



## Sarcoidosis deaths in the United States: 1999–2016

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### ABSTRACT

**Background:** It has been over a decade since a comprehensive study has been published that has examined sarcoidosis deaths at the national level. The purpose of this study was to analyze sarcoidosis as the underlying cause of death using current national death certificate data. Results from this project can be used to evaluate and compare trends of sarcoidosis reported deaths across the U.S.

**Methods:** Mortality data from 1999 to 2016 were provided by the National Vital Statistics System (NVSS) with sarcoidosis (ICD-D86.X) as the underlying cause of death from all resident death certificates filed in the 50 states and the District of Columbia (DC). Data were analyzed using CDC WONDER, a web-based public health database and analysis tool. Queries were used to generate number of deaths, along with unadjusted and age-adjusted death rates with 95% confidence intervals and standard errors for groups including year, census region, gender, age group, race/ethnicity and state. Joinpoint regression analysis was used to test the significance of trends in race and gender-specific rates for the 1999–2016 study period.

**Results:** From 1999 to 2016, there were a total of 16,665 sarcoidosis reported deaths in the U.S. The overall age-adjusted mortality rate increased from 2.1 (deaths per 1,000,000) in 1999 to 3.1 in 2002, but then remained relatively stable thereafter until the end of the study period. Female deaths increased 32.0% (from 2.5 to 3.3 per 1,000,000), while male deaths increased 73.3% (from 1.5 to 2.6 deaths per 1,000,000). The highest age-adjusted death rates were among black females (17.0 deaths per 1,000,000), and black males (12.4 deaths per 1,000,000). At the regional level, the southern U.S. had the highest overall mean age-adjusted mortality rate (3.7 deaths per 1,000,000), while black females in the Midwest (18.7 per 1,000,000) had the highest race-specific reported death rate.

**Discussion:** The detected increase in the total number of deaths and age-adjusted rates of sarcoidosis deaths in the U.S. is a serious health concern. Factors that contribute to sarcoidosis deaths remain uncertain and more epidemiological research studies are needed to compliment current bench science to explore and examine factors that contribute to this multifactorial, chronic disease.

### 1. Introduction

Sarcoidosis is a multi-system granulomatous disorder associated with variable prognosis that predominantly affects the lungs, lymph nodes, eyes, and skin, sometimes resulting in death [1,2]. Despite recent advances in discoveries of the pathobiology of sarcoidosis over the past decade [3], isolating specific biomarkers for making clinical decisions has been challenging [4] and its etiology remains an enigma [5,6]. Pulmonary hypertension and respiratory failure from pulmonary fibrosis are recognized as the most common complications associated

with cause of death in sarcoidosis [7–10], however, other major causes of death includes cardiac, neurologic and hepatic involvement [8].

Considerable disparity has been described in the incidence, prevalence and disease course of sarcoidosis between regions and populations. Worldwide, African Americans and northern Europeans have been reported to be most affected [11]. In the U.S., incidence and mortality disease rate differences between race groups have been reported with black males and females consistently having higher rates than whites [7,12–14]. Explanations between racial differences in sarcoidosis deaths remains largely unknown [14]. Data from population-

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**Table 1**  
Sarcoidosis deaths, by gender, age and race in the United States, 1999–2016\*.

