, which can be due to non-specific symptom presentation and age-related therapeutic interventions in therapeutic approaches in older adults, may further impact prognosis. (35) Taken together, these findings suggest that older age is a critical risk factor in SSc-related mortality and should be considered when designing screening strategies, management plans, and allocating health resources for this vulnerable group.

Marked racial disparities were evident across the study period. Non-Hispanic (NH) Black individuals consistently had the highest AAMRs, although they also exhibited the steepest decline, indicating potential gains in disease recognition or access to care over time. Despite this improvement, multiple structural and clinical factors continue to place Black patients at elevated risk for poor outcomes. These include lower rates of private insurance coverage and more limited access to follow-up or humanitarian care services [36], as well as the pervasive impact of structural and interpersonal racism, including medical mistrust, implicit bias, and diagnostic delays, which have been shown to negatively affect chronic disease outcomes [37]. Biological differences may also contribute to disparities; Black SSc patients are more likely to exhibit distinct autoantibody patterns (e.g., anti-topoisomerase I, anti-RNP) associated with more severe disease phenotypes, including higher rates of interstitial lung disease (ILD) and pulmonary hypertension (PH), both leading causes of SSc-related mortality [38]. Additionally, the physicians treating Black patients may have comparatively fewer clinical resources or less specialized training, which could further compound disparities in care delivery and outcomes [39]. Geographic trends revealed considerable regional variability in systemic sclerosis (SSc)-related mortality. The South initially exhibited the highest AAMRs, although all four U.S. census regions demonstrated significant temporal declines. Recent data show that the lowest AAMRs are now concentrated in the Northeast and the West. These regional differences may be attributable to variation in healthcare access, socioeconomic conditions, environmental exposures, and systemic healthcare capacity. Notably, individuals residing in the South have been shown to engage in significantly fewer healthcare encounters, particularly specialist visits, than those in other regions, even after adjusting for individual-level cardiovascular risk factors [40]. This pattern suggests that limited access to specialized care may be a key driver of the observed disparities. In addition, the elevated burden of pulmonary and infectious (P&I) hospitalizations in Southern states has been linked to lower staffing ratios, weaker vaccination infrastructure, and other region-specific health system challenges, rather than demographics alone [41]. At the state level, South Dakota reported the highest AAMR, while Nevada reported the lowest. Urbanization also influenced mortality outcomes. AAMRs were higher in metropolitan areas compared to non-metropolitan regions; however, both settings demonstrated steady declines over time. The steeper reduction observed in urban areas may reflect more robust healthcare infrastructure, including greater access to rheumatology specialists, earlier diagnosis, and the availability of tertiary care centers. In contrast, rural and micropolitan areas continue to face persistent disparities, often attributable to ongoing shortages of

rheumatologists [42], with current workforce projections indicating a worsening shortage and maldistribution. The interdisciplinary nature of rural health, encompassing geography, nursing, midwifery, sociology, economics, and the use of telemedicine, adds further complexity to care delivery in non-urban settings [43]. Additionally, the presence of demographic patterns and reported clusters of higher SSc incidence in certain areas may point to underlying environmental risk factors influencing disease development [44].

Future directions

These findings bring attention to the need for more personalized and inclusive approaches to SSc care. Sex-informed surveillance and therapeutic strategies are essential to address biological differences in disease patterns and outcomes. Development of geriatric-focused screening tools and treatment approaches may improve outcomes in older adults with SSc. At the same time, race-conscious efforts, including culturally competent care and targeted research, are critical to confronting the social, structural, and biological drivers of racial inequities. Region-specific public health strategies are also needed to reduce geographic disparities, particularly by expanding access to rheumatologic care in high-burden and neglected areas. Prioritizing local interventions that close specialist care gaps and tackle underlying structural barriers will be key to achieving more equitable outcomes in SSc.

Limitations

The analysis used CDC WONDER data from 1999 to 2023 to provide a reliable, in-depth assessment. Stratification by age, sex, and race revealed key disparities in SSc-related mortality. However, the study has several limitations. It relies on ICD-10 coding, which may lead to misclassification of SSc-related deaths. The absence of clinical details like disease severity, duration, and comorbidities hinders understanding of the mortality-driving factors. Regional, racial, and urbanization level disparities suggest underlying differences in healthcare access and reporting quality. Changes in practices and treatments over this period, along with inconsistent death certification and incomplete data, may also affect the accuracy of trends. Lastly, the exclusion of socioeconomic factors and intervention data constrains the analysis of disparity patterns.

