

# Sarcoidosis Diagnosed After September 11, 2001, Among Adults Exposed to the World Trade Center Disaster

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**Objective:** Explore relationships between World Trade Center (WTC) exposures and sarcoidosis. **Methods:** Sarcoidosis has been reported after exposure to the WTC disaster. We ascertained biopsy-proven post-9/11 sarcoidosis among WTC Health Registry enrollees. Cases diagnosed after Registry enrollment were included in a nested case-control study. Controls were matched to cases on age, sex, race or ethnicity, and eligibility group (eg, rescue or recovery worker). **Results:** We identified 43 cases of post-9/11 sarcoidosis. Twenty-eight incident cases and 109 controls were included in the case-control analysis. Working on the WTC debris pile was associated with sarcoidosis (odds ratio 9.1, 95% confidence interval 1.1 to 74.0), but WTC dust cloud exposure was not (odds ratio 1.0, 95% confidence interval 0.4 to 2.8). **Conclusions:** Working on the WTC debris pile was associated with an elevated risk of post-9/11 sarcoidosis. Occupationally exposed workers may be at increased risk.

Sarcoidosis is a rare, multisystem granulomatous disease of unknown etiology that can involve any organ but most often affects the lungs, skin, and/or eyes. A definitive diagnosis of sarcoidosis requires identification of a characteristic pattern of immune cells (a noncaseating granuloma) on a tissue biopsy and the exclusion of infection and other illness with similar clinical presentations. Although common symptoms include cough, shortness of breath, and wheezing, a substantial proportion of persons with sarcoidosis are asymptomatic. In such individuals, the disease is most often diagnosed after abnormalities are incidentally detected on chest radiographs. Whether asymptomatic disease is recognized thus depends upon the frequency with which diagnostic imaging is performed in a particular population.<sup>1</sup> Those with significant symptoms may require treatment with corticosteroids or other immunosuppressive medications. Approximately two thirds of persons with sarcoidosis experience remission within a decade of diagnosis whereas the remaining one third develops progressive disease. Less than 5% of those affected die because of sarcoidosis.<sup>2</sup>

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This article is dedicated to the memory of Dr. Alvin Teirstein, an internationally recognized researcher and expert in the care of patients with sarcoidosis.

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## Learning Objectives

- Demonstrate familiarity with the diagnosis and treatment of sarcoidosis, along with the environmental and occupational exposures linked to this disease.
- Discuss the new findings on sarcoidosis and World Trade Center (WTC) exposure.
- Identify specific factors associated with sarcoidosis risk among people exposed to conditions at the WTC site.

Although the cause of sarcoidosis is unknown, a leading hypothesis is that certain environmental exposures interact with genetic factors to trigger an inflammatory response in susceptible individuals.<sup>3,4</sup> This theory is supported by the occurrence of sarcoidosis clusters among persons with shared work or home environments<sup>5-7</sup> and by observed associations between sarcoidosis and several environmental exposures including indoor exposure to mold, mildew, musty odors, or wood-burning stoves.<sup>3,8,9</sup> Several exposures that may be encountered in occupational settings have been implicated as potentially inciting agents, including microbial bioaerosols, insecticides<sup>3</sup>, metals<sup>9</sup>, and inorganic particles.<sup>10</sup>

Firefighting is among the occupations that have been associated with sarcoidosis. An elevated incidence of sarcoidosis was described among members of the Fire Department of New York (FDNY) between 1985 and 1998,<sup>11</sup> and a further increase in sarcoidosis-like granulomatous pulmonary disease (SLGPD) was observed during the first 5 years after the September 11, 2001, World Trade Center (WTC) disaster (9/11) among FDNY members who had performed postdisaster rescue or recovery work.<sup>12</sup> Sarcoidosis-like granulomatous pulmonary disease was also described among 38 rescue or recovery workers enrolled in the WTC Medical Monitoring and Treatment Program,<sup>13</sup> and among 23 lower-Manhattan area residents, workers, and cleanup workers receiving medical care at Bellevue Hospital,<sup>14</sup> as well as in smaller case reports.<sup>15</sup>

These reports suggest a potential relationship between sarcoidosis and 9/11-related exposures; however, there are only limited epidemiologic data on the relationship between specific 9/11-related exposures and sarcoidosis among rescue or recovery workers, and even less for other exposed populations. We sought to describe post-9/11 sarcoidosis in a diverse group of persons exposed to the disaster and to examine associations between specific exposures and the development of post-9/11 sarcoidosis.