Characteristic	Males		Females		Total	Overall Death rate	(95% CI)*	SE
	No. of deaths	Death Rate	No. of deaths	Death Rate				
Total	6481	2.4	10184	3.7	16665	2.9	2.9–2.9	< 0.1
Age group (yrs) <sup>a</sup>								
5–14	4	< 0.01	1	< 0.01	5	0.0	0.0–0.0	< 0.1
15–24	38	0.1	22	0.1	60	0.0	0.0–0.0	< 0.1
25–34	338	0.9	193	0.5	531	0.7	0.7–0.8	< 0.1
35–44	1037	2.7	1032	2.7	2069	2.7	2.6–2.8	0.1
45–54	1642	4.4	2220	5.7	3862	5.1	4.9–5.2	0.1
55–64	1533	5.3	2495	8.1	4028	6.7	6.5–7.0	0.1
65–74	1088	6.1	2203	10.6	3291	8.5	8.2–8.8	0.1
75–84	638	6.5	1479	10.7	2117	9.0	8.6–9.4	0.2
85+	163	5.5	539	8.5	702	7.5	7.0–8.1	0.3
Race/Ethnicity								
White	2727	1.2	4040	1.5	6767	1.4	1.3–1.4	0.0
Black	3689	12.4	6056	17.0	9745	15.0	14.7–15.3	0.1
Am Indian/Alaska Native	18	0.5 <sup>a</sup>	30	1.1	48	0.9	0.7–1.3	0.1
Asian/Pacific Islander	47	0.4	58	0.5	105	0.4	0.4–0.5	0.0
Hispanic	175	0.7	240	0.9	415	0.8	0.7–0.9	0.0

\*Statistically significant difference ( $p < 0.05$ ) in rates using the z statistic test score.

<sup>a</sup> Age groups are unadjusted rates.

based setting studies have suggested that mortality is independent of race, and at least part of the differential outcome may be related more to access to medical care than to inherent differences in disease behavior [12,15].

While numerous published studies exist on the pathophysiology and clinical disease presentation of sarcoidosis, few studies have examined the trends of sarcoidosis mortality. To our knowledge, there has not been a published mortality study of sarcoidosis in the U.S. in the past decade [7]. Among the earlier mortality literature, Gideon et al., identified that death rates increased from 1.3 deaths per 1,000,000 in 1979 to 1.6 deaths per 1,000,000 in 1991 with age-adjusted rates consistently higher among blacks than whites, particularly in Mid-Atlantic and northern Midwestern states (1996) [12]. In a subsequent study, Swigris et al. (2011) analyzed mortality rates of sarcoidosis from 1988 to 2007 using death certificates that included “any mention of sarcoidosis” on the death certificate. Results from that study found that regardless of sex or race, mortality rates increased significantly among decedents 55 years and older, particularly among non-Hispanic black females (4.3 deaths per 1,000,000).

The primary purpose of this study was to analyze sarcoidosis as the primary underlying cause of death using current national level, death certificate data. Results from this project can be useful for making comparisons of mortality rates and examining demographic and geographic trends of reported sarcoidosis deaths across the U.S.

## 2. Methods

Mortality data for 1999–2016 were analyzed using Centers for Disease Control and Prevention, Wide-ranging Online Data for Epidemiologic Research (CDC WONDER; <https://wonder.cdc.gov>). CDC WONDER is an on-line data repository for health statistics that incorporates a web-based application tool that provides public-use data available to the public health community for research, decision making, priority setting, program evaluation and resource allocation [16]. Data in CDC WONDER is provided by the National Vital Statistics System (NVSS) and based on information from all resident death certificates filed in the 50 states and the District of Columbia (DC). The study period analyzed for this project represented all years of U.S. mortality data available at the time of analysis using the International Classification of Disease, Tenth Revision (ICD-10) code set, which was implemented in 1999.

Web queries in CDC WONDER were made using sarcoidosis (ICD-

10-D86.X) as the reported underlying cause of death to generate the number of deaths, unadjusted and age-adjusted death rates expressed as deaths per 1,000,000 population with 95% confidence intervals and standard errors for groups defined by characteristics including year (1999–2016), sex, age group (5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and  $\geq 85$  years), race/ethnicity (non-Hispanic white, non-Hispanic black, American Indian/Alaska Native, Asian/Pacific Islander, or Hispanic), U.S. region (northeast, south, Midwest and west) and states (including District of Columbia) within each respective region. The percent of change in mortality rates from 1999 to 2016 were calculated to determine increases or decreases in the number, unadjusted and age-adjusted rates of sarcoidosis related mortality for U.S. regions, age groups sex, race/ethnicity, urban-rural classifications.

