"Sarcoid Like" Granulomatous Pulmonary Disease in World Trade Center Disaster Responders

Laura E. Crowley, MD,[1]* Robin Herbert, MD,[1] Jacqueline M. Moline, MD, MSc,[1] Sylvan Wallenstein, PhD,[1] Gauri Shukla, MPH,[1] Clyde Schechter, MD,[2] Gwen S. Skloot, MD,[1] Iris Udasin, MD,[3] Benjamin J. Luft, MD,[4] Denise Harrison, MD,[5] Moshe Shapiro, MS,[1] Karen Wong, MPH,[6] Henry S. Sacks, MD, PhD,[1] Philip J. Landrigan, MD, MSc,[1] and Alvin S. Teirstein, MD[1]

Background *More than 20,000 responders have been examined through the World Trade Center (WTC) Medical Monitoring and Treatment Program since September 11, 2001. Studies on WTC firefighters have shown elevated rates of sarcoidosis. The main objective of this study was to report the incidence of "sarcoid like" granulomatous pulmonary disease in other WTC responders.*

Methods *Cases of sarcoid like granulomatous pulmonary disease were identified by: patient self-report, physician report and ICD-9 codes. Each case was evaluated by three pulmonologists using the ACCESS criteria and only "definite" cases are reported.*

Results *Thirty-eight patients were classified as "definite" cases. Six-year incidence was 192/100,000. The peak annual incidence of 54 per 100,000 person-years occurred between 9/11/2003 and 9/11/2004. Incidence in black responders was nearly double that of white responders. Low FVC was the most common spirometric abnormality.*

Conclusions *Sarcoid like granulomatous pulmonary disease is present among the WTC responders. While the incidence is lower than that reported among firefighters, it is higher than expected. Am. J. Ind. Med. © 2010 Wiley-Liss, Inc.*

KEY WORDS: a case control etiologic study of sarcoidosis (ACCESS); forced vital capacity (FVC); granulomatous disease; sarcoidosis; World Trade Center (WTC)

INTRODUCTION

In the aftermath of the World Trade Center (WTC) disaster on September 11, 2001, the WTC site was reduced to a complex environment consisting of building debris, burning jet fuel and human remains. Due to the collapse of the WTC towers the air over lower Manhattan was filled with an alkaline and highly caustic dust composed of pulverized cement, glass fibers, asbestos, lead, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), organochlorine pesticides and polychlorinated furans, dioxins and fragmented building materials [Chen and Thurston, 2002; Lioy et al., 2002; Landrigan et al., 2004; Herbert et al., 2006]. Those who worked or volunteered in these conditions, the WTC responders, are a diverse group and include: firefighters, law enforcement officers, workers in the building trades, utility workers, transportation workers, health workers, cleaning and maintenance and others [Landrigan et al., 2004; Herbert et al., 2006].

Abbreviations: ACCESS, a case control etiologic study of sarcoidosis; BD, bronchodilator; CDC, Centers for Disease Control; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; FDNY, Fire Department of New York; ICD, International Classification of Diseases; NHANES III, Third National Health and Nutrition Examination Survey; NYC, New York City; NY/NJ, New York/New Jersey; NIOSH, National Institute for Occupational Safety and Health; SLGPD, "Sarcoid-like" granulomatous pulmonary disease; WTC, World Trade Center; WTCMMTP, World Trade Center Medical Monitoring and Treatment Program.

[1]Mount Sinai School of Medicine, New York, New York
[2]Albert Einstein College of Medicine, Bronx, New York
[3]University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey
[4]SUNY at Stony Brook, Stony Brook, New York
[5]New York University/Bellevue, New York, New York
[6]Columbia University Medical Center, New York, New York

Contract grant sponsor: CDC/NIOSH; Contract grant numbers: U10 0H008232. U10 0H008225. U10 0H008239. U10 0H008275. 0H008216. U10 0H008223.

*Correspondence to: Laura E. Crowley, MD, The Mount Sinai Medical Center, P.O. Box 1057, One Gustave L. Levy Place, New York, NY 10029. E-mail: laura.crowley@mssm.edu

Accepted 2 November 2010
DOI 10.1002/ajim.20924. Published online in Wiley Online Library (wileyonlinelibrary.com).

