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Publication Date

2023-05-01

DOI

10.1093/rheumatology/kead233

Revised Manuscript: **CLEAN COPY**

Steady Decrease in Systemic Sclerosis Mortality Rates at Younger Ages Over the Past Five Decades

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Running Title: **Improving Systemic Sclerosis Mortality Prior to Age 45**

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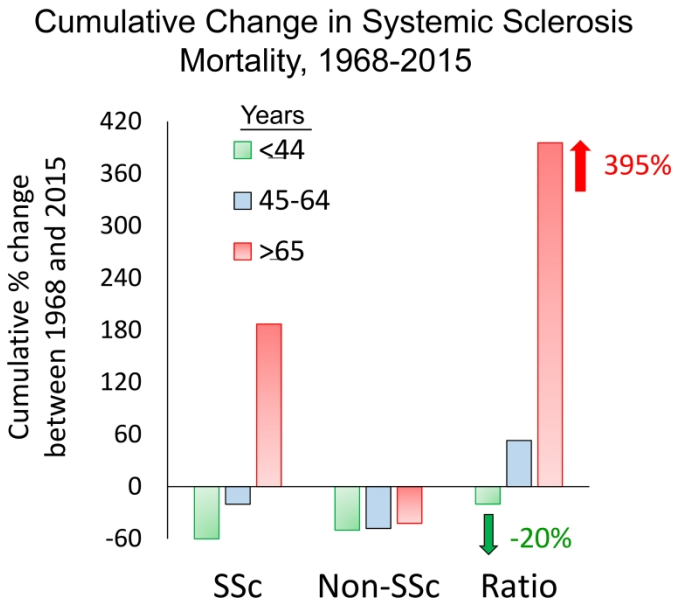
Manuscript word count: 2,534



SSc, systemic sclerosis; Ratio, Ratio of age-standardized mortality rates for SSc to non-SSc (all other causes)

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Abstract

Objective: We aimed to assess systemic sclerosis (SSc) mortality by age in the general population over the past five decades.

Methods: This is a population-based study using a national mortality database and census data of all United States residents. We calculated the proportions of deaths for SSc and for all other causes (non-SSc) by age, and calculated age-standardized mortality rate (ASMR) for SSc and non-SSc, and the ratio of SSc-ASMR to non-SSc-ASMR by age groups for each year from 1968 through 2015. We performed joinpoint regression to estimate average annual percent change (AAPC) for each of these parameters.

Results: SSc was recorded as the underlying cause of death in 5,457 decedents aged ≤44 years, 18,395 aged 45-64, and 22,946 aged ≥65 from 1968 through 2015. At ages ≤44, the proportion of annual deaths decreased more for SSc than for non-SSc: AAPC, -2.2% (95% CI, -2.4% to -2.0%) for SSc *vs.* -1.5% (-1.9% to -1.1%) for non-SSc. Consistently, SSc-ASMR decreased from 1.0 (95% CI, 0.8-1.2) in 1968 to 0.4 (0.3-0.5) per million persons in 2015, a cumulative decrease of 60% at an AAPC of -1.9% (95% CI, -2.5% to -1.2%) at ages ≤44. The ratio of SSc-ASMR to non-SSc-ASMR ratio also decreased (cumulative -20%; AAPC -0.3%) in ≤44-year group. In contrast, those aged ≥65 experienced a steep increases in SSc-ASMRs (cumulative 187.0%; AAPC 2.0% [95% CI, 1.8-2.2]) and SSc-ASMR:non-SSc-ASMR ratio (cumulative 395.4%; AAPC 3.3% [95% CI, 2.9-3.7]).

Conclusion: Mortality for SSc has steadily decreased at younger ages over the past five-decades.

Keywords: Age; Epidemiology; Large Database; Mortality; Systemic sclerosis

Key messages:

Scleroderma mortality rates at ages <45 years steadily decreased over the past five-decades.

Premature mortality decreased at a higher pace for scleroderma than from all other causes, 1968-2015.

Scleroderma mortality rates steeply increased in those aged ≥65 over the past five-decades.