## MATERIALS AND METHODS

### Data Collection

Our study population was the WTC Health Registry (the Registry), a voluntary cohort formed to track the long-term health of persons who were likely to have been highly exposed to the events of 9/11. The Registry's methods were described previously.<sup>16-18</sup> Lists of potentially eligible persons were obtained from area employers and government agencies (list-identified enrollees), and broad-based, multilingual media campaigns were used to encourage potentially eligible persons to enroll via a

toll-free telephone number or a Web site (self-identified enrollees). Potential enrollees were recruited from the following groups: rescue or recovery workers and volunteers, lower Manhattan residents, lower Manhattan office workers, area school staff and schoolchildren, and passersby on September 11. From September 2003 to November 2004, 71,437 persons completed a Wave 1 (W1) enrollment questionnaire administered by computer-assisted telephone interview (95%) or in-person interview (5%) after providing informed consent. Wave 1 included questions on demographics, exposures incurred during and after the 9/11 disaster, and health information. Between November 2006 and January 2008, 46,322 enrollees completed the Wave 2 (W2) questionnaire (available at: [http://nyc.gov/html/doh/wtc/downloads/pdf/wtc/adult\\_survey2006-2007.pdf](http://nyc.gov/html/doh/wtc/downloads/pdf/wtc/adult_survey2006-2007.pdf)) via mail (46%), Web site (42%), or computer-assisted telephone interview (12%). Wave 2 included additional detailed exposure questions and questions about mental and physical health, including whether the respondent had ever been diagnosed with sarcoidosis by a doctor or other health care professional.

Persons who reported a diagnosis of sarcoidosis on W2 were mailed an in-depth sarcoidosis questionnaire (available from the authors) and forms requesting permission to review medical records and/or contact the respondent's personal physician. The questionnaire inquired about symptoms, timing and method of diagnosis, and functional status. Reminder telephone calls were attempted for each eligible enrollee. We requested medical records and/or interviews with physicians for all consenting participants. Medical record abstractions and physician interviews were conducted by New York City (NYC) Department of Health and Mental Hygiene physicians. The Centers for Disease Control and Prevention and NYC Health Department institutional review boards approved the Registry protocol.

### Case Definition

Cases were defined as sarcoidosis confirmed by demonstration of noncaseating granulomas and the absence of any known granulomagenic organism or particle on a tissue biopsy performed after October 2001 (verified by H.J. by medical record review or verbal confirmation from the treating physician; subsamples of records were independently reviewed by J.C. ( $n = 20$ ), A.T. ( $n = 19$ ), and D.P. ( $n = 6$ ); no disagreements among reviewers were identified). Records were de-identified before review by A.T. or D.P. Enrollees who did not report sarcoidosis on W2 and those determined not to have diagnosis of sarcoidosis based on response to the sarcoidosis questionnaire and/or medical record review were considered to have no history of sarcoidosis. Enrollees who reported a history of sarcoidosis on W2 but were diagnosed before November 2001, did not have a definitive biopsy, or whose sarcoidosis could not be confirmed medically were excluded.

### Study Variables

We categorized enrollees into mutually exclusive and hierarchical eligibility groups on the basis of likelihood of degree of exposure, with rescue or recovery enrollees followed by lower Manhattan residents, lower Manhattan area workers, and passersby on September 11. Exposures were defined on the basis of responses to W1 and W2 questions. *Dust cloud exposure* was defined as being caught in the dust cloud on the morning of September 11 and reporting a geocodable location in lower Manhattan<sup>17</sup> or endorsing any of the following: could not see a couple of feet in front of me; had trouble walking or finding my way because the dust was so thick; had to find shelter such as under a car or in a doorway; was covered from head to toe with dust or debris; or could not hear anything.<sup>16</sup> For rescue or recovery enrollees, exposure variables also included duration of work (categorized as  $>$  or  $\leq 55$  days), arrival time (arrival by vs after September 12), and whether work had been performed on the debris pile resulting from the collapse of the WTC and surrounding buildings. Among those who worked on the pile,

we examined the following specific tasks: firefighting, hand digging, welding, and light construction. Respiratory protection was defined as reporting the use of a full- or half-face respirator or disposable mask with National Institute for Occupational Safety and Health's N95 to P100 rating during the period of arrival at the WTC site (categorized as arrival on September 11, 2001; between September 12, 2001, and December 31, 2001; or after December 31, 2001). Those who reported using no mask or a dust or surgical mask during their arrival period were considered unprotected. Smoking status at the time of the W1 survey was categorized as having ever or never smoked. Self-reported physician-diagnosed asthma status and demographic characteristics were obtained from the W1 or W2 survey. Race or ethnicity was defined on the basis of the methods described for the 2000 US Census.<sup>19</sup> Sarcoidosis illness characteristics were taken from the in-depth sarcoidosis survey, and clinical information was obtained from medical records.

### Data Analysis

Enrollees aged 18 years and older at the time of W1 who also completed W2 were eligible for this analysis. We compared demographic and exposure characteristics of case patients with those of enrollees with no history of sarcoidosis using chi-square or Fisher exact test. The Wilcoxon ranked sum test was used to compare medians.