Mortality rates were calculated using population estimates produced by the U.S. Census Bureau. Age-adjusted death rates were calculated using the direct method and age-adjusted to the 2000 standard population. Joinpoint regression analysis was used to test the significance of trends in race and gender-specific rates for the period 1999–2016 [17,18].

## 3. Results

Over the 18-year study period, there were a total of 16,665 deaths in the U. S. with sarcoidosis (ICD-D86.X) listed as the primary underlying cause of death (Table 1). During this period, the overall, age-adjusted mortality rate attributed to sarcoidosis was 2.9 deaths per 1,000,000 persons. Among both genders, unadjusted death rates were exceedingly higher for those age groups 35 and older with the highest death rates observed among the 65–74 (8.5 deaths per 1,000,000) and 75–84 (9.0 per 1,000,000 persons) age groups.

Among race and ethnic groups, blacks, experienced the highest overall number of deaths and average age-adjusted death rate of 15.0 deaths, nearly 14 times higher than rates for whites. The age-adjusted death rate for black females was 17.0, nearly 16 times higher than white females (1.5 per 1,000,000), while the black male death rate was 12.4 deaths compared to 1.2 deaths of white males. The overall death rate among reported Hispanic ethnicity was 0.8 deaths with females having a higher death rate (0.9 deaths per 1,000,000) compared to males (0.7 deaths per 1,000,000).

Over the entire study period, the overall age-adjusted mortality rate for sarcoidosis deaths increased from 2.1 deaths to 3.0 deaths in 2016

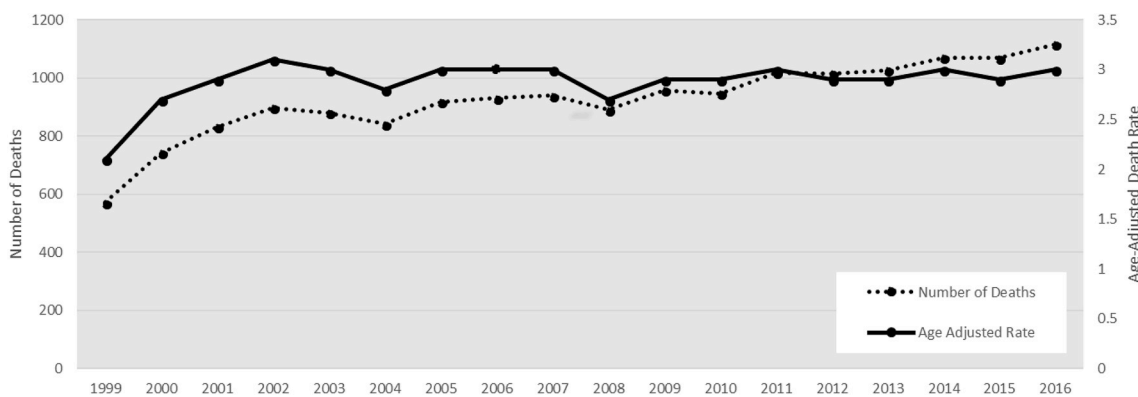


Fig. 1. Number of deaths and age-adjusted death rates of sarcoidosis: United States, 1999–2016.