INTRODUCTION

Mortality for systemic sclerosis (SSc) has begun to decline in the 2000s, but still remains high relative to mortality from all other (non-SSc) causes (1). Most patients with SSc are young: 91% patients had SSc onset prior to age 65 and 46% before age 45 in a large United States cohort (2). Young patients also had a delayed diagnosis and more cumulative organ damage, including esophageal disease and myositis (3). Young patients with SSc can die prematurely of these complications. Conflicting information has been reported on SSc mortality by age. While some studies found no significant difference in standardized mortality ratios in SSc patients younger or older than 65 at diagnosis (4), others found standardized mortality ratio to be higher in younger patients (3). In other studies, older age at disease onset was an independent predictor of SSc mortality risk (5, 6). Most previous studies describing SSc mortality by age were based on patient cohorts at referral centers (3-8), which does not capture changes in SSc incidence over time and does not reflect the true burden of SSc mortality in the general population. These limitations might have contributed to inconsistent findings across previous studies.

We used the Centers for Disease Control and Prevention (CDC)'s national mortality database that encompasses >99% of deaths across the United States to calculate population-based estimates of SSc deaths and age-standardized mortality rates (ASMR) by age over a period of 48 years from 1968 to 2015. To evaluate SSc mortality in the context of improvement in overall mortality for all causes in the general population over time (9), we computed the ratio of SSc mortality rates to non-SSc mortality rates by age groups.

Methods

Data Source

We used the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) web application to gather data on SSc deaths from 1968 (the earliest year for which the CDC published county-level mortality data) through 2015. Deaths were attributed to SSc if an international classification of diseases (ICD) code for SSc was listed as the underlying cause of death on the death certificates: ICD-8, 734.0; ICD-9, 710.1; and ICD-10, M34 (1). Information on age was ascertained using standard methods (10).

We obtained annual death counts in the entire United States population and separately by age. We then calculated the percent of total SSc and non-SSc deaths in different age groups for each year over the 48-year period.

Mortality rates

For calculation of mortality rates, the size of the population (total and each group) was obtained from the United States Census Bureau files for each year. We quantified age-specific crude mortality rates for SSc and non-SSc for each year from 1968 through 2015 as the number of deaths in each year divided by the number of persons in the United States general population in that same year (11). This was done within age strata for the total United States population for different age groups, and repeated for non-SSc deaths.

To calculate the ASMR for the population for each year from 1968 through 2015, we combined the yearly age-specific crude mortality rates with the age distribution of the United States population in 2000, as described previously (11). This was done separately for each age

group and for both SSc deaths and non-SSc deaths. We then computed the ratio of SSc-ASMR to non-SSc-ASMR for each year by age groups.

Statistical Analysis

We used joinpoint regression to fit piecewise-linear (or broken-line) trends to the annual percent SSc and non-SSc deaths, the annual SSc-ASMR, non-SSc-ASMR, and SSc-ASMR to non-SSc-ASMR ratio by age groups over the 48-year period (1). Joinpoint regression identifies a set of joinpoints – the calendar years at which the change in the slope (of proportions of death or ASMR) is statistically significant – and computes the slope (year-to-year percentage change in annual ASMR or in percent of deaths) and the 95% CI over each linear trend segment between adjacent joinpoints (11, 12). This approach identifies the year when the trend (i.e., slope) changes significantly and determines the magnitude of the change. Joinpoint regression analyses were conducted using the National Cancer Institute Joinpoint Regression Program, which uses a grid search method to find the best locations for the joinpoints based on a least-squares fit of the data and uses a permutation test with Monte Carlo simulation to determine the optimal number of joinpoints (**Supplemental Methods**).

We calculated the annual percent change (APC) for each trend, and then calculated the average annual percent change (AAPC) with 95% CI for the entire study period. AAPC represents changes in trends and offers the advantage of reporting a weighted average of the APCs for each segment (12).

To investigate whether the differences in the proportions of SSc and non-SSc deaths in different age groups is more than expected by chance, we performed Chi-square statistics with

Yates's correction (GraphPad Prism 6.07) and quantified the odds ratio with its 95% confidence interval (CI).

Results

SSc was recorded as the underlying cause of death in 5,457 decedents aged ≤44 years, 18,395 aged 45-64, and 22,946 aged ≥65 in the United States from 1968 through 2015. The proportions of deaths in those aged ≤44 and those aged 45-64 were higher for SSc than for non-SSc deaths (**Table 1**).

