

# Association Between Occupational Exposures and Sarcoidosis



## An Analysis From Death Certificates in the United States, 1988-1999

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**BACKGROUND:** Sarcoidosis is a disease that is associated with occupational and environmental antigens, in the setting of a susceptible host. The aim of this study was to examine the association between sarcoidosis mortality and previously reported occupational exposures based on sex and race.

**METHODS:** The decedents enrolled in this study were derived from United States death certificates from 1988-1999. Cause of death was coded according to ICD-9 and ICD-10. The usual occupation was coded with Bureau of the Census Occupation Codes. Mortality odds ratio (MOR) were determined and multiple Poisson regression were performed to evaluate the independent exposure effects after adjustment for age, sex, race and other occupational exposures.

**RESULTS:** Of the 7,118,535 decedents in our study, 3,393 were identified as sarcoidosis-related, including 1,579 identified as sarcoidosis being the underlying cause of death. The sarcoidosis-related MOR of any occupational exposure was 1.52 (95% CI, 1.35-1.71). Women with any exposure demonstrated an increased MOR compared to women without (MOR 1.65, 95% CI, 1.45-1.89). The mortality risk was significantly elevated in those with employment involving metal working, health care, teaching, sales, banking, and administration. Higher sarcoidosis-related mortality risks associated with specific exposures were noted in women vs men and blacks vs whites.

**CONCLUSIONS:** Findings of prior occupations and risk of sarcoidosis were verified using sarcoidosis mortality rates. There were significant differences in risk for sarcoidosis mortality by occupational exposures based on sex and race. CHEST 2016; 150(2):289-298

**KEY WORDS:** mortality; mortality OR; occupational exposure; sarcoidosis

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**ABBREVIATIONS:** MOR = mortality OR; UCD = underlying cause of death

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Sarcoidosis is a multisystem, granulomatous disease, characterized by noncaseating epithelioid cell granulomas, usually in more than one organ. Recent studies suggest sarcoidosis-related mortality has been increasing over the past few decades.<sup>1-3</sup> A prevailing theory is that a genetically susceptible host is exposed to yet unknown antigens,<sup>4,5</sup> through occupational and/or environmental exposures, and subsequently develops sarcoidosis.<sup>6,7</sup> Supporting this notion, a case-control study reported the occurrence of sarcoidosis clusters among individuals with shared work.<sup>8</sup> A number of investigators have described an increased risk of sarcoidosis among those with specific occupational exposures,<sup>9-11</sup> including firefighters,<sup>12,13</sup> navy recruits,<sup>14-16</sup> workers in the lumber industry,<sup>17</sup> rock wool or glass wool workers,<sup>18</sup> and sales.<sup>19</sup> Other specific exposures, such as the World Trade Center 9/11 event, have also been found to be associated with an increased risk of sarcoidosis.<sup>20,21</sup>

Difficulties characterizing and collecting germane data regarding occupational exposures over an individual's life span produce limited understanding of the relationship between such exposures and sarcoidosis. In only a few studies have investigators attempted to systematically and

fully assess the association between occupation and sarcoidosis; most have instead chosen to focus on a single or small group of occupational exposures while ignoring others. Although a study of siblings with sarcoidosis considered many occupational exposures, the occupational factors were only limited to those held by the affected siblings prior to the date of diagnosis.<sup>22</sup>

Previous studies have shown that sarcoidosis is relatively more common in women than in men, and in black subjects than in white subjects,<sup>23,24</sup> and that the phenotype of disease and genetic risk differs according to sex and race. These findings prompted us to question if differences in sarcoidosis risk for women and men could be explained, in part, by differences in occupational exposures<sup>25</sup> or if specific exposures would induce a stronger response in women than in men. In the United States, when a person dies, a death certificate is generated; in addition to data on cause of death, it contained (for certain years) information on occupation. The aims of our study were to use death certificate data to investigate the link between sarcoidosis and certain occupational exposures previously reported as being associated with this disease and to determine which exposures were associated with sarcoidosis-related death.