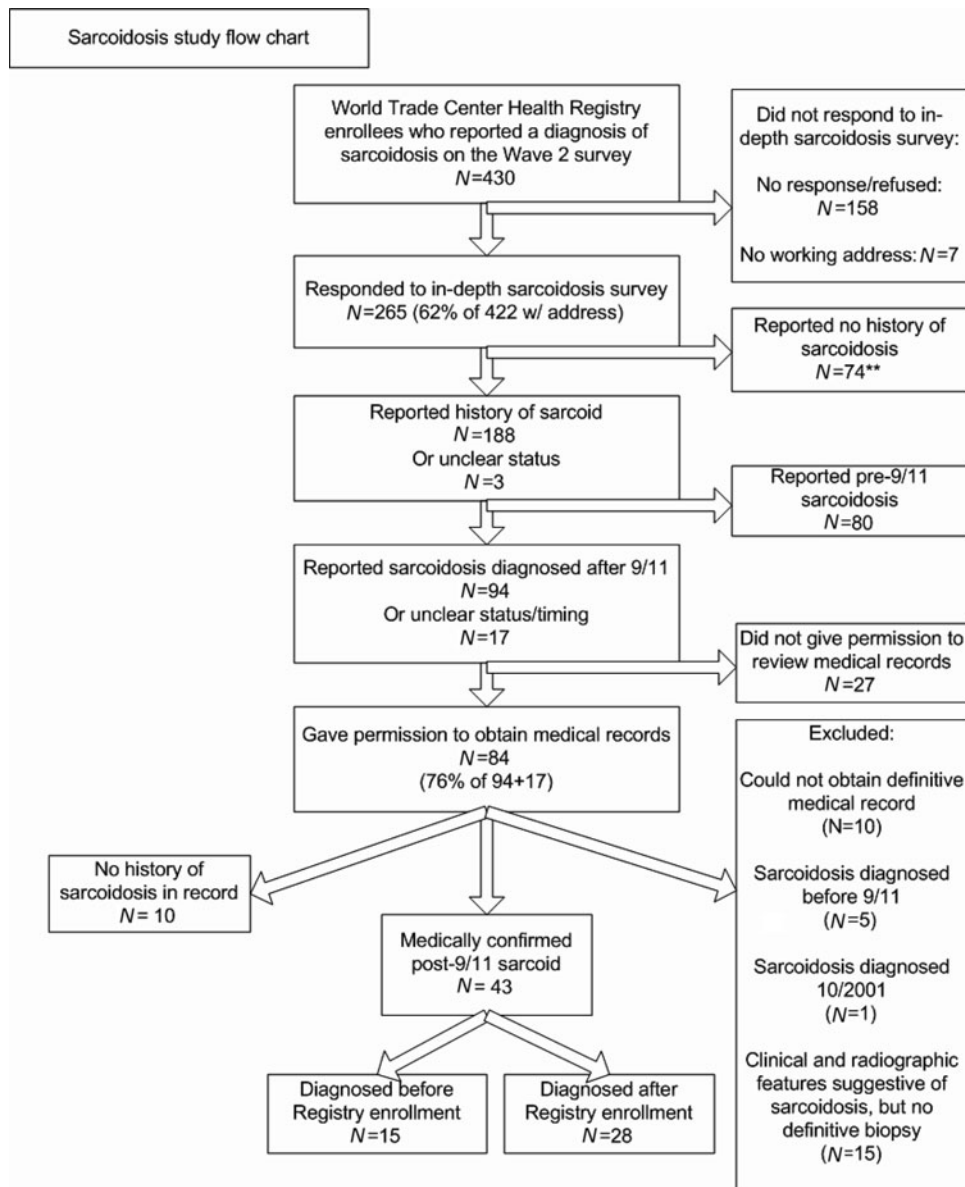
Confirmed cases diagnosed after an individual had enrolled in the Registry were included in a nested case-control study; cases diagnosed after 9/11 but before Registry enrollment ( $n = 15$ ) were excluded from the case-control analysis. Incidence-density sampling was used to select up to four Registry controls with no history of sarcoidosis for each case, individually matched on sex, race or ethnicity (non-Hispanic white, non-Hispanic black, or Hispanic), eligibility group(s), and age; for age, eligible controls for each respective case were those who, during the study period, attained the age of the case patient at the time of sarcoidosis diagnosis.<sup>20</sup> Conditional logistic regression was used to examine the relationship between post-9/11 sarcoidosis and 9/11-related exposures, smoking, study recruitment source, and demographic factors. Separate models were created for rescue or recovery enrollees and nonrescue or recovery enrollees. Independent variables associated with sarcoidosis with a  $P \leq 0.20$  in bivariable analysis were entered into multivariable models. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.  $P < 0.05$  were considered significant.

## RESULTS

Of 45,899 eligible Registry enrollees, 430 reported having been diagnosed with sarcoidosis on the W2 screening question and were mailed in-depth sarcoidosis surveys (Fig. 1). Of these, 265 (62%) responded, 158 (37%) refused or did not respond, and 7 (1%) had invalid addresses. Among respondents to the in-depth survey, 174 confirmed a history of sarcoidosis (80 before and 94 after September 11, 2001), 17 reported an unclear history and/or timing of diagnosis, and 74 denied having sarcoidosis. Permission to review medical records and/or contact physicians was given by 84 (76%) of the 111 participants who reported sarcoidosis diagnosed after 9/11 or at an unclear time or did not clearly state whether they had been diagnosed with sarcoidosis. Records were obtained for 74, of which 43 met the definition of post-9/11 sarcoidosis. The remainder had illnesses that were suggestive of sarcoidosis without a definitive biopsy ( $n = 15$ ), had no history of sarcoidosis in the medical record ( $n = 10$ ), were diagnosed with sarcoidosis before September 11, 2001 ( $n = 5$ ), or had a biopsy in October 2001 ( $n = 1$ ).