5. CONCLUSION

While the overall mortality impact of SSc in the United States has undergone a substantial drop over the last two decades, disparities across different groups, such as sex, race, region, and place of death, were observed. These findings highlight the need for continued efforts to mitigate healthcare imbalances, bridge the gap in speciality care availability, and refine end-of-life healthcare provisions, particularly in high-risk states and neglected demographic groups. Going forward, more inclusive and patient-centred care practices are essential, one that integrates not only cutting-edge interventions but also contextualized strategies and grassroots involvement. Addressing these inequities requires more than therapeutic improvement; it demands structural transformation across healthcare systems, education, and policy to ensure that improvements in survival are universally realized.

Declarations

Clinical Trial Number:

Not applicable.

Ethics, Consent to Participate, and Consent to Publish:

Not applicable

Funding Declaration

The authors received no specific funding for this work.

Author Contribution

N.K., M.U., and A.A. conceptualized and designed the study. N.K., M.U., T.R., and S.A.K. performed data collection and analysis. U.T., N.A., M.K., and K.R. contributed to literature review and interpretation of data. A.K., S.A., and K.A. prepared the figures, tables, and supplementary materials. N.K., M.U., and A.A. drafted the main manuscript text. All authors critically revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Data Availability

The datasets generated and/or analysed during the current study are publicly available in the CDC WONDER (Wide-ranging Online Data for Epidemiologic Research) Multiple Cause of Death database, maintained by the Centers for Disease Control and Prevention, National Center for Health Statistics, accessible at <https://wonder.cdc.gov/mcd-icd10.html> (for 1999–2020 data) and <https://wonder.cdc.gov/mcd-icd10-expanded.html> (for 2018–2023 data).

References

1. Denton CP, Khanna D. Systemic sclerosis. The Lancet [Internet]. 2017;390(10103):1685–99. Available from: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)30933-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30933-9/fulltext)
2. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Annals of the Rheumatic Diseases [Internet]. 2010 Oct 1 [cited 2021 Apr 2];69(10):1809–15.
3. Armstrong F. Improving quality of life for patients with systemic sclerosis. Nurs Made Incredibly Easy! 2024;23(1):14–22.

4. Nikpour M, Stevens WM, Herrick AL, Proudman SM. Epidemiology of systemic sclerosis. *Best Pract Res Clin Rheumatol*. 2010;24(6):857–69.
5. Rosendahl A, Schönborn K, Krieg T. Pathophysiology of systemic sclerosis (scleroderma). *Kaohsiung J Med Sci*. 2022;38(3):187–95.
6. Distler JHW, Györfi AH, Ramanujam M, Whitfield ML, Königshoff M, Lafyatis R. Shared and distinct mechanisms of fibrosis. *Nat Rev Rheumatol*. 2019;15(12):705–30.
7. Suliman Y, Distler O. Novel Aspects in the Pathophysiology of Peripheral Vasculopathy in Systemic Sclerosis. *Curr Rheumatol Reviews*. 2014;9(4):237–44.
8. Gabrielli A, Avvedimento EV, Krieg T, Scleroderma. *N Engl J Med*. 2009;360(19):1989–2003.
9. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, Matucci-Cerinic M. Raynaud phenomenon and digital ulcers in systemic sclerosis. *Nat Rev Rheumatol*. 2020;16(4):208–21.
10. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. *Rheumatology*. 2010;50(4):762–7.
11. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007;66(7):940–4.
12. Krieg T, Takehara K. Skin disease: a cardinal feature of systemic sclerosis. *Rheumatology*. 2006;48(suppl3):iii14–8.
13. Komócsi A, Vorobcsuk A, Faludi R, Pintér T, Lenkey Z, Költő G, Czirják L. The impact of cardiopulmonary manifestations on the mortality of SSc: a systematic review and meta-analysis of observational studies. *Rheumatology*. 2012;51(6):1027–36.
14. Hachulla E, Launay D. Diagnosis and Classification of Systemic Sclerosis. *Clinical Reviews in Allergy & Immunology* [Internet]. 2010;40(2):78–83. Available from: <https://link.springer.com/article/10.1007%2Fs12016-010-8198-y>
15. Ingegnoli F, Ughi N, Mihai C. Update on the epidemiology, risk factors, and disease outcomes of systemic sclerosis. *Best Pract Res Clin Rheumatol*. 2018;32(2):223–40.
16. De Martinis M, Ciccarelli F, Sirufo MM, Ginaldi L. An overview of environmental risk factors in systemic sclerosis. *Expert Rev Clin Immunol*. 2015;12(4):465–78.
17. Abbot S, Bossingham D, Proudman S, de Costa C, Ho-Huynh A. Risk factors for the development of systemic sclerosis: a systematic review of the literature. *Rheumatol Adv Pract*. 2018;2(2).
18. Nandan MDA, Scleroderma. Practice Essentials, Background, Pathophysiology. *eMedicine* [Internet]. 2021; Available from: <https://emedicine.medscape.com/article/331864-overview#a3>
19. Peoples C, Medsger TA, Lucas M, Rosario BL, Feghali-Bostwick CA. Gender differences in systemic sclerosis: relationship to clinical features, serologic status and outcomes. *J Scleroderma Relat Disorders*. 2016;1(2):204–12.
20. Reveille JD, Fischbach MA, McNearney TA, Friedman AD, Aguilar MR, Lisse JR, et al. Systemic sclerosis in 3 US ethnic groups: A comparison of clinical, sociodemographic, serologic, and