## Materials and Methods

### Study Population and Design

The dataset was derived from US death certificates that had been compiled by the National Center for Health Statistics from 1988 to 1999. Our study dataset only included 25 states' decedents with Occupational Classification Codes (e-Table 1). Cause of death was coded according to the *International Classification of Diseases, Ninth Revision*, from 1988 to 1998<sup>26</sup> and the *International Classification of Diseases, 10th Revision*, after 1999.<sup>27</sup> The ninth revision code 135 and the tenth revision code D86 were used to identify decedents with sarcoidosis (all 4-digit subcodes were also included). Following convention, we considered death to be sarcoidosis-related if sarcoidosis was recorded as one of the multiple causes of death, or the underlying cause of death (UCD), among all certified causes. If only sarcoidosis was recorded as the UCD or the immediate cause of death, the cause of death was then termed "sarcoidosis-UCD" for the purposes of our study.

### Codes of Occupational Exposure

Occupational Classification Codes were available in 25 states during the years 1988 to 1999. For individuals whose death was recorded before 1993, the usual occupation on the death certificate was coded according to the 1980 Bureau of the Census classification system.<sup>28</sup> Starting in 1993, 1990 Occupational Classification Codes were used. There is considerable overlap between the 1980 and 1990 codes, as stated by the bureau: "classifications used for the 1990 Census... were similar to those used in 1980, with no major changes." To address the few instances in which minor changes or additions were made to the coding system, a crosswalk was created for any codes that were not the same in the 1990 codes as the 1980 codes.

For the purposes of this study, we considered exposures and job titles that were found in previous studies to be associated with sarcoidosis.<sup>9-22</sup> An industrial hygienist created an exposure matrix, linking occupational codes to these specific jobs, and then designated how likely various exposures were for the individuals (e-Table 1). The abbreviations of specific occupational exposures are listed in Table 1 and are used to describe the findings in the Results and Discussion. Decedents with more than one potential occupational exposure were categorized as having "any exposure."

### Statistical Analysis

Counts and crude mortality rates were calculated for the different occupational exposures among decedents with sarcoidosis. Because the total number of individuals holding a given occupation at any one time is generally unknown (ie, the denominator is indeterminable, making it impossible to generate an incidence rate), mortality ORs (MOR) were used to measure the association between occupational exposures and sarcoidosis mortality.<sup>29</sup> Because of the disparity of the incidence and mortality of sarcoidosis in sex and race,<sup>23,24,30</sup> and the possible interaction of occupational exposures, multiple Poisson regression was used to evaluate the risk effect of certain occupational exposures on sarcoidosis mortality after adjustment for age, year of death, and other occupational exposures. To further examine the effect of occupational exposure, we conducted the same analyses for the decedents for whom sarcoidosis was coded as the UCD instead of excluding those decedents whose deaths were sarcoidosis-related but were not directly attributable to sarcoidosis (ie, those without sarcoidosis-UCD).

Analyses were performed by using SAS version 9.3 (SAS Institute, Inc). Multiple Poisson regression was performed by using PROC GENMOD with a log link function, and the natural log of the population size was treated as an "offset" in the calculations of MOR.

**TABLE 1 ]** Abbreviations of Occupational Exposures and Occupational Text

Abbreviation	Related Occupations	Occupational Text
Lumber	Lumber	Forestry and logging occupations
Metal	Metal	Metal-related, including repairers, operators, engineers, installers, cutters, and workers
Agri	Agriculture	Related agricultural occupations, including farmer, gardener, nursery workers, and groundskeepers
Fire	Firefighting	Firefighting and fire prevention occupations
Silica	Silica-related	Related to mine, tile, oil, stone, glass, earth, and concrete, including drillers, installers, scrapers, operators, sculptors, and plasterers
Health	Health care	Medical staff touching patients, including health aids, dentists, physicians, and therapists
Child	Child care	Child care work, except private household
Teach	Teaching-related	Teachers except for postsecondary, counselors, and teacher aides
Animal	Animal	People touching animals, including animal caretaker, farmers, gardener, and pest control occupations
College	College	Teachers for postsecondary, counselors
Organic	Job-related to organic materials	Occupations that have some exposure to organic materials when working, including bakers, carpenters, dressmakers, food makers, garbage collectors, plasterers, and shoe repairers
Mechanic	Mechanic	Machinery-related, including repairers, operators, supervisor in aircraft, automobile mechanics, and bus
Mold	Job-related to mold	Biology-related, including janitors, cleaners, geodesists, geologists, and housemen
Military	Military	Armed forces
Mail	Mail	Postmasters and mail superintendents
Rad	Radiation	Nuclear engineers, medical appliance technicians, and airplane navigators
Bird	Bird	Animal caretakers, except for farm
Sale	Sale-related	Sales occupations, including services, representatives, and wholesale in business and personal goods
Bank	Banking-related	Financial records, processing occupations
Admin	Administration	Miscellaneous administrative occupations, secretaries, typists, stenographers, legal assistant