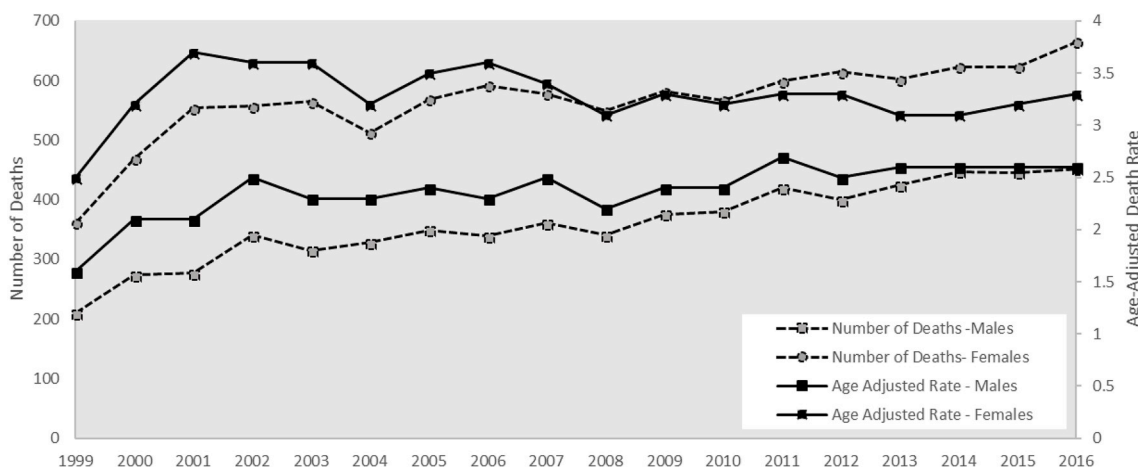


Fig. 2. Number of deaths and age-adjusted death rates of sarcoidosis, by gender: United States, 1999–2016.

(Fig. 1). When we examined deaths by gender, age-adjusted death rates increased for both males and females (Fig. 2). Among males, the age-adjusted mortality rate increased from 1.6 deaths in 1999 to 2.6 deaths in 2016, while the female death rate rose from 2.5 in 1999 to 3.3 deaths in 2016.

When mortality data were stratified by race and gender, age-adjusted death rates among white males increased from 0.7 in 1999 to 1.4 in 2016 (Fig. 3). Age-adjusted death rates among black males increased from 9.3 in 1999, to 12.2 in 2016. The age-adjusted rate among white females doubled, from 0.8 in 1999 to 1.6 in 2016 (Fig. 4). For black females, the age-adjusted mortality rate was 15.0 in 1999, increased to 21.0 in 2003, but then steadily declined before settling to 15.6 in 2016.

When looking at the percent of rate change differences between 1999 and 2016, age-adjusted mortality rates for sarcoidosis increased from 2.1 (per 1,000,000) in 1999, to 3.0 (per 1,000,000) in 2016, for an overall 42.9% increase in age-adjusted death rates over the entire study period (Table 2). At the regional level, the largest percent increase of sarcoidosis deaths occurred in the western U.S. (216.7%), while the northeast had the smallest percent increase (40.7%).

The percent of deaths in younger age groups (25–34 and 35–44) declined (–50.0% and –37.9%, respectively). However, older age groups, specifically those 65–74 and 75–84 categories, experienced an increase in death rates (175.6% and 148.8%, respectively). Females had the highest age-adjusted death rates, but white males experienced the