- immunogenetic determinants. *ScienceDirect*. 2001;30(5):332–46.
21. Yen EY, Singh DR, Singh RR, Trends in Systemic Sclerosis Mortality Over Forty-Eight Years., 1968–2015: A US Population-Based Study. *Arthritis Care Res (Hoboken)*. 2021;73(10):1502–1510. doi: 10.1002/acr.24411. Epub 2021 Aug 31. PMID: 32770721; PMCID: PMC7868470. Centers for Disease Control and Prevention. CDC WONDER: Wide-ranging online data for epidemiologic research. Available from: <https://wonder.cdc.gov>
 22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–9. <https://doi.org/10.1016/j.jclinepi.2007.11.008>.
 23. Ingram DD, Franco SJ. (2014). 2013 NCHS Urban-Rural Classification Scheme for Counties. *Vital and health statistics. Series 2, Data evaluation and methods research*, (166), 1–73.
 24. National Cancer Institute. Joinpoint Regression Program [Internet]. Bethesda (MD): Division of Cancer Control and Population Sciences; [cited 2025 May 22]. Available from: <https://surveillance.cancer.gov/help/joinpoint>
 25. de França JFeijó et al. Aug. *Using Near Infrared Spectroscopy and Machine Learning to Diagnose Systemic Sclerosis*. arXiv:1908.06137, arXiv, 16 2019. [arXiv.org](https://doi.org/10.48550/arXiv.1908.06137), <https://doi.org/10.48550/arXiv.1908.06137>
 26. Volkman ER, et al. Systemic Sclerosis'. *Lancet (London, England)*. PubMed Cent. Jan. 2023;401(10373):304–18. [https://doi.org/10.1016/S0140-6736\(22\)01692-0](https://doi.org/10.1016/S0140-6736(22)01692-0).
 27. Truchetet M, Elise, et al. Current Concepts on the Pathogenesis of Systemic Sclerosis'. *Clinical Reviews in Allergy & Immunology*. Springer Link. Jun. 2023;64(3):262–83. <https://doi.org/10.1007/s12016-021-08889-8>.
 28. Sakkas LI. 'Sex Bias in Systemic Sclerosis: From Clinical to Immunological Differences'. *Clinical Reviews in Allergy & Immunology*, vol. 68, no. 1, 2025, p. 51. *Springer Link*, <https://doi.org/10.1007/s12016-025-09062-1>
 29. Oliver JE, Alan J. Silman. 'Why Are Women Predisposed to Autoimmune Rheumatic Diseases?' *Arthritis Research & Therapy*. BioMed Cent. Oct. 2009;11(5):252. <https://doi.org/10.1186/ar2825>.
 30. Zheng Y et al. Sep. 'Immune Aging - A Mechanism in Autoimmune Disease'. *Seminars in Immunology*, vol. 69, 2023, p. 101814. *PubMed*, <https://doi.org/10.1016/j.smim.2023.101814>
 31. Cullivan S et al. Jun. 'Pulmonary Hypertension in Systemic Sclerosis'. *Seminars in Respiratory and Critical Care Medicine*, vol. 45, no. 3, 2024, pp. 411–18. *PubMed*, <https://doi.org/10.1055/s-0044-1782607>
 32. Perelas A et al. Mar. 'Systemic Sclerosis-Associated Interstitial Lung Disease'. *The Lancet. Respiratory Medicine*, vol. 8, no. 3, 2020, pp. 304–20. *PubMed*, [https://doi.org/10.1016/S2213-2600\(19\)30480-1](https://doi.org/10.1016/S2213-2600(19)30480-1)
 33. Cole A et al. Jun. 'Renal Disease and Systemic Sclerosis: An Update on Scleroderma Renal Crisis'. *Clinical Reviews in Allergy & Immunology*, vol. 64, no. 3, 2023, pp. 378–91. *PubMed*,