## Results

### *Characteristics of Sarcoidosis Decedents*

From 1988 to 1999 in the United States, 26,449,303 individuals died. Analysis was limited to 7,118,535 decedents aged > 14 years from 25 states with occupational coding. Of these 7,118,535 decedents, 3,393 deaths were coded as sarcoidosis-related, including 1,579 coded as UCD. According to [Table 2](#), the proportion of men and women was approximately 1:1, but sarcoidosis-related mortality was higher in women than in men. The adjusted-MOR for sarcoidosis-related death was 2.25 (95% CI, 2.10-2.42;  $P < .0001$ ) for women compared with men. There were 2,763,665 decedents with any occupational exposure. The adjusted-MOR for sarcoidosis-related death was

1.52 (95% CI, 1.35-1.71;  $P < .0001$ ) for any occupational exposure (reference, no exposure). Among women, those with any exposure had greater odds of sarcoidosis-related death than those without exposures (MOR, 1.65 [95% CI, 1.45-1.89];  $P < .0001$ ); this scenario was not observed for men (MOR, 1.12 [95% CI, 0.86-1.46];  $P = .408$ ).

### *Characteristics of Occupational Exposures*

[Figure 1](#) displays the significant differences in occupations between women and men; female decedents were more likely to have worked in the following job categories: “Admin,” “Health,” “Teach,” “Organic,” and “Sale”; men were more likely to have worked in “Organic,” “Metal,” “Silica,” “Animal,” and “Agri.” The distribution of occupations between white and

**TABLE 2 ] Basic Characteristics of Sarcoidosis Decedents According to Sex and Race**

Characteristic	All			Any Exposure		
	No.	Sarcoidosis-Related	Sarcoidosis-UCD	No.	Sarcoidosis-Related	Sarcoidosis-UCD
Female subjects	3,549,946	2,064 (0.058)	977 (0.027)	1,002,806	833 (0.083)	403 (0.040)
Black	379,289	1,220 (0.322)	651 (0.172)	104,873	533 (0.508)	285 (0.272)
Other	41,025	5 (0.012)	4 (0.010)	10,411	1 (0.010)	1 (0.010)
White	3,129,632	839 (0.027)	322 (0.010)	887,522	299 (0.034)	117 (0.013)
Male subjects	3,568,589	1,329 (0.037)	602 (0.017)	1,760,859	594 (0.034)	289 (0.016)
Black	412,680	754 (0.183)	387 (0.094)	206,915	343 (0.166)	187 (0.090)
Other	51,704	6 (0.012)	3 (0.006)	26,134	3 (0.011)	2 (0.008)
White	3,104,205	569 (0.018)	212 (0.007)	1,527,810	248 (0.016)	100 (0.007)
Total	7,118,535	3,393 (0.048)	1,579 (0.022)	2,763,665	1,427 (0.052)	692 (0.025)

Unless otherwise indicated, data are presented as No. (%). UCD = underlying cause of death.

black individuals was similar, although the absolute number of white subjects working in those occupations was higher than black subjects.