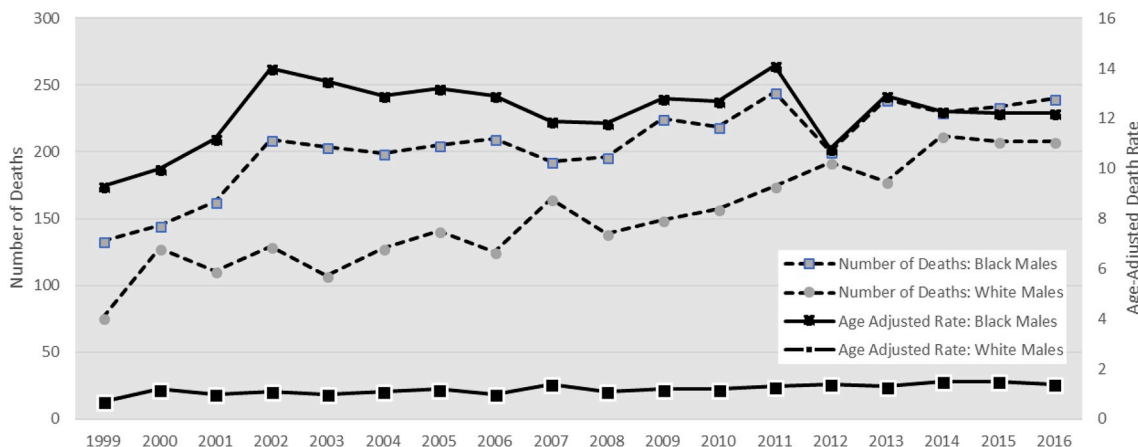


Fig. 3. Number and age-adjusted death rates of sarcoidosis, by race and gender (males): United States, 1999–2016.

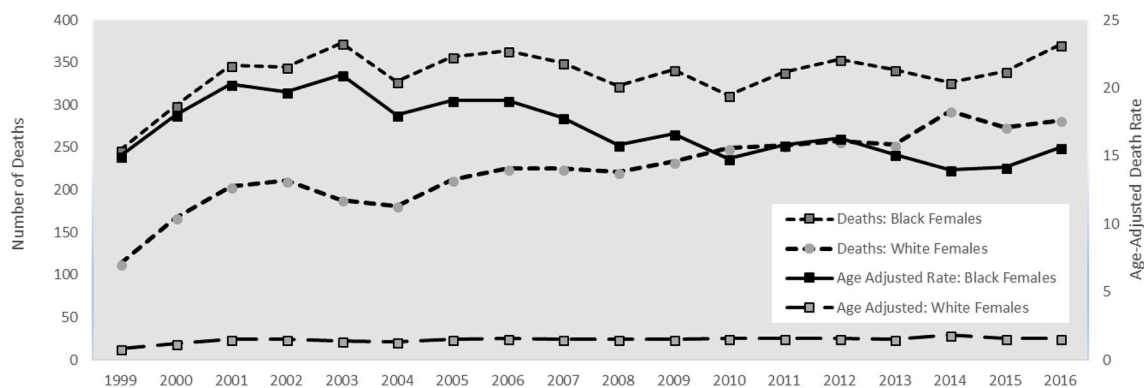


Fig. 4. Number and age-adjusted death rates of sarcoidosis, by race and gender (females): United States, 1999–2016.

Table 2

Number, unadjusted rates and age adjusted rates for sarcoidosis by region, age group, sex, race/ethnicity, urban-rural classification and state, in the United States 1999–2016.

Characteristic	1999			2016			% rate change from 1999 to 2016†
	No.	Rate	(95% CI)	No.	Rate	(95% CI)	
United States Unadjusted Rate	NA	2.0	1.9–2.2	NA	3.5	3.3–3.7	
Age-Adjusted Rate	NA	2.1	1.9–2.2	NA	3.0	2.8–3.1	42.9
Region							
Northeast	146	2.7	2.3–3.2	214	3.8	3.3–4.3	40.7
Midwest	131	2.0	1.7–2.4	243	3.6	3.1–4.0	80.0
South	256	2.6	2.3–2.9	516	4.2	3.9–4.6	61.5
West	39	0.6	0.4–0.9	144	1.9	1.6–2.2	216.7
Age group (yrs)†							
25–34	39	1.0	0.7–0.3	23	0.5	0.3–0.8	–50.0
35–44	132	2.9	2.4–3.4	74	1.8	1.4–2.3	–37.9
45–54	141	3.9	3.2–4.5	183	4.3	3.7–4.9	10.3
55–64	100	4.2	3.4–5.0	296	7.1	6.3–8.0	69.0
65–74	83	4.5	3.6–5.6	295	10.3	9.1–11.5	128.9
75–84	55	4.5	3.4–5.9	177	12.4	10.6–14.3	175.6
85 +	18	4.3	2.6–6.8	68	10.7	8.3–13.5	148.8
Sex							
Male	210	1.5	1.3–1.7	452	2.6	2.6–3.1	73.3
Female	362	2.5	2.3–2.8	665	3.3	3.7–4.4	32.0
Race/Ethnicity							
White	189	0.8	0.7–0.9	490	1.9	1.8–2.1	137.5
Black	380	10.5	9.4–11.6	611	13.5	12.4–14.6	28.6
American Indian/Alaska Native	1	0.4	0.0–2.0	7	1.5	0.6–3.1	275.0
Asian/Pacific Islander	2	0.2	0.0–0.6	9	0.4	0.2–0.8	100.0
Hispanic	13	0.38	0.2–0.7	23	0.4	0.3–0.6	5.3
Urban-rural classification							
Large central metro	234	2.9	2.5–3.3	369	3.4	3.1–3.8	17.2
Large fringe metro	115	1.8	1.4–2.1	268	2.9	2.5–3.2	61.1
Medium metro	109	1.9	1.6–2.3	232	3.0	2.6–3.4	57.9
Small metro	42	1.6	1.2–2.2	102	2.9	2.4–3.5	81.3
Microropolitan (nonmetro)	42	1.6	1.1–2.1	82	2.2	1.7–2.8	37.5
Non-core (nonmetro rural)	30	1.2	1.0–2.1	64	2.6	1.9–3.3	116.7