Since the tragedy, WTC responders have reported adverse upper and lower respiratory symptoms, including cough, wheezing, chest tightness, shortness of breath, and heartburn or reflux. They have also been diagnosed with conditions such as: reactive upper and lower airways dysfunction syndrome and gastroesophageal reflux disease [Prezant et al., 2002; Banauch et al., 2005; Herbert et al., 2006]. In a study by Izbicki et al. [2007] sarcoidosis or sarcoid like granulomatous pulmonary disease was reported in 26 WTC dust- exposed Fire Department of New York (FDNY) rescue workers. The lay press has also reported four case fatalities due to interstitial pulmonary fibrosis, sarcoidosis (cardiopulmonary involvement) and granulomatous pneumonitis in non-FDNY subjects who were exposed to the WTC dust [Izbicki et al., 2007]. Additionally, sarcoidosis with extrapulmonary rheumatologic manifestations was also reported in two New York City police officers following exposure to pollutants during their rescue operations at Ground zero [Bowers et al., 2010].

Sarcoidosis is a multisystem granulomatous disease of undetermined etiology that usually presents with bilateral mediastinal lymphadenopathy, pulmonary infiltration, ocular and skin lesions [American Thoracic Society (ATS), 1999]. Many patients with sarcoidosis are asymptomatic. Clinical features of sarcoidosis vary and may include: constitutional symptoms (fatigue), respiratory symptoms (dry cough, dyspnea, chest pain, and wheeze), skin rash, neurologic dysfunction, ocular symptoms, cardiac dysfunction, and muscle and joint pain [Thomas and Hunninghake, 2003; Iannuzzi et al., 2007]. Definitive diagnosis of sarcoidosis requires that particular autoimmune disorders, infections, chronic beryllium disease (CBD), and other interstitial diseases such as hypersensitivity pneumonitis be considered. Sarcoidosis affects people of all racial and ethnic backgrounds but has the highest prevalence among Swedes, Danes, and African Americans [American Thoracic Society (ATS), 1999; Iannuzzi et al., 2007].

Although the cause of sarcoidosis is unknown, it has been associated with multiple environmental and occupational exposures [Newman et al., 2004]. In the A Case Control Etiologic Study of Sarcoidosis (ACCESS) study, exposure to insecticides, mold/mildew, musty odors at work place, use of central air conditioning at home and employment in pesticide using industries were positively associated with sarcoidosis [Newman et al., 2004]. Other reported associations include: firefighting, service in the US Navy, metalworking, handling of building supplies, exposure to metal dust such as aluminum, zirconium, titanium, earth metals, and talc [Drent et al., 2000; Iannuzzi et al., 2007].

This report presents the results of preliminary surveillance of sarcoid like granulomatous pulmonary disease [Izbicki et al., 2007] among 19,756 responders who had an initial monitoring examination in the WTC Medical Monitoring and Treatment Program (MMTP) between July 16, 2002 and September 11, 2007. Unlike sarcoidosis, which is frequently due to unknown etiology and as these cases maybe secondary to WTC dust exposure and since it is difficult to distinguish between this mix of sarcoidosis and dust induced cases on clinico-pathologic grounds, we decided to classify these cases as sarcoid like granulomatous pulmonary disease. Additionally, this report was also undertaken in follow-up to the study of sarcoidosis or SLGPD in WTC-exposed firefighters [Izbicki et al., 2007] and to determine whether the incidence of sarcoid like granulomatous pulmonary disease is increased in other groups of WTC responders.