Trends in Annual Percent Deaths

The proportion of annual SSc deaths in ≤44-year age group decreased from 23.4% in 1968 to 5.7% in 2015, at an AAPC of -2.2% (95% CI, -2.4% to -2.0%) (**Figure 1**). The percent of SSc deaths also decreased in the 45-54-year age group over the 48-year period. No statistical change was noted in the 55-64-year age group, but in ≥65-year age group the proportion of SSc deaths increased from 23.8% in 1968 to 59.3% in 2015 at an AAPC of 2.0% (95% CI, 1.3 to 2.7).

Noticeably, the proportions of annual deaths decreased at a higher pace for SSc than for non-SSc causes in the ≤44 and 45-54 years age groups, but increased more for SSc than for non-SSc causes in the ≥65 age group (non-overlapping confidence interval for AAPCs).

In 1968, the proportions of total deaths in ages ≤44 year was higher for SSc than for non-SSc (23.4% vs. 13.5%, P < 0.0001), but in 2015 the proportion of total deaths was slightly lower for SSc than for non-SSc (5.7% vs. 6.9%, P = 0.1 [NS]) (**Supplemental Figure S1**). The 4.1-fold decrease in the proportion of SSc deaths (23.4% in 1968 to 5.7% in 2015) was due to both decreased absolute SSc death counts at ages ≤44 year (from 109 deaths in 1968 to 68 deaths in 2015) and increased absolute SSc death counts at ages ≥65-year (from 111 deaths in 1968 to 709 deaths in 2015) (**Table 2**).

Further analysis of SSc deaths at younger ages revealed that in those aged ≤19 years, the proportions of total SSc deaths decreased from 2.4% in 1968 to 0% in 2015, and in those aged ≤34 years, it reduced from 10.5% to 1.9% in 2015.

Trends in SSc Mortality Rate According to Age Groups

The ≤44-year age group did not experience a period of statistically significant increase in SSc-ASMR at any time over the 48-year period (**Figure 2**, left panel). In contrast, those aged ≥65 had a continuous increase in SSc-ASMR for 32 years before decreasing in the last 16 years of the study period. The 45-64-year age group exhibited two each of increase and decrease trends over the 48-year period.

In contrast to the increase-and-decrease trends in SSc-ASMRs, non-SSc-ASMRs decreased or stayed stable throughout the 48-year period in all age groups (**Figure 2**, middle panel). Consequently, the SSc to non-SSc ASMR ratio initially increased at greater APCs in ≥65 and 45-64-year age groups, but not in ages ≤44 (**Figure 2**, right panel). Starting in the 2000s, the ratio decreased in all age groups, although the differences were not statistically significant in those aged ≥65 years.

The AAPC showed significant decreases in non-SSc-ASMR in all age groups (**Figure 3**). For SSc-ASMR, only persons aged ≤44 years had a significant annual decline (AAPC, -1.9%), whereas those aged ≥65 had the highest annual increases (AAPC, 2.0%).

Similar trends were seen in the cumulative percent change in ASMRs between 1968 and 2015 (**Table 2**). Persons aged ≤44 years experienced a 60% cumulative decrease in SSc-ASMR in the 48-year period, whereas those aged ≥65 had the largest cumulative increase (187.0%). Of all age groups, only persons aged ≤44 had a cumulative decrease in the ratio of SSc-ASMR to

non-SSc-ASMR in 48 years (-20.0%), whereas those aged ≥65 had a dramatic cumulative increase (395.4%).

Discussion

Analyses of all deaths recorded across the United States over a 48-year period revealed that the proportions of deaths in younger age groups have decreased at a higher rate for SSc than for non-SSc causes. The mortality attributed to SSc has steadily and significantly improved in the younger age group (≤44-year) over the past 48 years, but those ≥65 years age had a dramatically increased SSc mortality relative to mortality from all other causes. The decreases in absolute SSc death counts, proportionate SSc death burden, and in the ratio of SSc mortality rates to non-SSc mortality rates at ages ≤44-year suggest that the premature mortality at the population level has reduced more for SSc than for non-SSc (general population) over the 48-year study period, which is remarkable for SSc that has had no FDA-approved treatment until recently.