### Occupational Exposures Associated With Sarcoidosis

Table 3 displays crude mortality rates and adjusted-MORs for specific occupational exposures (compared with no exposure) among decedents with sarcoidosis-related death and decedents for whom sarcoidosis was considered the UCD. The crude mortality rates of sarcoidosis-related deaths were the highest in decedents with occupations that involved “Child” (0.16%). No decedents worked in “Mail.” The risk for sarcoidosis-related death was elevated among decedents exposed to the following occupation categories: “Metal,” “Health,” “Teach,” “Sale,” “Bank,” and “Admin.” However, “Silica” had a protective effect on sarcoidosis-related death (adjusted-MOR, 0.56 [95% CI, 0.42-0.74]) and sarcoidosis-UCD (adjusted-MOR, 0.44 [95% CI, 0.29-0.66]). For the sarcoidosis-UCD decedents, the risks of the same occupational exposures were found to be significantly elevated except for “Metal” and “Sale,” which were not statistically significant in the analyses. The MOR for “Bank” occupation was 44.9% greater for sarcoidosis-UCD than sarcoidosis-related death.

### Differences of Occupational Exposures According to Sex and Race

Table 4 displays the statistically significant adjusted-MORs for the sample stratified according to sex and race. There was a statistically significant excess sarcoidosis-related mortality risk among black women with the following occupational job categories:

“Metal,” “Teach,” “Bank,” and “Admin.” These findings were further verified based on elevated sarcoidosis-UCD mortality risk. Among black male decedents, some occupational exposures were also significantly associated with increased mortality risk for sarcoidosis-related deaths. With only five individuals with sarcoidosis-related death in other races except for black and white subjects, occupational exposures did not significantly impact the sarcoidosis-related mortality in other race, regardless of sex. Table 5 illustrates that some occupational exposures had a higher mortality risk in women than in men except for “Child” and that black subjects had a statistically significant excess sarcoidosis-related risk based on occupation. The results were also identified in the analyses of sarcoidosis-UCD.

### Discussion

There are several studies showing that specific occupational exposures are associated with increased risk of sarcoidosis.<sup>11,17,19,22</sup> These studies imply that occupational exposures may be of particular importance in sarcoidosis risk and/or in conjunction with a susceptible genotype,<sup>31</sup> as demonstrated in the study of firefighters exposed to the World Trade Center disaster.<sup>32</sup> Our results showed that sarcoidosis mortality was higher among those with “any exposure” than without exposure, and sarcoidosis mortality risk was higher in women than men. However, of decedents with any exposure, the MOR of sarcoidosis-related deaths was considerably increased among women compared with men, at about 35.4%. These results in total further support the existing evidence that occupational exposure is important in the development of sarcoidosis because sarcoidosis risk is increased in