METHODS

The WTC Medical Monitoring and Treatment Program (WTCMMTP)

The WTCMMTP is designed to monitor and treat those responders who develop WTC related conditions. Responders who were part of the 9/11 rescue, recovery, and cleanup efforts are enrolled in the program on the basis of eligibility criteria which include: having worked as a 9/11 responder, having fulfilled a variety of specified duties, having served at a site known to be contaminated with WTC dust, and having worked as a responder during certain dates and hours [Herbert et al., 2006]. Each eligible participant is consented for aggregated data use for research purposes and Health Insurance Portability and Accountability Act 1996 (HIPAA) as per our Institutional Review Board approval for the project. Participants receive an interviewer-administered questionnaire about health and exposures, an initial screening examination that includes a physical examination, posterior anterior (PA) and lateral chest radiographs, and spirometry. They are then scheduled for follow-up medical monitoring exams at 18-month intervals. In November 2006, a federally funded treatment program was added to the program to provide coverage for sarcoidosis and other conditions. Patients contacted were informed about the treatment program and encouraged to follow up.

Population

Estimates of the size of the population of WTC responders have varied from 40,000 to 90,000. The 90,000 figure appears artificially inflated by a combination of a lenient definition of WTC exposure plus over reporting of numbers by some of the volunteer organizations that participated in the response effort. With nearly 30,000 eligible workers having made at least one telephone contact with the WTCMMTP, Savitz et al. [2008] estimated that the proportion of eligible responders who had registered for the WTCMMTP as of Fall 2007 was between 50% and 70%, and is increasing steadily

as new participants continue to call in Savitz et al. [2008]. Thus a reasonable estimate of the true population of WTC responders eligible for the WTCMMTP would appear to between 60,000 and 70,000. The dataset for this study was created on April 8, 2008.

Identification of Potential Cases

Three processes were employed to identify potential cases of sarcoid like granulomatous pulmonary disease. First, during initial and follow-up examinations, physicians, nurse practitioners or physician assistants routinely asked if the responder had ever been diagnosed with sarcoidosis or any chest illness that required surgery. Secondly, the WTCMMTP database was searched for sarcoidosis (ICD-9 code 135) and other interstitial or alveolar diseases (ICD-9 code 516.3) [Hart et al., 2009]. Finally all physicians conducting medical monitoring and treatment examinations, members of the WTC medical steering group in the NY/NJ metropolitan area and administrative staff logging patient inquiries were asked to report any known cases among the WTC patient cohort.

Case Confirmation

For case confirmation all potential cases of sarcoid like granulomatous pulmonary disease were reviewed independently by three pulmonologists for radiographic and pathologic evidence supporting a diagnosis of sarcoid like granulomatous pulmonary disease. Cases were considered ''definite'' if they fulfilled the ACCESS criteria [Judson et al., 1999, 2006]. All cases required a biopsy report revealing a non-caseating epithelial granuloma or a positive Kveim test and diagnostic imaging consistent with a diagnosis of sarcoid like granulomatous pulmonary disease. Cases without a positive biopsy and chest X-ray report confirming a diagnosis of granulomatous disease were excluded from the study. All available monitoring chest radiographs and reports were reviewed by the study pulmonologists and were scored according to Scadding radiographic stages: (0) normal findings, (I) bilateral hilar adenopathy with normal parenchyma, (II) bilateral hilar adenopathy with pulmonary infiltrates, (III) pulmonary infiltrates without hilar lymphadenopathy, (IV) pulmonary fibrosis/fibrocystic parenchymal changes [Judson et al., 2003]. The categorization of definite and excluded cases was agreed upon by all three pulmonologists.

Spirometry

Spirometric examinations used standard techniques [Miller et al., 2005]. Only acceptable quality control grades A, B, C were analyzed [Ferguson et al., 2000]. Results were compared to reference values derived from the Third National Health and Nutrition Examination Survey (NHANES III) [Hankinson et al., 1999], and were interpreted using American Thoracic Society and European Society guidelines [Pellegrino et al., 2005]. Spirometry was categorized as ''Obstruction'' if forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) was below the lower limit of normal (LLN) with a normal FVC, ''Low FVC'' if FVC $<$ LLN but FEV1/FVC $\geq$ LLN and ''Mixed pattern'' (Low FVC and Obstruction) if FEV1/FVC $<$ LLN and FVC $<$ LLN [Herbert et al., 2006] (Table I). For each trial, the flow-volume data with the highest total FEV1and FVC were retained. When both pre-and post-bronchodilator (BD) pulmonary function data were available, the post-BD values are used for analysis. Pre-BD values were used for individuals missing post-BD values.