Several factors may underlie the age-related pattern of changes in SSc mortality that we observed. The significantly reduced mortality at ages ≤44-year may reflect improved survival in younger patients owing to increasing use of disease-modifying drugs over time (1, 13). Cumulative toxicities of these medications with time could account for increasing SSc mortality in older age (1). Greater risks of pulmonary hypertension, renal impairment and cardiac disease among those with late-age (>65 years) onset SSc (2) could also contribute to higher mortality in old age. Nevertheless, the ratio of SSc to non-SSc mortality rates has begun to decrease from 2000 onwards for those aged ≥65 years. Many advances in SSc evaluation and management in the late-1990s to the early-2000s, such as the introduction of prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors to treat pulmonary arterial hypertension, early screening for alveolitis and selected use of cyclophosphamide and mycophenolate for SSc lung disease, early recognition and treatment of SSc renal crisis with angiotensin converting enzyme inhibitors, establishment of classification criteria for early SSc, and identification of relation

between autoantibodies and prognosis could have contributed to decreasing SSc mortality in all age groups in the 2000s.

Improving detection of SSc disease over time, identification of SSc-associated autoantibodies, and the introduction of classification criteria for early SSc in 2001 might have led to increasing recognition of SSc with earlier interventions at younger ages and more older individuals with SSc. Increasing detection of anti-centromere antibody positive individuals with age could also result in more people with a SSc diagnosis at older ages (2). The mean age at SSc diagnosis in the Danish National Registry increased from 53.7±15.6 during 1995-2001 to 56.1±15.5 during 2009-2015 (14), which could partly account for increasing SSc prevalence and mortality rates at older ages. Finally, changes in physicians' practice of recognizing SSc and recording it on the death certificates, including electronic reporting and usage of ICD-10, over decades could have partly contributed to SSc mortality trends that we observed.

The age-related SSc mortality trends could also be related to differences in SSc mortality by race/ethnicity. Indeed, black persons have a 13-years lower median age of death from SSc compared to white persons, and a 5.1-times the odds of dying from SSc before 65 years of age (15). Disconcertingly, the gap in the proportions of premature SSc deaths between black and white persons have widened over the last five decades (15). Efforts are underway to evaluate relationship between race/ethnicity, age, and other demographic factors in influencing SSc mortality.

Limitations of studies using mortality databases were recently elaborated (1, 16), such as difficulty in ascertaining the accuracy of the physicians' coding on death certificates. However, misclassification of SSc (i.e., recording SSc as the cause of death on death certificates for decedents that did not have SSc) is unlikely to have influenced our inferences in a substantial

way (1). Unlike administrative healthcare databases where possible and probable diagnoses are often recorded, death certificates usually have the most proximate illness recorded as the cause of death. Consequently, SSc is unlikely to be recorded as a cause of death for decedents that did not have SSc. However, SSc may be under-recorded as the cause of death in some proportion of patients whose proximate causes of death were cardiovascular disease, cancer, and infection (8, 17), which are common in older individuals (16). However, such underreporting (i.e., SSc not recorded as the cause of death on death certificates when in fact SSc predisposed to the listed proximate cause of death) in older patients would underestimate SSc mortality at older ages, where we found a cumulative increase of 187% in SSc mortality rate and of 395% in the ratio of SSc-ASMR to non-SSC-ASMR. Thus, the profound age-related trends in SSc mortality we detected cannot be explained by a low specificity of the cause of death on death certificates, as random misclassification increases the similarity between study groups. Other limitations of our study include lack of data on disease severity, treatment history, organ involvement, and social variables. Finally, the inferences made using aggregate mortality data in this study must be verified by collecting individual-level data to account for population heterogeneity.

Under-recording of SSc on death certificates may occur, because at the time of death many SSc patients may be under care of physicians who may have a limited awareness of SSc as the cause of death. SSc mortality studies like ours may help improve this knowledge gap in healthcare workers, with increased recognition of SSc and its varied complications as the cause of death and improved physicians' coding on death certificates.

Nevertheless, our study provides an unbiased assessment of population-based burden of SSc mortality by age using a large sample size. Such mortality statistics from national databases serve as important indicators of the burden of specific diseases at the population level, with

implications for health policy planning and resource allocation. Thus, until we have large-scale, population-based, prospective studies on SSc outcomes, mortality data from studies like ours may influence research and healthcare policy, such as allocating resources to elderly at risk of high SSc mortality. Use of direct age standardization to calculate annual mortality rates, use of joinpoint regression as a computational approach to identify mortality trends, and calculation of the ratios to assess SSc mortality trends relative to changes in mortality from all other causes in the general population are other strengths of our approach.