### Characteristics of Enrollees With Post-9/11 Sarcoidosis

Table 1 shows demographic characteristics of enrollees with and without post-9/11 sarcoidosis. Although there were no



**FIGURE 1.** Ascertainment of post-9/11 sarcoidosis cases occurring among World Trade Center Health Registry enrollees.

statistically significant differences between the two groups, a higher proportion of enrollees with post-9/11 sarcoidosis (86%) were self-identified compared with persons with no history of sarcoidosis (73%,  $P = 0.06$ ).

Selected characteristics of enrollees with post-9/11 sarcoidosis are shown in Table 2. Although we identified fewer cases diagnosed in 2007 to 2008 compared to earlier years, W2 (the source of case ascertainment) began in 2006, and 70% of Registry enrollees who completed W2 did so in 2006 or within the first 3 months of 2007, and therefore did not have an opportunity to report diagnoses made later. Most case patients (88%) reported having had at least one sarcoidosis-related symptom. Among the 23 enrollees with cough, 17 (74%) reported exacerbation with exercise. Thirteen reported having been diagnosed with asthma, six before 9/11, six after, and one at an unspecified time. Only two had no evidence of intrathoracic disease. Among the 19 persons with documented extrathoracic involvement, the most common sites were the skin ( $n = 6$ ), extrathoracic lymph nodes ( $n = 6$ ), liver ( $n = 3$ ), and eye ( $n = 3$ ). Nephrolithiasis was

reported in three cases, and central nervous system manifestations were reported in two cases.

### 9/11 and Other Exposures

Of the 43 persons with confirmed post-9/11 sarcoidosis, 19 (44%) performed rescue or recovery work, 8 were NYC firefighters, 2 were members of other fire departments, 4 were NYC Police Department employees, 3 worked for utility companies, 1 provided administration and support, and 1 worked for an unspecified NYC agency. Eight of the workers arrived on 9/11, seven on 9/12, one on 9/13, and three on 9/14; of the eight who arrived on 9/11, five were caught in the dust cloud. Fifteen rescue or recovery enrollees reported working on the debris pile. The median duration of work among rescue or recovery enrollees with sarcoidosis was 55 days (interquartile range, 5–98 days), compared with 19 days (interquartile range, 5–52 days) for workers with no history of sarcoidosis ( $P = 0.12$ ).

**TABLE 1.** Characteristics of Registry Enrollees With and Without Confirmed Post-9/11 Sarcoidosis\*

Characteristic†	No History of Sarcoidosis (N = 45,899)		Post-9/11 Sarcoidosis (N = 43)	
	N	%	N	%
Sex				
Male	28,080	61.2	29	67.4
Female	17,800	38.8	14	32.6
Age on September 11, 2001, yrs				
<35	12,463	27.2	9	20.9
35–44	14,644	31.9	18	41.9
45 +	18,773	40.9	16	37.2
Race or ethnicity				
Non-Hispanic white	31,945	69.6	28	65.1
Non-Hispanic black	4,638	10.1	6	14.0
Hispanic	5,227	11.4	9	20.9
Asian	2,545	5.6	0	0
Multiracial	844	1.8	0	0
Other	681	1.5	0	0
Eligibility group				
Rescue and recovery workers and volunteers	21,414	46.7	19	44.2
Lower Manhattan residents	6,491	14.1	5	11.6
Lower Manhattan office workers	15,624	34.1	15	34.9
Passersby on September 11	2,266	4.9	4	9.3
Area school students or staff on September 11	85	0.2	0	0
Registry recruitment source				
Identified by building or employer list	12,106	26.4	6	14.0
Self-referred to Registry	33,774	73.6	37	86.1
Residence on September 11, 2001				
NYC	27,745	60.5	30	69.8
Outside NYC	18,135	39.5	13	30.2
Education				
Non-high school graduate	1,672	3.7	1	2.3
High school or GED or up to 3 years of college	19,772	43.4	24	55.8
College graduate	14,743	32.3	14	32.6
Postgraduate degree	9,399	20.6	4	9.3
Total household income in 2002				
<\$50,000	11,850	28.6	11	26.8
\$50,000–\$74,999	9,013	21.8	14	34.2
≥\$75,000	20,530	49.6	16	39.0
Smoking status at W1 survey				
Never	25,829	56.6	29	67.4
Current or former	19,789	43.4	14	32.6
Exposure to dust cloud				
Unexposed	24,142	54.7	19	47.5
Exposed	19,994	45.3	21	52.5

\*No differences were statistically significant by chi-square or Fisher exact test.