Incidence

Incidence was estimated using two methods:

Method 1: This was applied for both the overall population and for subgroups defined by age, gender, race, occupation, and smoking status. This 6-year cumulative incidence was calculated by dividing the total number of cases of sarcoid like granulomatous pulmonary disease diagnosed post-9/11/01, by the number of

TABLE I. Spirometry Patterns in Cases* and Non-Cases**

Pattern	Cases (N = 38)*, n (%)	Non-cases (N = 19,718)**, n (%)	*P*-Value
Normal	14 (53.9%)	12,669 (76.7%)	
Obstruction[a]	0 (00.0%)	557 (3.4%)	>0.99
Low FVC[b]	11 (42.3%)	3,101 (18.8%)	0.01
Mixed (low FVC/obstruction)[c]	1 (3.9%)	199 (1.2%)	0.42

*Responders with sarcoid like granulomatous pulmonary disease who were confirmed using the ACCESS criteria.
**Responders with neither a history of sarcoidosis nor a confirmed diagnosis of granulomatous disease in this study.
[a]FEV1/FVC $<$ LLN (lower limit of normal) with a normal FVC [Pellegrino et al., 2005; Herbert et al., 2006].
[b]FVC $<$ LLN but FEV1/FVC $\geq$ LLN [Pellegrino et al., 2005; Herbert et al., 2006].
[c]FEV1/FVC $<$ LLN and FVC $<$ LLN [Pellegrino et al., 2005; Herbert et al., 2006].

responders (in a particular subgroup) with neither a history of sarcoidosis nor a confirmed diagnosis of granulomatous disease in this study as of 9/11/2001. Confidence intervals around this cumulative incidence were calculated based on the binomial distribution. The Chi-square test, and when necessary, Fisher's exact test, was used to compare the incidence for the different demographic subgroups, as well as to evaluate difference between cases and non-cases for the spirometry interpretation. We used the Cochran–Armitage trend test to assess significance of trends in the incidence across exposure categories by date of arrival and exposure to the dust cloud, categorized as follows: arrived on 9/11 and in the dust cloud, arrived on 9/11 but not in the dust cloud, arrived 9/12–9/13, arrived 9/14–9/30 and arrived on or after 10/1 [Herbert et al., 2006].Specific attention was given to the Black/Non-black comparison, since prior studies suggest such a difference. To allow comparison of this rate to previously reported incidence rates of sarcoidosis, which were based on populations with different age distributions, we age-adjusted the rates based on the 1990 US age distributions for both White and Black and males and females and compared our findings to those of Rybicki et al. [1997] limiting comparison to Whites and Blacks. In performing these age-adjustments we did not use age as of 9/11/01, but rather aged our population over the 6-year interval. That is, if a responder was 38 years old on 9/11/2001, we used for the calculation of expected values the 35–40 range for the first 2 years of follow-up and the 40–45 range for the remaining years.

Method 2: The first method of estimating incidence underestimates the true responder incidence as some cases are missed either because a responder did not return for a scheduled monitoring or treatment visit or did not call in after he or she was diagnosed. Therefore, an alternative estimate of incidence was computed based on life-table methods, using only those cases who reported sarcoid like granulomatous pulmonary disease for the first time at their monitoring visit with a biopsy that had been performed before the responder came in for that monitoring visit. Of the 38 cases, 32 were reported in that manner. This calculation thus excluded six cases identified after their last monitoring visit. The time-of-event is thus the time of diagnosis, and observations are censored at the responder's last monitoring visit. The Kaplan–Meier product limit formula [Kaplan and Meier, 1958] was used to estimate the overall incidence rate over 6 years, and also to calculate incidence for each 365-day interval from 9/11 of 1 year to 9/10 of the next year. Analyses were performed using SAS (version 9.1) and STATA (version 9.2). All statistical tests were two tailed, and the 0.05 level was used to define statistical significance.