<https://doi.org/10.1007/s12016-022-08945-x>

34. Kernder A et al. Aug. 'Time Interval between the Onset of Connective Tissue Disease Symptoms and First Contact with a Rheumatologist: Results from the German National Database of Collaborative Arthritis Centers'. *Rheumatology International*, vol. 43, no. 8, 2023, pp. 1453–58. *Springer Link*, <https://doi.org/10.1007/s00296-023-05335-0>
35. Nietert PJ et al. Oct. 'Demographic and Clinical Factors Associated with In-Hospital Death among Patients with Systemic Sclerosis'. *The Journal of Rheumatology*, vol. 32, no. 10, 2005, pp. 1888–92.
36. Onibada A. 'Why You Might Have a Higher Risk of Heart Disease as a Black Person—And What to Do About It'. *SELF*, 20 Dec. 2023, <https://www.self.com/story/black-people-heart-disease-risk-factors>
37. Silver RM, et al. Racial Differences between Blacks and Whites with Systemic Sclerosis'. *Current Opinion in Rheumatology*. PubMed Cent. Nov. 2012;24(6):642–48. <https://doi.org/10.1097/BOR.0b013e328356d9dc>.
38. Bach PB et al. Aug. 'Primary Care Physicians Who Treat Blacks and Whites'. *New England Journal of Medicine*, vol. 351, no. 6, 2004, pp. 575–84. *DOI.org(Crossref)*, <https://doi.org/10.1056/NEJMsa040609>
39. Enyeji AM et al. Jul. 'Regional Variation in Health Care Utilization Among Adults With Inadequate Cardiovascular Health in the USA'. *Cureus*, vol. 15, no. 8, p. e44121. *PubMed Central*, <https://doi.org/10.7759/cureus.44121>. Accessed 7 2025.
40. Parcha V, Kalra R, Suri SS et al. Geographic Variation in Cardiovascular Health Among American Adults. *Mayo Clin Proc*. 2021;96(7):1770–1781. 10.1016/j.mayocp.2020.12.034
41. Desilet LW et al. Mar. 'Urban and Rural Patterns of Health Care Utilization Among People With Rheumatoid Arthritis and Osteoarthritis in a Large US Patient Registry'. *Arthritis Care & Research*, vol. 77, no. 3, 2025, pp. 412–18. *PubMed Central*, <https://doi.org/10.1002/acr.25192>
42. Rural Health. Wikipedia [Internet]. 2025 Jun 28 [cited 2026 May 3]. Available from: https://en.wikipedia.org/w/index.php?title=Rural_health&oldid=1297746390
43. Kanecki K et al. May. 'Incidence and Prevalence of Systemic Sclerosis (SSc) in Poland - Differences between Rural and Urban Regions'. *Annals of Agricultural and Environmental Medicine: AAEM*, vol. 24, no. 2, 2017, pp. 240–44. *PubMed*, <https://doi.org/10.5604/12321966.1233570>