In conclusion, the reduced mortality burden from SSc relative to mortality from all other causes in the general population prior to age 45 is encouraging. However, the relative mortality burden for SSc is still high in age 45-64, and has dramatically increased in those aged ≥65 over the past 5 decades. These observations emphasize the need for prospective studies to collect individual-level data with a goal to identify SSc mortality risk factors that could be modified to improve outcomes in older individuals with SSc.

Authors' Contributions

Drs. Yen and Singh had full access to the data and take full responsibility for the integrity of the data and the accuracy of the analysis. Dr. Yen performed data collection and data analysis. All three authors contributed to literature search, figures, tables, study design, data analysis, data interpretation, and writing. RRS supervised all aspects of this study.

Financial Support

This work was supported in part by the National Institutes of Health (R01-AI080778 and R01-AR056465). EY was supported by NIH T32-DK-07789, NIH T32-HD-007512, and UCLA Children's Discovery and Innovation Institute.

Disclosures

The authors declare no conflicts of interest.

Data Availability

Data used in this study are national mortality database maintained by the Centers for Disease Control and Prevention (CDC)'s National Vital Statistics System.

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FIGURE LEGENDS

Figure 1. Trends in Annual Percent Death According to Age Groups for SSc and Non-SSc causes, 1968-2015.

The percent of total deaths for each year from 1968 to 2015 in the four age groups was calculated for SSc and non-SSc causes. Data are displayed per calendar year of death with lines fitted on the basis of joinpoint analysis.

Numbers on each panel denote the AAPC (95% CI) for SSc and non-SSc deaths. *P < 0.05 for slope change.

Abbreviations: SSc, systemic sclerosis.

Figure 2. Trends in Age-Standardized Mortality Rate (ASMR) for SSc and Non-SSc (All Causes Other than SSc) and in the Ratio of SSc to Non-SSc ASMRs by Age Groups, 1968-2015.

Results are shown as SSc-ASMRs per million persons (left panel), non-SSc-ASMR (middle panel), and the ratio of SSc to non-SSc mortality rates (right panel). Data are displayed per calendar year of death with lines fitted on the basis of joinpoint trend analysis.

The annual number of SSc deaths ranged from 68 to 158 among those aged ≤44, 246 to 548 among 45-64, and 111 to 768 among those ≥65 years.

The APC for each trend for each subpopulation is presented as stack bars below each panel. Each stack is segmented at the year in which the change in slope is statistically significant and is aligned with the trend line. Numbers in each stack denote the APC (95% CI). The red-shaded stacks indicated an increasing trend, unshaded stacks represent a non-significant trend, and the green-shaded stacks represent a decreasing trend. *P < 0.05 for slope change.

Abbreviations: APC, annual percent change; ASMR age-standardized mortality rate; CI confidence interval; NA, not available; SSc, systemic sclerosis.

Figure 3. Average Annual Percent Change (AAPC) Over 48-Years (1968-2015) in SSc ASMR, Non-SSc ASMR, and Ratio of SSc to Non-SSc ASMR by Age Groups (≤44, 45-64, and ≥65 years). * P<0.05.

Abbreviations: AAPC, average annual percent change; ASMR, age-standardized mortality rate; CI, confidence interval; SSc, systemic sclerosis.

Table 1. Demographic Characteristics of SSc and Non-SSc Deaths by Age Groups, 1968-2015 *

Characteristic	Deaths †				Average Population	
	SSc (*n* = 46,798)		Non-SSc (*n* = 106,058,839)		(*n* = 258,208,302) ‡	
Age, years						
≤44	5,457	(11.7)	10,339,653	(9.7)	170,405,217	(66.0)
45-64	18,395	(39.3)	20,819,276	(19.6)	56,343,421	(21.8)
≥65	22,946	(49.0)	74,899,910	(70.6)	31,459,664	(12.2)

* Values are numbers (percentages).