RESULTS

As indicated in Figure 1, from the 19,805 responders examined between July 16, 2002 and September 11, 2007 we excluded 49 responders with sarcoidosis diagnosed pre 9/11/2001, leaving us with 19,756 responders. From the 19,756 responders, we found 38 cases of sarcoid like granulomatous pulmonary disease diagnosed post-9/11/2001 and 19,718 responders without a diagnosis. The range for age on 9/11/01 was 18–80 years with a mean age of 39.3 years. There were 86% males, 63.6% Whites, 11% Blacks, and 16.9% Hispanics. Law enforcement was the highest occupation category among the 38 cases as seen in Table II. Similarly, law enforcement accounted for the highest (16 cases) pre-9/11 occupation category among these cases. There were two cases post-9/11 who were non-FDNY firefighters (Table II). Additionally, one of these two cases also belongs to the firefighter occupation category pre-9/11. In this preliminary analysis, we found no statistically significant trend between diagnosis of granulomatous disease such as sarcoid like granulomatous pulmonary disease and the level of exposure.

Based on all reported cases of sarcoid like granulomatous pulmonary disease using Method 1, the 6-year incidence was 192 per 100,000 (0.00192) (95% confidence interval 136 per 100,000 to 246 per 100,000). Table II lists and compares the 6-year incidence by gender, race, age, occupation, and smoking status, and also tabulates the cumulative incidence for the subgroups of White and Black males and females. As indicated in the last column of Table II, there were no significant differences in incidence by age, gender, occupation, and smoking status. Blacks had an over twofold increase as compared to all others combined (including those for whom race-ethnicity was not reported). This difference was close to being statistically significant ($P = 0.064$).

As per the alternative calculation of incidence, Method 2, the overall incidence rate was 229 per 100,000 person-years (95% confidence interval of 136 per 100,000) to 322 per 100,000 person years slightly higher than the cumulative incidence obtained by Method 1. Table III gives the Kaplan–Meier estimate of the overall and yearly incidence rate of sarcoid like granulomatous pulmonary disease, based on Method 2. (For added information, Table III also gives the person-years of observation for each 365-day period.) The highest incidence rates of about 54 per 100,000 person-years were observed in the years ending in 9/11/2003 and 9/11/2004. The incidence rate for the year ending 9/11/2007 was also high, but the rate was based on only two cases, and the last year had relatively few person-years of observation.

Table IVa compares the age-adjusted annual incidence for our Black and White responders with the age-adjusted annual rates reported by Rybicki et al. [1997] and with age-adjusted rates in Whites that can be extracted from Henke et al. [1986]. (Our adjusted rates follow the procedure of Rybicki, who used the 1990 US population, while those for