Figures

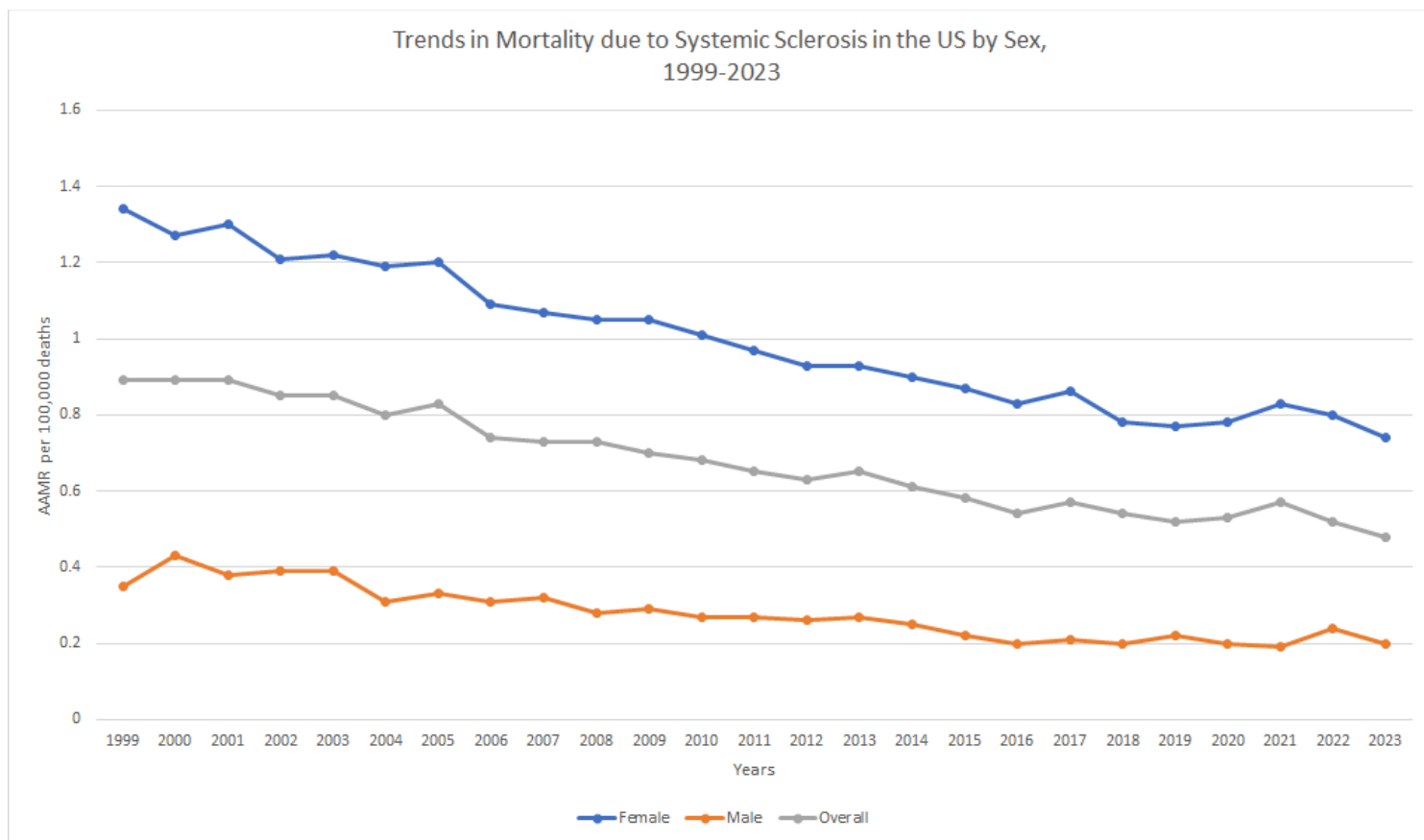


Figure 1

Systemic Sclerosis AAMRs per 100,000 stratified by gender and overall, in the population of the United States, 1999 to 2023