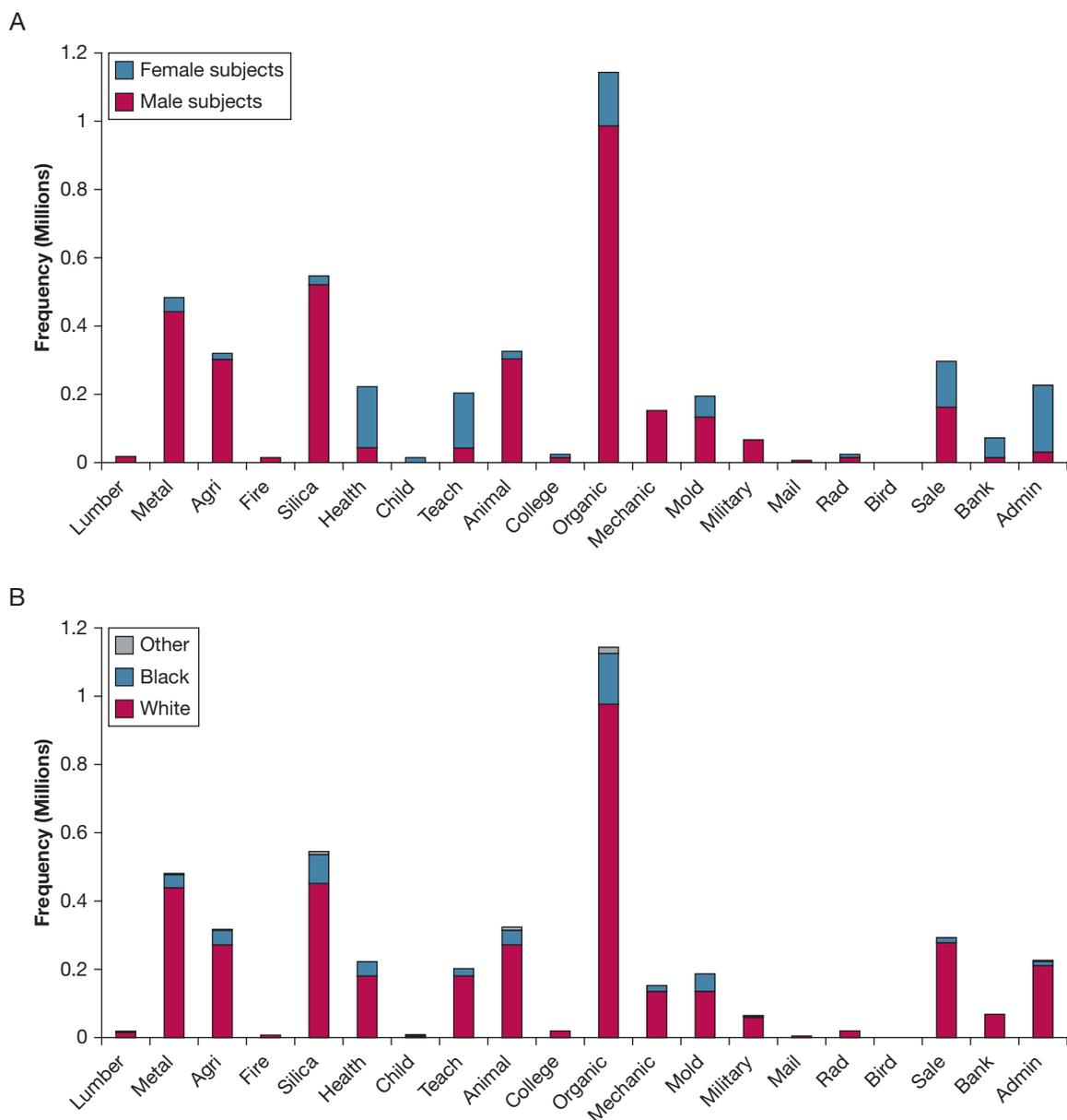


Figure 1 – A–B, Distribution of different occupational exposures according to sex (A) and race (B).

women.<sup>33</sup> Our results suggest that certain occupational exposures have an association with specific sexes and race.

In the present study, “Admin” occupation had a larger impact on sarcoidosis mortality among women. The finding of this occupation and its relationship to sarcoidosis is limited, however.<sup>22</sup> Furthermore, the possible exposures that these individuals sustained, as well as the mechanism that would put individuals with sarcoidosis at greater risk, are uncertain. Employment in “Bank” demonstrated an increased risk for sarcoidosis mortality in women, especially in black women. The potential exposures in “Admin,” “Teach,” and “Bank”

are similar in occupational characteristics, in that there is often person-to-person contact, which could be associated with transmission of an exposure. In addition, these occupations are unlikely to result in exposure to chemicals or particles, such as dust and organic material. The disparity in exposures between sexes may explain the increasing risk of sarcoidosis in women, which should be further evaluated in future studies.

We also found that all statistically significant occupational exposures associated with sarcoidosis-related deaths were further confirmed in the analyses of sarcoidosis-UCD, regardless of race or sex. The