largest percent increase compared with females (73.3% vs. 32.0%). Blacks had the highest death rates of sarcoidosis deaths, but other race groups experienced a higher percent of change over the study period.

Among urban-rural classification, the largest percent of change of sarcoidosis deaths from 1999 to 2016 occurred in non-core, nonmetro areas (116.7%).

As shown in Table 3, the south region had the overall, highest average age-adjusted death rate attributed to sarcoidosis, with a mean of 3.7 deaths (per 1,000,000). This was followed by the northeast (3.1 deaths), the Midwest (2.8 deaths), and west regions (1.6 deaths). Southern states reporting the highest mortality rates in the U.S., included, District of Columbia (13.8 deaths), South Carolina (6.6 deaths), Maryland (5.7 deaths), and North Carolina (5.4 deaths).

When the data was stratified by region, race and gender (Fig. 5), the highest age-adjusted death rates were found among black females in the Midwest (18.7 deaths per 1,000,000) and black males in the northeast (13.2 deaths per 1,000,000). White females in the south and white males in the west had the lowest rates (1.1 and 1.0 deaths per 1,000,000, respectively).

#### 4. Discussion

Overall, sarcoidosis deaths increased from 2.1 in 1999 to 3.0 in 2016, for an annual average increase of 5% of sarcoidosis deaths per year. A steady increase in mortality was seen from 1999 to 2002, but in 2003 the rates declined and then fluctuated throughout the remainder of the study period before settling back to the 2002 death rate of 3.0 in 2016. The steady increase of sarcoidosis deaths from 1999 to 2002 is difficult to explain as incidence rates across this time period are not readily available [19]. However, it is important to note that while mortality across both genders increased during that period, deaths were more pronounced in black females. It is plausible to consider whether the increase was driven by other underlying co-morbidities. Tukey and colleagues noted in the Black Women's Health Study that approximately 25% of deaths were directly attributable to actual sarcoidosis disease itself, while the remainder of deaths were attributed to other co-morbidities [19]. In a separate study, Swigris et al. [7] found the age adjusted mortality rate increased 50% from 1988 to 2007 with a similar upward trend during the same (1999–2002) timeframe. In another study sarcoidosis study, Mirsaeidi [14] found an overall mortality rate of 2.8 from 1999 to 2010. Our project is consistent with findings of both studies for overall age adjusted death rate trends.