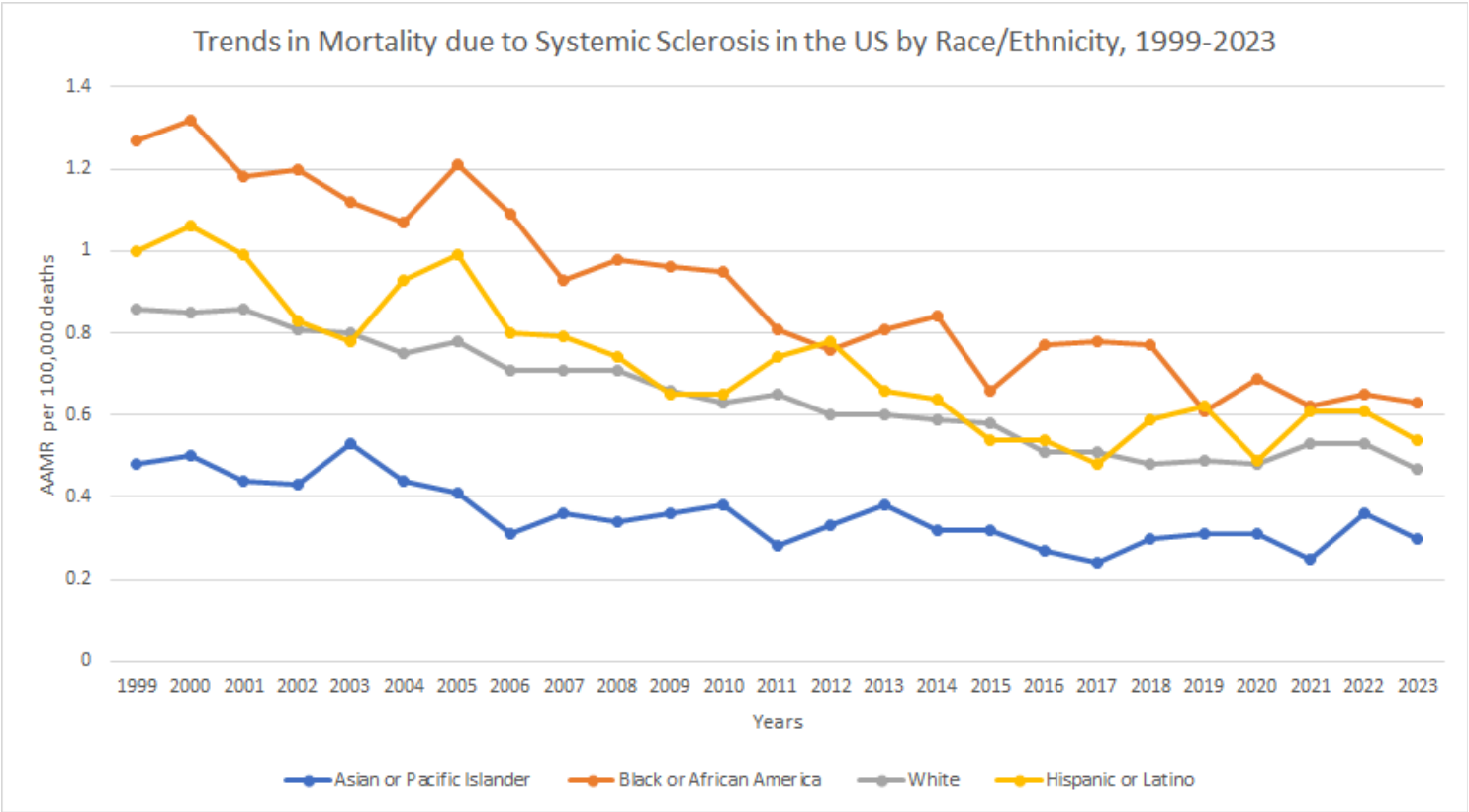


Figure 2

Systemic Sclerosis AAMR per 100,000 stratified by Race/Ethnicity in the population of United States, 1999 to 2023