†Counts may not sum to total because of missing values.

GED, general educational development.

The 24 nonrescue or recovery enrollees with post-9/11 sarcoidosis were lower Manhattan residents ( $n = 5$ ), area workers ( $n = 15$ ), or passersby on September 11, 2001 ( $n = 4$ ). Fifteen were exposed to the dust cloud, six reported that their workplaces had been damaged by the disaster, three evacuated their homes, and one reported his or her home being covered by a heavy layer of dust.

### Case-Control Study

Twenty-eight cases were eligible for inclusion in the case-control analysis. Eleven of these were rescue or recovery enrollees, 11 were lower Manhattan area workers, 5 were area residents, and 1 was a passerby. Ten case patients were former smokers but none smoked at the time of Registry enrollment. Exposures related to 9/11 and specific occupation at the time of 9/11 are shown for the

**TABLE 2.** Characteristics of 43 World Trade Center Health Registry Enrollees With Confirmed Post-9/11 Sarcoidosis

Characteristic	N	%
Age at diagnosis, yrs*		
30–39	14	32.6
40–49	15	34.9
50+	14	32.6
Year of diagnosis†‡		
2002	8	18.6
2003	6	14.0
2004	8	18.6
2005	8	18.6
2006	9	20.9
2007	2	4.7
2008	2	4.7
Biopsy site†§		
Mediastinum	11	25.0
Transbronchial	9	20.5
Lung	12	27.3
Other	11	25.0
Chest CT or x-ray results†¶		
Mediastinal or hilar adenopathy	27	62.7
Parenchymal abnormalities	7	16.3
Both	4	9.3
No abnormalities	2	4.7
Not available	3	7.0
Extrathoracic involvement†		
Present	19	44.2
Reported as absent	4	9.3
Not mentioned in medical record	20	46.5
Received systemic therapy†		
Yes	13	30.2
No	11	25.6
Not mentioned in medical record	19	44.2
Self-reported symptoms (not mutually exclusive)		
Fatigue	30	69.8
Shortness of breath	28	65.1
Chest tightness	24	55.8
Joint pain	24	55.8
Cough	23	53.5
Wheezing	21	48.8
Weight loss	16	37.2
Chest pain	15	34.9
Eye symptoms	15	34.9
Rash	11	25.6
Fever	7	16.3
Self-reported change in exercise tolerance due to sarcoidosis		
Decreased tolerance for vigorous activities only	4	9.3
Decreased tolerance for moderate and vigorous activities	4	9.3
Decreased tolerance for light, moderate, and vigorous activities	5	11.6
No reported change	5	11.6
Missing	10	23.3

\*Age at diagnosis missing for one individual.

†Information obtained from medical record review.

‡70% of Registry enrollees completed W2 before April 2007, and therefore did not have an opportunity to report diagnoses made later in 2007 or in 2008.

§Individuals who had biopsies of the lung plus other tissues were categorized under lung biopsy.

||Other biopsy sites: cervical lymph nodes (4); liver (2); axillary lymph nodes (1); skin (1); supraclavicular and groin lymph nodes (1); Kveim (1); unknown (1).

¶Parenchymal abnormalities: ground glass opacities, diffuse infiltrates, consolidation, nodules, and mosaic attenuation.

**TABLE 3.** Exposures Reported by 11 Rescue and Recovery Workers With Post-9/11 Sarcoidosis Included in the Case–Control Study

Worker Category	Arrival Date	Work Duration (Days)	WTC Dust Cloud Exposure	Any Work on Debris Pile	Firefighting on Pile	Hand Digging on Pile	Welding on Pile	Light Construction on Pile	Heavy Dust Present in Office	Worked at Staten Island Recovery Operation	Used Respiratory Protection*
NYC firefighter	09/11	98	X	X	X	X			X		
NYC firefighter	09/11	6		X	X	X					
NYC firefighter	09/12	23		X	X	X				X	
NYC firefighter	09/11	43	X	X	X	X	X				
Firefighter (non-NYC)	09/12	3		X		X					X
Firefighter (non-NYC)	09/11	5		X	X	X					
Utility company	09/11	210		X		X		X			X
Utility company	09/14	143	X	X		X	X	X			X
NYC Police Department	09/12	144		X		X				X	X
Administration and support	09/14	87							X		
Unspecified NYC agency	09/12	89		X							

\*Respiratory protection was defined as reporting the use of a full- or half-face respirator or a disposable mask with N95 to P100 rating during the period of arrival at the WTC site (arrival on September 11, 2001, between September 12, 2001 and December 31, 2001, or after December 31, 2001).

rescue or recovery enrollees in Table 3. All of these case patients arrived within 3 days after the disaster, and most worked on the debris pile.