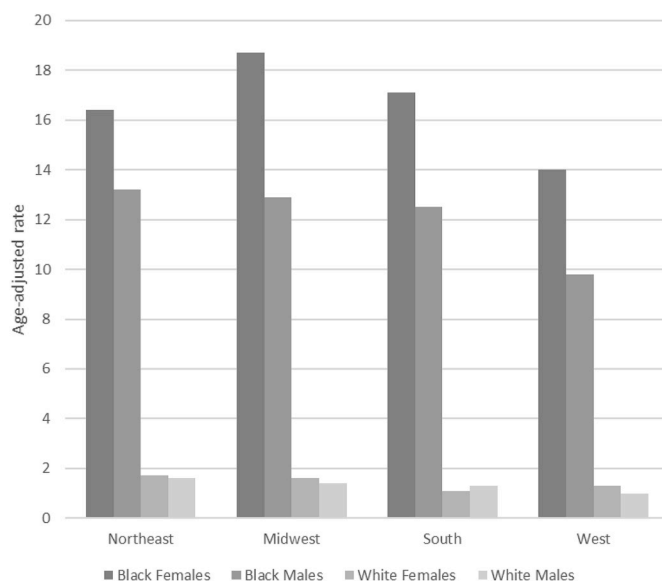
In general, our findings appear consistent with other previously published mortality studies in the U.S. that found demographic factors, including race and gender as risk factors for sarcoidosis death. We found blacks had higher mortality rates than whites with the highest rates among black females and descendants in the older age group strata. While mortality rates increased significantly among black males (9.3 in 1999 to 12.2 in 2016), mortality rates doubled for white males (0.7 in 1999 to 1.4 in 2016) and white females (from 0.8 in 1999 to 1.6 in 2016). Trends among black female sarcoidosis deaths saw age-adjusted death rates increase from 15.0 deaths in 1999 to 21.0 deaths in

**Table 3**  
Age adjusted death rates for sarcoidosis by region and state in the United States, 1999–2016.

U.S. Region	Number of Deaths	Rate	(95% CI)
South	7662	3.7	3.6–3.7
Alabama	475	5.3	4.8–5.8
Arkansas	151	2.8	2.4–3.3
Delaware	78	4.6	3.7–5.8
District of Columbia	147	13.8	11.5–16
Florida	947	2.5	2.3–2.6
Georgia	780	4.7	4.4–5
Kentucky	188	2.3	1.9–2.6
Louisiana	385	4.5	4.1–5.0
Maryland	626	5.7	5.3–6.2
Mississippi	256	4.8	4.2–5.4
North Carolina	940	5.4	5.0–5.7
Oklahoma	125	1.8	1.5–2.1
South Carolina	571	6.6	6.1–7.2
Tennessee	387	3.2	2.9–3.5
Texas	894	2.2	2.0–2.3
Virginia	631	4.3	3.9–4.6
West Virginia	81	2.0	1.6–2.5
Northeast	3398	3.1	3.0–3.2
Connecticut	193	2.7	2.3–3.1
Maine	70	2.4	1.9–3.1
Massachusetts	272	2.1	1.8–2.3
New Hampshire	38	1.4	1.0–2.0
New York	1276	3.4	3.2–3.6
Pennsylvania	850	3.2	3.0–3.5
Rhode Island	52	2.4	1.8–3.1
Vermont	37	2.9	2.0–4.0
Midwest	3618	2.8	2.8–2.9
Illinois	736	3.1	2.9–3.3
Indiana	299	2.5	2.2–2.7
Iowa	99	1.6	1.3–2.0
Kansas	120	2.3	1.8–2.7
Michigan	756	3.9	3.6–4.2
Nebraska	59	1.7	1.3–2.2
North Dakota	17	1.4	0.7–1.9
Minnesota	182	1.8	1.6–2.1
Missouri	276	2.4	2.2–2.7
Ohio	744	3.2	3.0–3.5
South Dakota	26	1.5	1.0–2.3
Wisconsin	304	2.8	2.5–3.1
West	1987	1.6	1.5–1.6
Alaska	25	2.4	1.5–3.7
Arizona	123	1.1	0.9–1.2
California	1008	1.6	1.5–1.7
Colorado	154	1.8	1.5–2.1
Idaho	43	1.6	1.1–2.2
Montana	31	1.5	1.0–2.1
Nevada	65	1.4	1.1–1.8
New Mexico	41	1.1	0.8–1.5
Oregon	118	1.6	1.3–1.9
Utah	96	2.7	2.2–3.3
Washington	256	2.1	1.8–2.4
Wyoming	20	2.1	1.3–3.2

\*Data not available for Hawaii.