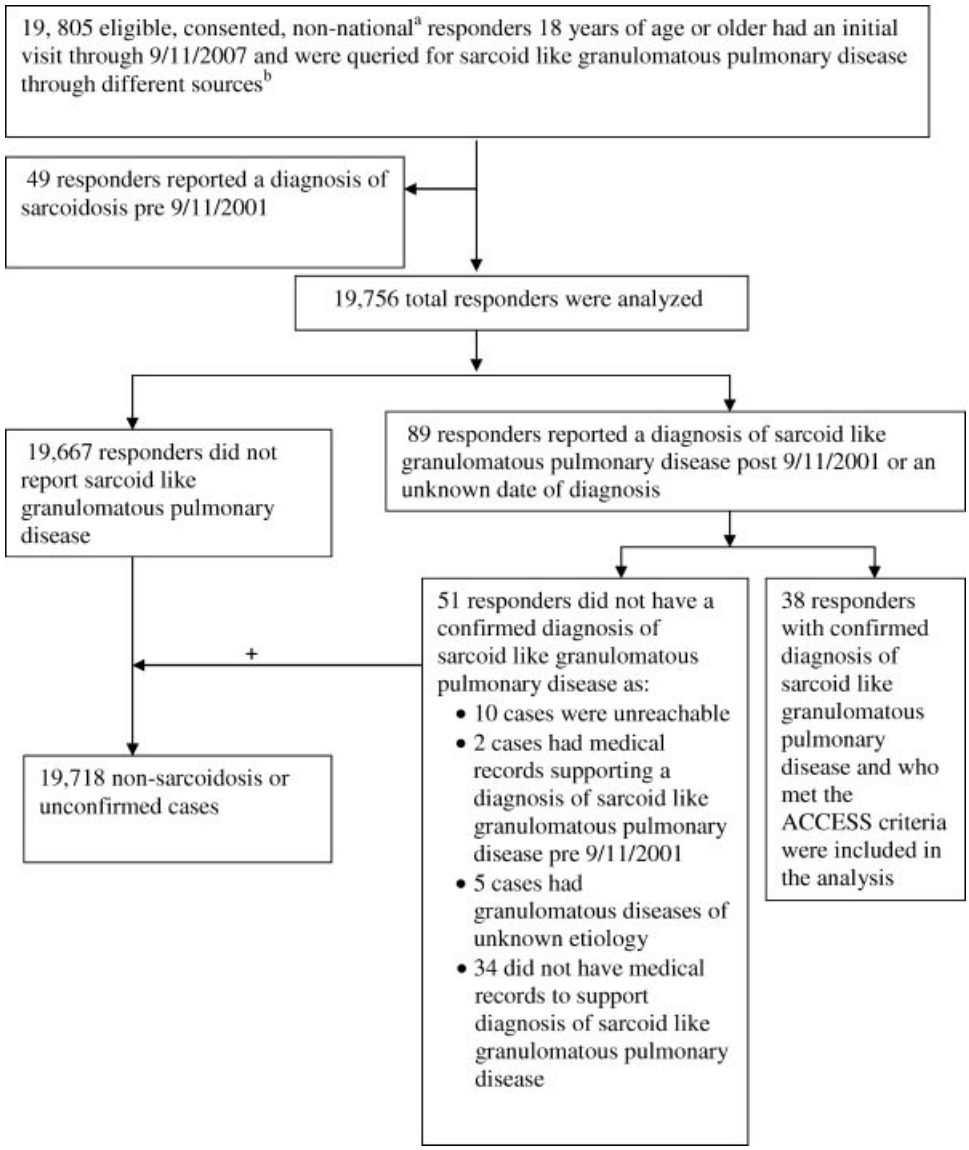

FIGURE 1. Sarcoid like granulomatous pulmonary disease case ascertainment flow chart.

Henke required a very slight adjustment as they used 1950 as a basis.) Table IVb also compares age-specific incidence of the largest subgroup in our study, 30- to 49-year-old white males, with (i) those found by Rybicki et al. [1997] and (ii) those found by Henke et al. [1986]. From these comparisons, an increased incidence of sarcoid like granulomatous pulmonary disease diagnosed after 9/11/01 was observed among the WTC responders in our study.

Clinical Features

Cases of sarcoid like granulomatous pulmonary disease had significantly more dry cough ($P = 0.0028$), lower exercise tolerance ($P = 0.0039$), and more shortness of breath ($P = 0.003$) than non-cases (Table V). Symptoms of productive cough with phlegm and wheezing were elevated, but differences between the groups were not statistically significant. Of the 38 cases, 32 had lymphadenopathy, and 19 had systemic manifestations such as uveitis, subcutaneous nodules or erythematous rash, joint pains or swelling, seizures, and cardiac arrhythmia. Twenty-six of the 38 cases had acceptable quality of spirometry. Of these, 14 were normal, 1 had a mixed pattern, none reported a purely obstructive pattern, and 11 had a low FVC (Table I). Responders with sarcoid like granulomatous pulmonary disease had a greater prevalence of low FVC than those without the disease ($P < 0.01$); differences for obstruction were not statistically significant. Of the 38 cases, 3 were Stage 0, 19 were Stage I, 8 Stage II, 5 Stage III, 2 Stage IV, and 1 did not have a monitoring chest radiograph available for review.