Table 4 shows odds ratios (ORs) for 9/11-related exposures and risk of post-9/11 sarcoidosis for the 28 cases and 109 age-, sex-, race/ethnicity-, and eligibility group-matched controls. One case was matched to a single control; the remaining cases were matched to four controls each. We did not find significant associations between post-9/11 sarcoidosis and dust cloud exposure, or between post-9/11 sarcoidosis and workplace or home damage among nonrescue or recovery enrollees. Among rescue or recovery enrollees, working on the debris pile was significantly associated with sarcoidosis. Specific tasks performed on the pile that were associated with sarcoidosis were firefighting and hand digging. The conditional logistic regression model for the relationship between post-9/11 sarcoidosis and search and rescue did not converge because the risk set with the single unexposed case did not contain any exposed controls; however, the crude OR for hand digging was 13.5 (95% confidence interval 1.6 to 117.1). Use of respiratory protection was not significantly associated with sarcoidosis. Multivariable models including exposures associated with sarcoidosis in bivariable conditional logistic regression were constructed, but the resulting ORs were neither substantially altered, nor was model fit significantly improved.

**DISCUSSION**

Among rescue or recovery enrollees, who responded to the 9/11 disaster, working on the debris pile resulting from the collapse of the WTC and nearby structures were associated with an elevated risk of developing sarcoidosis. The specific tasks that were associated with sarcoidosis (firefighting, hand digging, and search and rescue) were performed by many of the same individuals, so each task's discrete contribution to the risk for sarcoidosis cannot be determined. Instead, these activities collectively suggest that individuals who executed the most complex, intensive rescue, and recovery activities were at greatest risk. We did not identify risk factors for post-9/11

sarcoidosis among enrollees who did not perform rescue or recovery work, perhaps because of low statistical power. It is also likely that the greater intensity of exposure generally experienced by rescue or recovery workers compared with other enrollees enabled us to discern a relationship between 9/11 exposures and sarcoidosis in the former group but not in the latter.

By comparing the study period for the report by Izbicki et al<sup>12</sup> with the diagnosis dates for firefighters in our study, we estimate that up to six of the 43 cases described in this article (up to three in the case–control analysis) also may have been included in the report of post-9/11 SLGPD among FDNY rescue workers. We repeated the case–control analysis without the three potentially overlapping cases and found no material changes in ORs relating to any task except firefighting. Our results thus corroborate and extend the findings of Izbicki et al by identifying risk factors for post-9/11 sarcoidosis and describing cases among non-FDNY members. Whereas the elevation in post-9/11 SLGPD cases described by Izbicki et al occurred primarily during the year after 9/11, our case–control study identified an association between sarcoidosis and 9/11-related exposures even though cases included in this analysis were all diagnosed in 2003 or later. This suggests that the increased risk was not limited to the years immediately after 9/11, underscoring the importance of continued monitoring for sarcoidosis among exposed persons.

The 43 cases we identified represent the largest study of sarcoidosis among persons exposed to 9/11 and one of the largest groups of biopsy-proven sarcoidosis described in the medical literature. The clinical characteristics of these case patients are similar to previous reports, including a case–control etiologic study of sarcoidosis,<sup>21</sup> a multicenter case–control study of 736 incident cases of biopsy-proven sarcoidosis conducted in the United States from 1997 to 1999. The peak age at diagnosis (40 to 49 years in our study vs 35 to 45 years in a case–control etiologic study of sarcoidosis), proportion with extrathoracic disease (44% vs 52%), and proportion with disease limited to extrathoracic organs (5% vs 2%) were comparable.<sup>22,23</sup> We did not have sufficient data to report

**TABLE 4.** Odds Ratios for Post-9/11 Sarcoidosis Diagnosed After Enrollment in the World Trade Center Health Registry\*

9/11-Related Exposures	Cases		Controls		Odds ratio	95% CI		P
	N	%	N	%				
<b>All cases and controls†</b>								
Dust cloud exposure								
Unexposed	11	42.3	40	41.2	ref			0.99
Exposed	15	57.7	57	58.8	1.0	0.4	2.8	
<b>Rescue or recovery enrollees†</b>								
Arrival time								
9/11/2001 or 9/12/2001	9	81.8	26	60.5	2.9	0.6	14.7	0.21
After 9/12/2001	2	18.2	17	39.5	ref			
Duration of work at site (days)								
≤55	5	45.5	31	70.5	ref			
>55	6	54.6	13	29.6	3.0	0.7	13.0	0.13
Worked on debris pile (at any time)								
Yes	10	90.9	22	50.0	9.1	1.1	74.0	0.04
No	1	9.1	22	50.0	ref			
Worked on pile 9/11 or 9/12								
Yes	7	63.6	15	34.9	2.9	0.8	10.5	0.11
No	4	36.4	28	65.1	ref			
Performed firefighting on pile								
Yes	5	55.6	3	10.0	11.00	1.3	96.1	0.03
No	4	44.4	27	90.0	ref			
Performed hand digging on pile								
Yes	9	90.0	17	43.6	8.8	1.1	71.6	0.04
No	1	10.0	22	56.4	ref			
Performed welding on pile								
Yes	2	25.0	1	3.7	6.6	0.6	73.4	0.12
No	6	75.0	26	96.3	ref			
Performed light construction on pile								
Yes	2	22.2	4	12.9	2.1	0.3	12.7	0.44
No	7	77.8	27	87.1	ref			
<b>Nonrescue or recovery enrollees†</b>								
Workplace damage								
Some	4	23.5	20	30.8	0.7	0.2	2.3	0.51
None	13	76.5	45	69.2	ref			
Home damage								
Some	1	5.9	6	9.2	0.6	0.1	6.2	0.67
None	16	94.1	59	90.8	ref			

Abbreviation: CI, confidence interval.