2003, but then declined to 15.6 deaths (per 1,000,000) in 2016. Although the highest percent of sarcoidosis deaths increased among American Indians and Alaska Natives, interpolation of these result are difficult because of the relatively small number of deaths among these races. The highest overall regional age-adjusted mortality rate was identified among black race in the Mid-west. However, several geographical areas with the highest percent of African-American population, specifically District of Columbia, yielded the highest mortality rates for sarcoidosis. The observed increase in death rates among black female sarcoidosis deaths over the study period is concerning. However, the reason for this trajectory is unknown. One suggestion may be that an increased focus and higher awareness of the disease in black females is now yielding more reported deaths on the death certificate. By the same token, increased awareness of the disease in white females may



**Fig. 5.** Age-adjusted rates by region, race and gender: United States, 1999–2016.

also be the result of greater reporting. Discussions surrounding the increased mortality from sarcoidosis in older age groups abounds in the literature. As posited by Swigris et al. (2011) [4] and further discussed by Baughman et al. (2011) [20], the clue may lie in pulmonary fibrosis, a disease of the aging population [21,22,23], being a key driver of sarcoidosis related deaths.

Increasing mortality of sarcoidosis in the U.S. has been suggested by others [24] and appears consistent with the results from our study. From 1979 to 1991, Gideon and colleagues identified an increase in sarcoidosis mortality in the U.S. ranging from 1.3 to 1.6 deaths (per 1,000,000) in men and 1.9 to 2.5 deaths (per 1,000,000) for women [12]. Using death certificate data, Swigris et al., found from 1988 to 2007 a mortality rate of 4.32 deaths (per 1,000,000), or an overall 2% average annual increase, noting higher trends particular among black women, and older age groups [7]. Whether this variability within and among racial and ethnic groups is caused by actual differences in geographic distribution of disease (raising the question of whether environmental exposures influence disease development), caused by regional variation in methods to identify disease, or some other cause is uncertain but merits further exploration [2,7].

#### 4.1. Strengths and limitations

The results of our study were complimented by the ability to use a free and relatively easy web-based analysis tool to assist with identifying mortality trends of sarcoidosis across the U.S. The standardized manner of data collection and near complete coverage of death certificates are all strengths. However, as with any analysis using death certificate data, there are inherent concerns related to misclassification, incomplete data or inconsistent coding of cause of death. Therefore, these results must be interpreted with caution. In addition, because we were unable to analyze data at the individual level, we could not capture the sarcoidosis induced dysfunctional organ system directly responsible for death or other factors which may have influenced the death. Geographical areas that had small number estimates that were unstable may also have been inadequately captured. Several factors related to death investigation and reporting may also affect measurement of death rates involving sarcoidosis.

## 5. Conclusion

Overall, our project detected an increase in the total number of deaths and age-adjusted rates of sarcoidosis deaths in the U.S. over the study period. These results can help provide a basis for understanding mortality trends of sarcoidosis from a national, disease surveillance perspective. It is anticipated that this paper will spark new interest among others, particularly national funding agencies, to recognize the need for more advanced epidemiological research to examine this multifactorial, chronic health condition. More in-depth epidemiological studies that combine clinical findings with population-based studies to explore the interplay between socio-demographic factors (e.g., income, poverty, and occupation) or modifiable risk factors (e.g., obesity, fewer years of education) may provide vital clues for better understanding and evaluating causal relationships of this serious condition that can lead to death.

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