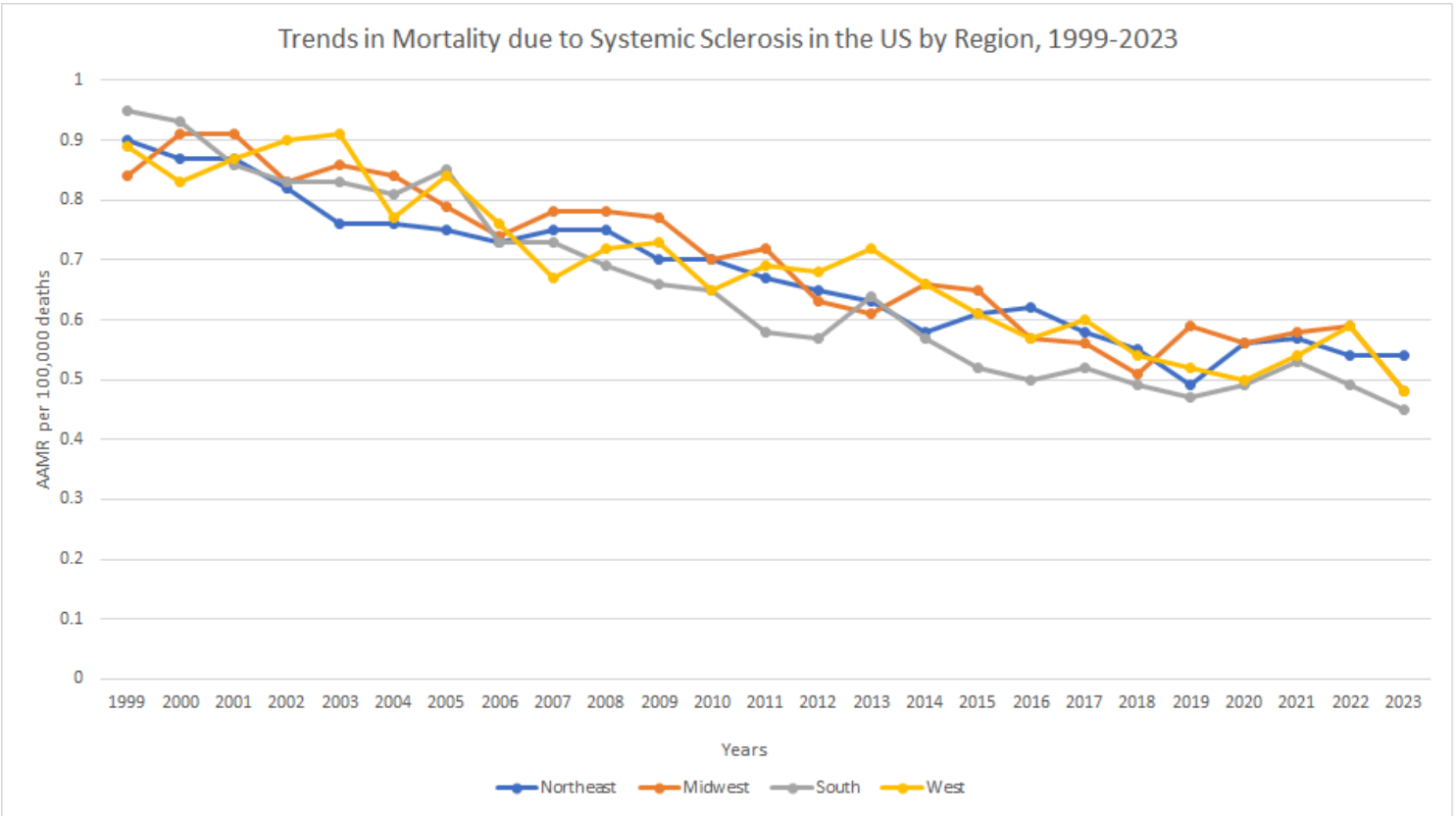


Figure 3

Systemic Sclerosis AAMRs per 100,000 stratified by Census Region in the population of the United States, 1999 to 2023