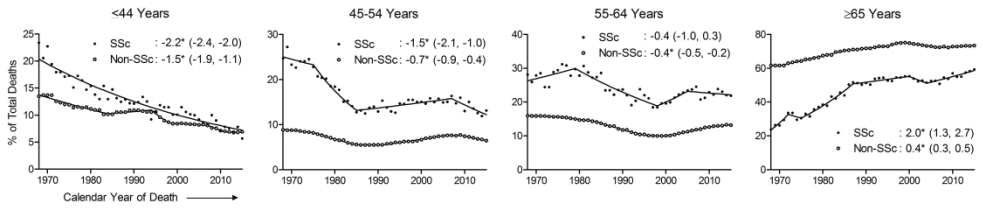
† Absolute number of deaths from all 50 states and the District of Columbia.

‡ Mean annual population derived from US Census Bureau files.

Table 2. Cumulative Percentage Change in SSc ASMR, Non-SSc ASMR, and in the Ratio of SSc ASMR to Non-SSc ASMR between 1968 and 2015 by Age Groups

Variable	SSc							Non-SSc			SSc:Non-SSc ASMR Ratio		
	ASMR per million (95% CI), No. of Deaths						% Change	ASMR per million		% Change	Ratio x 10^{-5}		% Change
	1968			2015			1968-2015	1968	2015	1968-2015	1968	2015	1968-2015
Age, years													
≤44	1.0	(0.8-1.2)	109	0.4	(0.3-0.5)	68	**-60.0**	2021.6	1010.3	-50.0	49.5	39.6	**-20.0**
45-64	5.9	(5.2-6.7)	246	4.7	(4.2-5.2)	418	-20.3	11251.7	5853.3	-48.0	52.4	80.3	53.1
≥65	5.4	(4.4-6.5)	111	15.5	(14.3-16.6)	709	**187.0**	72927.9	42251.6	-42.1	7.4	36.7	**395.4**

Abbreviations: ASMR, age-standardized mortality rate; CI, confidence interval; SSc, systemic sclerosis.



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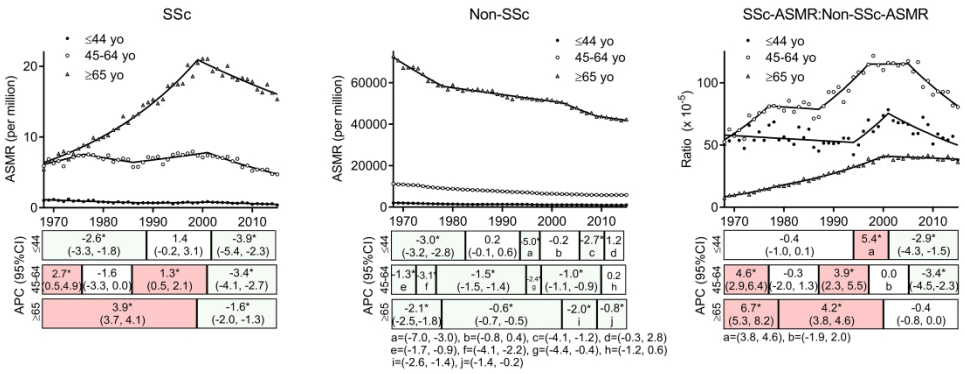

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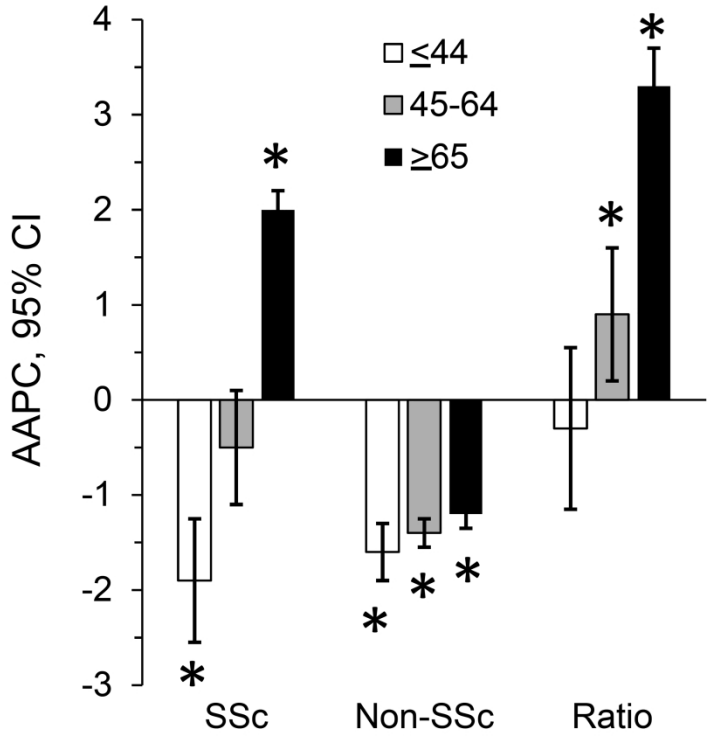

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Supplemental Materials

Steady Decrease in Systemic Sclerosis Mortality Rates at Younger Ages Over the Past Five Decades.