**TABLE 3 ] Crude Rate and Adjusted-MOR of Sarcoidosis in Different Occupational Exposures**

Occupation	Sarcoidosis-Related			Sarcoidosis-UCD		
	No.	Crude Rate (%)	Adjusted-MOR (95% CI) <sup>a</sup>	No.	Crude Rate (%)	Adjusted-MOR (95% CI) <sup>a</sup>
Lumber	4	0.022	0.47 (0.17-1.34)	3	0.017	0.57 (0.16-1.99)
Metal	197	0.041	1.41 (1.08-1.85) <sup>b</sup>	89	0.019	1.43 (0.98-2.09)
Agri	58	0.018	1.30 (0.28-6.04)	25	0.008	1.35 (0.13-14.57)
Fire	2	0.018	0.75 (0.19-3.03)	1	0.009	0.75 (0.11-5.40)
Silica	125	0.023	0.56 (0.42-0.74) <sup>b</sup>	54	0.010	0.44 (0.29-0.66) <sup>b</sup>
Health	261	0.117	1.61 (1.14-2.28) <sup>b</sup>	133	0.060	1.86 (1.11-3.11) <sup>b</sup>
Child	16	0.162	1.40 (0.78-2.52)	7	0.071	1.31 (0.54-3.16)
Teach	154	0.076	1.90 (1.34-2.71) <sup>b</sup>	74	0.037	2.25 (1.33-3.81) <sup>b</sup>
Animal	59	0.018	0.81 (0.18-3.76)	26	0.008	0.83 (0.08-8.83)
College	14	0.069	1.52 (0.87-2.66)	5	0.025	1.20 (0.48-2.98)
Organic	367	0.032	1.03 (0.76-1.40)	186	0.016	1.38 (0.87-2.17)
Mechanic	55	0.036	0.79 (0.57-1.10)	26	0.017	0.94 (0.57-1.55)
Mold	114	0.060	0.94 (0.65-1.36)	58	0.031	1.08 (0.62-1.86)
Military	33	0.050	1.20 (0.75-1.93)	18	0.027	1.58 (0.81-3.09)
Mail	0	0	...	...	...	...
Rad	29	0.128	1.16 (0.79-1.71)	13	0.057	1.02 (0.58-1.81)
Bird	1	0.072	1.18 (0.10-14.23)	1	0.072	2.04 (0.09-44.34)
Sale	126	0.043	1.23 (1.03-1.48) <sup>b</sup>	52	0.018	1.14 (0.86-1.51)
Bank	34	0.049	1.71 (1.22-2.40) <sup>b</sup>	20	0.029	2.48 (1.59-3.87) <sup>b</sup>
Admin	175	0.077	1.86 (1.59-2.18) <sup>b</sup>	83	0.037	1.98 (1.58-2.49) <sup>b</sup>

An individual can be counted in more than one category. MOR = mortality OR. See Table 2 legend for expansion of other abbreviation.

<sup>a</sup>Adjusted for age, sex, race, year, and other exposures.

<sup>b</sup>P < .05.

**TABLE 4 ] Sarcoidosis Mortality of Different Occupational Exposures With a Statistical Significance in Stratification of the Death Populations According to Sex and Race**

Variable	Sarcoidosis-Related		Sarcoidosis-UCD	
	Black Subjects	White Subjects (95% CI)	Black Subjects	White Subjects (95% CI)
<b>Women</b>				
Metal	2.62 (1.28-5.37)	NS	2.73 (1.04-7.17)	NS
Teach	2.74 (1.21-6.21)	NS	3.60 (1.15-11.24)	NS
Bank	3.36 (1.98-5.71)	NS	3.06 (1.45-6.47)	2.26 (1.26-4.05)
Admin	2.24 (1.78-2.81)	1.67 (1.32-2.11)	2.36 (1.75-3.18)	1.55 (1.05-2.29)
<b>Men</b>				
Metal	1.78 (1.16-2.74)	NS	NS	NS
Silica	0.56 (0.38-0.82)	NS	0.40 (0.24-0.68)	NS
Health	0.40 (0.24-0.68)	NS	NS	NS
Child	13.26 (4.31-40.80)	NS	NS	NS
Teach	2.94 (1.43-6.03)	2.65 (1.22-5.75)	3.57 (1.28-9.93)	NS
Military	2.32 (1.19-4.54)	NS	NS	NS
College	NS	2.78 (1.03-7.52)	NS	NS

The results on other race were not listed because they were statistically insignificant. The data were adjusted for age, year, and other occupational exposures. NS = not significant. See Table 2 legend for expansion of other abbreviation.