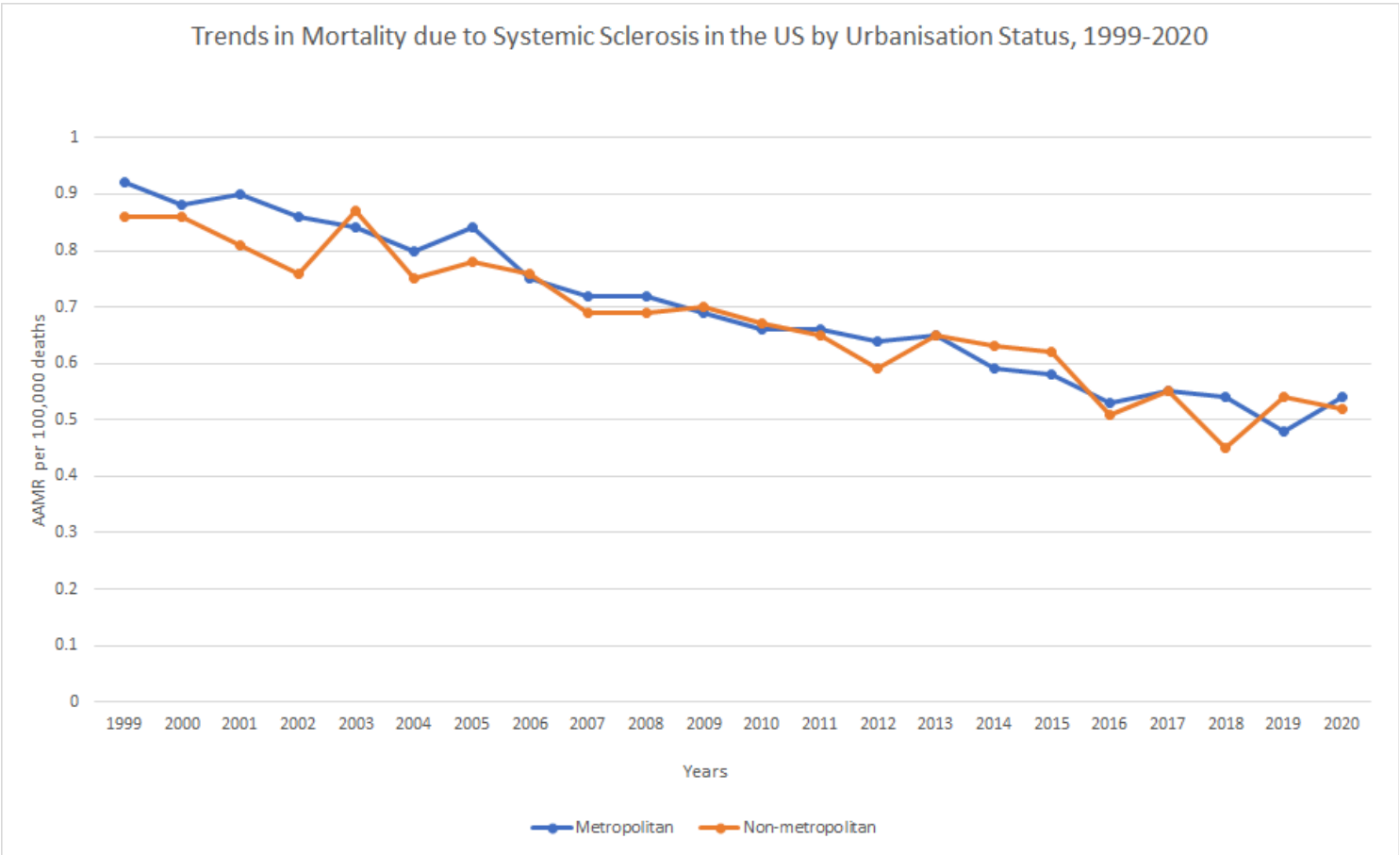


Figure 4

Systemic Sclerosis AAMRs per 100,000 stratified by 2013 Urbanization in the population of the United States, 1999 to 2023

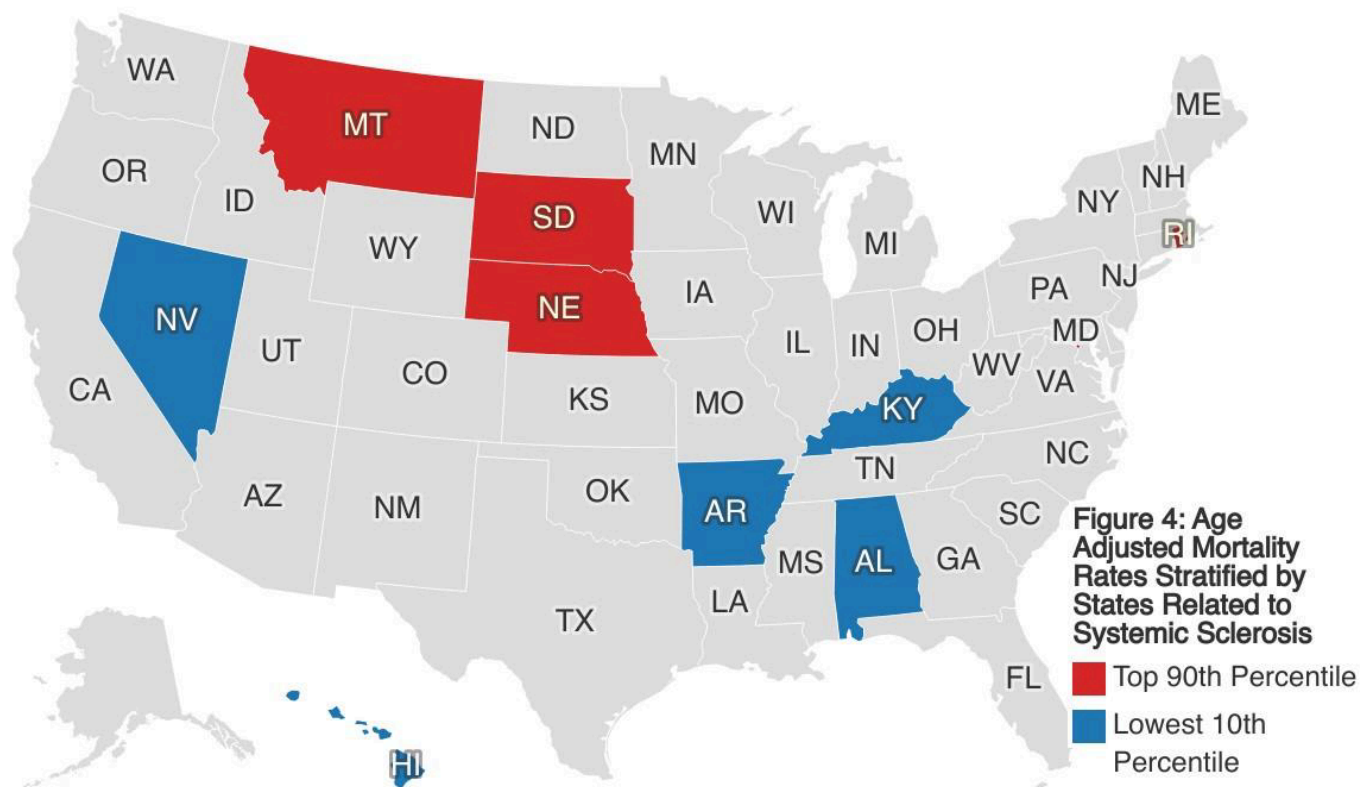


Figure 5

Systemic Sclerosis AAMRs per 100,000 stratified by States in the population of the United States, 1999 to 2023

Supplementary Files

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

- [floatimage6.png](#)