TABLE II. Incidence of Sarcoid Like Granulomatous Pulmonary Disease Stratified by Gender, Race, Occupation, and Smoking Status

	Total[a], N = 19,756		Cases[b],	6-year incidence	
Category	**n**	**%**	**N = 38 (n)**	**per 100,000**	***P*-Value**
Age on 9/11/01 (years)					
18–29	2,460	12.5	2	82	0.391
30–39	8,454	42.8	20	236	
40–49	6,128	31.0	14	229	
50–59	2,293	11.6	2	87	
60–80	421	2.1	0	0	
Gender					
Male	16,973	85.9	35	206	0.354
Female	2,783	14.1	3	108	
Gender—race subgroup					
White male	11,402	57.7	24	211	0.401
White female	1,160	5.9	2	172	
Black male	1,723	8.7	7	406	
Black female	461	2.3	1	217	
Race					
White	12,562	63.6	26	207	0.057
Black	2,184	11.1	8	367	
Hispanic	3,325	16.8	2	60	
Asian and other	718	3.6	2	278	
Not reported	967	4.9	0	0	
Occupation					
Law enforcement	7,374	37.3	16	217	0.388
Construction	4,916	24.9	7	142	
Public sector—blue collar	1,256	6.4	2	160	
Firefighters	328	1.7	2	613	
Health care	122	0.6	0	0	
Cleaning/maintenance	271	1.4	1	370	
News agencies	105	0.5	1	952	
Office/administration/professional	61	0.3	0	0	
Technical and utilities	940	4.8	2	213	
Transportation	775	3.9	2	258	
Volunteers	289	1.5	0	0	
Not categorized	1,477	7.5	3	203	
Miscellaneous[c]	1,847	9.3	2	108	
Smoking status					
Never smoked	9,978	50.5	24	240	0.155
Current smoker	2,973	15.0	2	67	
Former smoker	4,168	21.1	8	192	
Not reported	2,637	13.3	4	152	

[a]All responders evaluated in this study.
[b]Responders with sarcoid like granulomatous pulmonary disease who were confirmed using the ACCESS criteria.
[c]Includes occupation that cannot be categorized as any of the occupations mentioned above.

DISCUSSION

The main finding of this study is that incidence rates of sarcoid like granulomatous pulmonary disease appear increased among WTC responders after 9/11/2001 compared with other published background rates. Our ability to compare our incidence rates of sarcoid like granulomatous pulmonary disease with other rates reported in the literature is limited. It is difficult to find other studies with comparable populations, stratified according to age and race and with a

TABLE III. Incidence Rates of Sarcoid Like Granulomatous Pulmonary Disease in Each Year of Surveillance, Based on Those Reporting a Diagnosis at Monitoring Visits

Year ending 9/11	Person-years of follow-up	Total number of new cases diagnosed during year	Annual incidence per 100,000[a]
2002	19,742	2	10
2003	18,410	10	54
2004	16,570	9	55
2005	14,475	7	47
2006	10,716	2	18
2007	3,601	2	45
Total	83,514	32	229

[a]Based on Kaplan–Meier method.

case definition similar to our study. To the extent we could find comparable studies, we often had to limit attention either to Whites or to males. We found no published studies with adequate detail concerning Hispanic Americans, or Asian Americans.

The males in our responder population had a mean age of 39 years as of 9/11/01, which was similar to the mean age of about 40 years in different FDNY cohorts in different post-9/11/01 times periods. Our study included 11% Blacks which is somewhat higher than FDNY, but exact comparison is difficult because of possibly different methods of classifying Hispanics. The average annualized incidence proportion of 34 per 100,000 person-years in males implicit in Table II (based on 35 cases per 16,973 males $\times$ 6 years) is higher than the rate of 15 per 100,000 seen 5 years pre-9/11/01 in NYC firefighters [Izbicki et al., 2007]. Additionally, this annualized incidence in Table II is lower than the rate of 86 per 100,000 observed among NYC firefighters in the first year following 9/11/01 but higher than the rate of 22 per 100,000 reported in the NYC firefighters over the next 4 years [Izbicki et al., 2007]. Averaging across the 6 years of our study, our rates are nearly identical to those of the FDNY. The peak incidence of sarcoid like granulomatous pulmonary disease in our study is observed in the 2-year period starting 9/11/02, somewhat later than that reported for the FDNY presumably because our study started later than the FDNY study [Izbicki et al., 2007].