\*Cases and controls were matched on sex, age, race or ethnicity, and eligibility group(s). For age, eligible controls for each respective case were those whose age at study enrollment was less than or equal to the case-patient's age at the time of sarcoidosis diagnosis and whose age at W1 was more than or equal to the case-patient's age at the time of sarcoidosis diagnosis. Odds ratios were calculated using conditional logistic regression.

†For full case-control study,  $n = 28$  cases, 109 controls; among rescue or recovery enrollees,  $n = 11$  cases, 44 controls; and among nonrescue or recovery enrollees,  $n = 17$  cases, 65 controls. Cell counts may not sum to total because of missing values.

pulmonary function testing results, but a high proportion of case patients reported symptoms suggestive of asthma such as wheezing (49%); this is similar to the proportion with asthma-like symptoms among FDNY workers with SLGPD (58%) and the proportion with wheezing in the Bellevue Hospital case series (52%), and on the high end of airway hyperreactivity rates reported in other studies of sarcoidosis (21% to 50%), suggesting that persons with post-9/11 sarcoidosis may be particularly likely to benefit from treatment of airway hyperreactivity.<sup>24-28</sup>

The incidence of sarcoidosis in NYC is unknown, so we could not determine whether the number of cases observed during our study period exceeded the number that would have been expected in our

cohort had 9/11 not occurred. Furthermore, given previous reports of sarcoidosis among 9/11 survivors and the availability of WTC health monitoring and treatment programs, 9/11-exposed persons may be more likely to receive screening chest x-rays than the general public, creating the potential for detection bias that could spuriously elevate the ratio of observed to expected cases. Both cases and controls in our study are likely to have been subject to increased scrutiny for sarcoidosis compared with the general public, but this potential detection bias would not be expected to differ between cases and controls.

Because objective measurements of 9/11-related exposures are not available, we relied upon self-reported exposure data.

Although such data are subject to recall decay, they were gathered at study enrollment before cases included in the case–control analysis were diagnosed, decreasing the potential for differential misclassification of exposure. Because of a stringent case definition that could be confirmed only if we were granted permission to review medical records, our study is likely to have been limited by underascertainment of sarcoidosis cases and thus diminished statistical power. Because sarcoidosis is a diagnosis of exclusion; however, a rigorous case definition was required to ensure that our findings accurately reflect the clinical and epidemiologic features of post-9/11 sarcoidosis. Conversely, it is possible that ill persons were more likely to join the Registry than well persons, and that the Registry therefore overrepresents the proportion of 9/11-exposed persons who subsequently developed sarcoidosis. We attempted to minimize the potential for self-selection bias by restricting the case–control study to persons diagnosed with sarcoidosis after study enrollment, and by examining the relationship between study recruitment source and sarcoidosis. Although we reviewed medical records or contacted treating physicians for all included cases, the quality of available records varied, resulting in limited clinical information, including severity and course of disease. We also lacked information on family history of sarcoidosis and occupational and recreational exposures that have been associated with sarcoidosis in previous studies.

Despite these limitations, our study provides insight into the risk factors for and clinical presentation of sarcoidosis among persons exposed to 9/11, as well as sarcoidosis in general. The associations identified between post-9/11 sarcoidosis and specific activities performed on the debris pile substantiate the association between occupational exposures and sarcoidosis. Our results suggest that the yet-unidentified causative agent(s) may have been inhaled or absorbed during activities involving intense exposure to WTC dust and debris, strengthening the rationale for providing adequate respiratory and mucous membrane protection and improving engineering controls for dust suppression after future disasters.

## CONCLUSIONS

Our results suggest that clinicians who care for people who were exposed to the events of 9/11 should be aware of the association between intensive rescue and recovery work and post-9/11 sarcoidosis, and that the elevated risk of sarcoidosis was not limited to the year immediately after the disaster. Several questions, including whether the risk of post-9/11 sarcoidosis extended to nonrescue and recovery workers, remain unanswered. It will be crucial to gather such information through continued monitoring of the health of persons exposed to the events of 9/11. Meanwhile, our findings may guide health monitoring after future urban disasters and may inform studies of potential causative agents for sarcoidosis.