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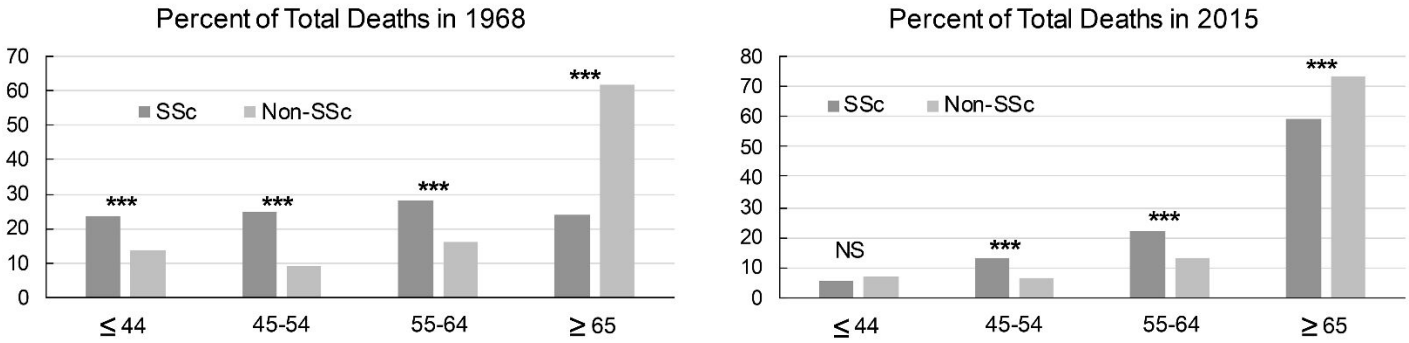
Supplemental Figure S1. Cumulative change in the percent of SSc and Non-SSc Deaths between 1968 and 2015 According to Age Groups



Percent of total deaths attributed to SSc and non-SSc causes at different age groups in 1968 and 2015. ***P < 0.0001, Chi-square with Yates' correction.

Supplemental Methods

The Joinpoint Regression Program uses a permutation test to find the optimal number of joinpoints. For greater consistency in the permutation test *P* values, the Joinpoint Regression Program runs at least 4,499 permutations to select the optimal number of linear segments to fit the model. Because fitting all 4,499! (factorial) possible permutations would be computationally intensive, the program uses a Monte Carlo simulation to conduct significance tests on a sample of the 4,499! permutations, which are adjusted using the Bonferroni correction to reduce the likelihood of false positive results (1).

The Joinpoint Regression Program (version 4.2.0.2; National Cancer Institute, Bethesda, MD) has an easy-to-use graphical user interface. The user inputs a formatted data file and selects the minimum and maximum number of joinpoints based on the observed data. For this study, we selected a maximum of 5 joinpoints. The user then selects 1 of 3 options for handling heteroscedastic errors: constant variance (homoscedasticity), SE, or Poisson variance. In addition, the user can select 1 of 2 methods for model fitting: the grid search method or the Hudson method. The grid search method identifies a discrete number of locations for testing for changes in slope (2), and the Hudson method allows for continuous model fitting but is more computationally intensive. Each trend can be as short as 1 year or can encompass several years, depending on the grid search method. For this study, we provided the SE and used the grid search method. Finally, there are advanced settings, which are described in the instruction manual (3).

1. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Statistics in medicine. 2000;19(3):335-51.
2. Lerman PM. Fitting segmented regression models by grid search. Appl Stat. 1980;29:77-84.
3. Joinpoint Help Manual. Statistical Methodology and Appplications Branch, Surveillance Research Branch.: National Cancer Institute. Accessed at https://surveillance.cancer.gov/joinpoint/Joinpoint_Help_4.5.0.0.pdf