**TABLE 5 ] Mortality Risk for Sarcoidosis in Certain Occupational Exposures Comparing Different Sex and Race**

Variable	Sarcoidosis-Related		Sarcoidosis-UCD	
	Sex (Female/Male) <sup>a</sup>	Race (Black/White) <sup>b</sup>	Sex (Female/Male) <sup>a</sup>	Race (Black/White) <sup>b</sup>
Lumber	NS	NS	NS	NS
Metal	2.99 (2.08-4.29)	10.57 (7.87-14.20)	2.68 (1.53-4.72)	12.41 (7.94-19.40)
Agri	NS	3.01 (1.73-5.21)	NS	3.78 (1.66-8.63)
Fire	NS	NS	NS	NS
Silica	2.31 (1.30-4.10)	4.32 (3.01-6.20)	NS	NS
Health	1.92 (1.30-2.83)	9.36 (7.03-12.46)	2.14 (1.22-3.76)	9.81 (6.49-14.83)
Child	0.28 (0.09-0.91)	10.73 (2.42-47.61)	NS	8.75 (1.05-73.18)
Teach	1.80 (1.20-2.70)	9.37 (6.69-13.11)	2.06 (1.12-3.77)	11.38 (6.88-18.84)
Animal	NS	3.17 (1.85-5.45)	NS	4.11 (1.85-9.13)
College	NS	8.51 (2.68-26.99)	NS	13.45 (1.93-93.81)
Organic	2.85 (2.22-3.65)	7.64 (6.11-9.55)	2.56 (1.81-3.63)	9.93 (7.17-13.77)
Mechanic	NS	8.11 (4.72-13.92)	NS	13.66 (5.98-31.17)
Mold	1.62 (1.11-2.38)	5.52 (3.58-8.61)	NS	8.27 (4.15-16.47)
Military	NS	19.70 (8.35-46.48)	NS	17.67 (5.65-55.33)
Mail	NS	NS	NS	NS
Rad	3.73 (1.31-10.66)	18.11 (7.03-46.66)		31.3 (5.70-172.02)
Bird	NS	NS	NS	NS
Sale	2.11 (1.47-3.02)	7.65 (5.14-11.40)	2.72 (1.513-4.89)	12.06 (6.62-21.97)
Bank	7.75 (1.05-57.19)	16.54 (7.45-36.73)	NS	14.04 (4.73-41.66)
Admin	3.86 (1.97-7.57)	11.37 (8.18-15.80)	3.46 (1.40-8.59)	16.71 (10.27-27.20)

See Table 2 and 4 legends for expansion of other abbreviations.

<sup>a</sup>Adjusted for age, year, race, and other occupational exposures.

<sup>b</sup>Adjusted for age, year, sex, and other occupational exposures.

consistency of these results provides evidence of a strong link between occupational exposures and sarcoidosis among women. According to A Case-Control Etiologic Sarcoidosis Study (ACCESS), case subjects or patients with sarcoidosis were more likely to be teachers in a middle or high school than control subjects (OR, 1.80 [95% CI, 1.14-2.83])<sup>8</sup>; these findings were similar to our findings of increased sarcoidosis risk in those with the occupation “Teach.”

It is interesting that among men, the occupations associated with sarcoidosis mortality varied more than those in women and did not include the occupations “Admin” and “Bank,” which were associated with increased risk in women. Based on our understanding of exposure in these occupations, men were more likely to inhale and/or have contact with inorganic or organic substances or microorganisms based on these occupations<sup>11,17-19</sup> and would be less likely to result in person-to-person contact. Our findings support sex-specific occupational exposures, with occupations related to “possible inhalational exposures” associated with sarcoidosis-related mortality in men, and

occupations related to “person-to-person contact” associated with sarcoidosis-related mortality in women. These findings may provide support to the studies showing that women are more prone to skin and eye involvement (organs affected by contact), whereas men tend to have higher rates of pulmonary and cardiac involvement, as inhalation of particulates is more likely to affect both the cardiac and pulmonary systems.<sup>34-36</sup> In addition, sex differences may also be related to genetics and/or other confounders. A recent study indicated that genetic and exposure interactions could result in the female predominance in many autoimmune diseases, including sarcoidosis.<sup>37</sup> Surprisingly, we found no associations between the risk of sarcoidosis and occupational exposures to pets, firefighting, and lumber in any of our analyses, although other studies have shown these associations.<sup>10,12,13,17</sup> It is possible that these exposures are associated with less severe forms of sarcoidosis that do not contribute to mortality. An episodic, high-intensity exposure might lead to an enhanced effect of specific occupation on sarcoidosis, such as those from the World Trade Center.<sup>32</sup> Certainly, these exposures, which may

have been misclassified or overlooked on the death certificates, could result in the differences between our study findings and others.