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## REFERENCES

1. Hennessy TW, Ballard DJ, DeRemee RA, Chu C, Melton LJ III. The influence of diagnostic access bias on the epidemiology of sarcoidosis: a population-based study in Rochester, Minnesota, 1935–1984. *J Clin Epidemiol.* 1988;41:565–570.
2. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med.* 2007;357:2153–2165.
3. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med.* 2004;170:1324–1330.
4. Rybicki BA, Iannuzzi MC, Frederick MM, et al; the ACCESS Research Group. Familial aggregation of sarcoidosis. A case–control etiologic study of sarcoidosis. *Am J Respir Crit Care Med.* 2001;164:2085–2091.
5. Hills SE, Parkes SA, Baker SB. Epidemiology of sarcoidosis in the Isle of Man—2: Evidence for space-time clustering. *Thorax.* 1987;42:427–430.
6. Kern DG, Neill MA, Wrenn DS, Varone JC. Investigation of a unique time-space cluster of sarcoidosis in firefighters. *Am Rev Respir Dis.* 1993;148:974–980.
7. Laney AS, Cragin LA, Blevins LZ, et al. Sarcoidosis, asthma, and asthma-like symptoms among occupants of a historically water-damaged office building. *Indoor Air.* 2009;19:83–90.
8. Kajdasz DK, Lackland DT, Mohr LC, Judson MA. A current assessment of rural linked exposures as potential risk factors for sarcoidosis. *Ann Epidemiol.* 2001;11:111–117.
9. Kucera GP, Rybicki BA, Kirkey KL, et al. Occupational risk factors for sarcoidosis in African-American siblings. *Chest.* 2003;23:1527–1535.
10. Rybicki BA, Amend KL, Maliarik MJ, Iannuzzi MC. Photocopier exposure and risk of sarcoidosis in African-American sibs. *Sarcoidosis Vasc Diffuse Lung Dis.* 2004;21:49–55.
11. Prezant DJ, Dhala A, Goldstein A, et al. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. *Chest.* 1999;116:1183–1193.
12. Izbicki G, Chavko R, Banauch GI, et al. World Trade Center “sarcoid-like” granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest.* 2007;131:1414–1423.
13. Crowley LE, Herbert R, Moline JM, et al. “Sarcoid-like” granulomatous pulmonary disease in world trade center disaster responders. *Am J Ind Med.* 2010;54:175–184.
14. Parsia SS, Yee H, Young S, et al. Characteristics of sarcoidosis in residents and workers exposed to World Trade Center dust, gas, and fumes presenting for medical care [Abstract]. Paper presented at: American Thoracic Society International Conference, 2010. Available at: <https://cms.psav.com/cAbstract/itinerary/day.html>. Accessed June 30, 2010.
15. Bowers B, Hasni S, Gruber BL. Sarcoidosis in World Trade Center rescue workers presenting with rheumatologic manifestations. *J Clin Rheumatol.* 2010;16:26–27.
16. Brackbill RM, Hadler JL, DiGrande L, et al. Asthma and posttraumatic stress symptoms 5 to 6 years following exposure to the World Trade Center terrorist attack. *JAMA.* 2009;302:502–516.
17. Farfel M, DiGrande L, Brackbill R, et al. An overview of 9/11 experiences and respiratory and mental health conditions among World Trade Center Health Registry enrollees. *J Urban Health.* 2008;85:880–909.
18. Murphy J, Brackbill RM, Thalji L, Dolan M, Pulliam P, Walker DJ. Measuring and maximizing coverage in the World Trade Center Health Registry. *Stat Med.* 2007;26:1688–1701.
19. US Census Bureau. *Census of Population and Housing*, Summary File 1: Technical documentation, 2007; 2000. Available at: <http://www.census.gov/prod/cen2000/doc/sf1.pdf>. Accessed February 8, 2011.
20. Richardson DB. An incidence density sampling program for nested case–control analyses. *Occup Environ Med.* 2004;61:e59.
21. ACCESS Research Group. Design of a case control etiologic study of sarcoidosis (ACCESS). *J Clin Epidemiol.* 1999;52:1173–1186.
22. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med.* 2001;164:1885–1889.



23. Yeager H, Rossman MD, Baughman RP, et al. Pulmonary and psychosocial findings at enrollment in the ACCESS study. *Sarcoidosis Vasc Diffuse Lung Dis.* 2005;22:147–153.
24. Bechtel JJ, Starr T III, Dantzker DR, Bower JS. Airway hyperreactivity in patients with sarcoidosis. *Am Rev Respir Dis.* 1981;124:759–761.
25. Marcias S, Ledda MA, Perra R, Severino C, Rosetti L. Aspecific bronchial hyperreactivity in pulmonary sarcoidosis. *Sarcoidosis.* 1994;11:118–122.
26. Olafsson M, Simonsson BG, Hansson SB. Bronchial reactivity in patients with recent pulmonary sarcoidosis. *Thorax.* 1985;40:51–53.
27. Presas F, Colomer P, Sanchón B. Bronchial hyperreactivity in fresh stage I sarcoidosis. *Ann N Y Acad Sci.* 1986;465:523–529.
28. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial involvement and airway hyperreactivity in patients with sarcoidosis. *Chest.* 2001;120:881–886.