In our study, the exposure to silica was found as a protective factor for sarcoidosis with an MOR < 1. The result is puzzling in light of other studies, which found that work with silica is positively associated with sarcoidosis, including a case-control study that observed a significant association between employment with crystalline silica exposures and sarcoidosis (OR, 13.2;  $P < .05$ ).<sup>38</sup> It is noteworthy that the results may be confounded by the fact that a person exposed to silica is more likely to be diagnosed with silicosis because of the following clinical findings: a history of occupational exposure and chest radiograph that may be similar between sarcoidosis and early silicosis. Indeed, one study with a negative association noted that once silicosis is diagnosed, it is difficult for individuals to change the diagnosis or to obtain another diagnosis such as sarcoidosis<sup>39</sup> because patients with silicosis are compensated by workers' compensation or the government.<sup>40</sup> A diagnosis of silicosis and sarcoidosis could end up being exclusive,<sup>41</sup> which could result in a false protective effect of silica exposure. In an animal model, silica dust induced an immune-mediated granulomatous and inflammatory reaction that is characteristics of sarcoidosis, supporting silica's involvement in granulomatous inflammation.<sup>42</sup> In addition, silica is likely a macrophage poison or toxin, and it may also function as an immunosuppressant. There is evidence that silica causes the production of free radicals and reactive oxygen species<sup>43-45</sup> and that alveolar macrophage cells die due to activation of the apoptotic cascade.<sup>46-48</sup> Although these molecular mechanisms are not entirely understood, it is possible that silica's potential immunosuppressant effects might explain the protective findings in our study.

Although the death certificate records lack information on length of employment and the time of diagnosis, and the dataset in our study may be a skewed population. There are advantages to the study design. Because individuals came from 25 states, and some individuals with mild forms of the disease may not have had sarcoidosis listed on their death certificate, the advantages of this approach over other studies include

its simple and relatively inexpensive approach, larger sample size, and broader geographic coverage.<sup>49</sup> Although the analysis of MORs cannot provide a causal relationship between occupational exposures and death, it is particularly useful for the study of occupational groups because it can be difficult to assemble occupational cohorts to obtain information regarding risk and occupational exposure, especially for a rare disease such as sarcoidosis. Using this dataset, the present analyses from death certificates provided associations between occupational exposures and sarcoidosis-related mortality risk. However, due to the limited data available, we did not consider some lifestyles, including smoking, use of hairspray and cosmetics, and environmental exposures. They could be indirectly related to sarcoidosis mortality in our study or a confounder. In this study, we focused on reported direct occupational exposure, which is an additional limitation. There may also have been miscoding of death cause and/or occupational exposures in this study when the death certificates were completed or due to our use of an exposure matrix. In all analyses, we had controlled for other occupational exposures; as a result, we did not further correct the  $P$  value for multiple tests to avoid the probability of increasing false-negative associations. Certainly, this method could be a limitation because some of the results could be false-positive findings.

## Conclusions

The present study verified findings of prior occupations and risk of sarcoidosis based on sarcoidosis-related mortality rates, mainly in the job categories "Metal," "Health," "Teach," "Sales," "Bank," and "Admin." The effects of occupational exposures on sarcoidosis-related mortality were more significant in women than in men and in black subjects than in white subjects, with the most prominent findings in black women. Although these findings are associative, they may suggest potential interactions between occupational exposures and sex and race that could spur the greater risk of death noted in women and black subjects. It is possible that differences in disease risk based on sex and race could be in part related to differences in exposure.

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