We are aware of a bias in which the enhanced treatment and monitoring provided by the WTCMMTP could have contributed to more cases being diagnosed, or being diagnosed earlier than if there were no WTC monitoring program. Selection bias is always a potential problem in a study such as this. As per the estimates by Savitz et al. [2008], the proportion of eligible responders and the number of new participants is increasing. The magnitude of any selection bias decreases, as the proportion of participating responders

TABLE IV. (a) Age-Adjusted Annual Incidence of Sarcoid Like Granulomatous Pulmonary Disease Per 100,000, Adjusted to the 1990 US Population (b) Age-Specific Annual Incidence of Sarcoid Like Granulomatous Pulmonary Disease Per 100,000, in 30- to 49-Year-Old White Males

Race/sex	Our study	Detroit HMO[a]	Mayo clinic[b] 1946–1975
(a)			
White male	23.1	9.6	5.9
White female	19.1	12.1	6.0
Black male	56.9	29.8	—
Black female	33.7	39.1	—
Age in years	**Our study**	**Detroit HMO[a]**	**Mayo clinic[b]**
(b)			
30–39	41.5	21	19
40–49	45.6	21	10

Difference in the manner of categorizing race, for example, our inclusion of Hispanics as a separate group, limits the comparability of the groups.
HMO, Health Maintenance Organization.
[a]Rybicki et al. [1997].
[b]Henke et al. [1986].

TABLE V. Proportion of Participants With Symptoms Since They Stopped Working or Volunteering at the WTC Site

Symptom	Cases (N = 38)[a], n (%)	Non-cases (N = 19,718)[b], n (%)	*P*-Value[c]
Dry cough			
Yes	22 (59.5%)	6,540 (34.8%)	0.0028
No	15 (40.5%)	12,230 (65.2%)	
Cough with phlegm			
Yes	12 (31.6%)	3,823 (20.5%)	0.1055
No	26 (68.4%)	14,858 (79.5%)	
Decreased exercise tolerance			
Yes	21 (63.6%)	6,389 (38.6%)	0.0039
No	12 (36.4%)	10,181 (61.4%)	
Shortness of breath			
Yes	22 (57.9%)	6,325 (33.9%)	0.0030
No	16 (42.1%)	12,318 (66.1%)	
Wheezing			
Yes	18 (48.6%)	6,733 (36.0%)	0.1231
No	19 (51.4%)	11,991 (64.0%)	
Any of above			
Yes	32(86.5%)	12,974(72.1%)	0.06
No	5 (13.5%)	5,014 (27.9%)	

[a]Responders with sarcoid like granulomatous pulmonary disease who were confirmed using the ACCESS criteria.
[b]Responders with neither a history of sarcoidosis nor a confirmed diagnosis of granulomatous disease in this study.
[c]Fisher's exact test (two-sided Pr $\leq$ *P*).

increases. The directionality of any selection bias in this population is not certain. Our rates would be increased if responders whose health was impacted by 9/11 were more likely to participate than an asymptomatic individual. Conversely our reported rates could be lower if a responder was too ill to participate in an exam or a responder moved out of the NY/NJ area.

Spirometry among cases of sarcoid like granulomatous pulmonary disease revealed an increased prevalence of a low FVC pattern. In a study by Herbert et al. [2006], low FVC was found to be the most common functional abnormality, seen in 21% (1,721) of the 8,384 participants who had acceptable pulmonary function tests. Of the 55.4% nonsmoker participants, the prevalence of low FVC was five times greater than that in US general population (20% vs. 4%) [Herbert et al., 2006]. Similarly, in a study by Skloot et al. [2009], low FVC was the most common abnormality seen on spirometry [Skloot et al., 2009]. This pattern may be due to true restriction related to parenchymal lung disease, mechanical factors such as obesity, pseudorestriction secondary to air trapping, submaximal efforts, or our choice of spirometry reference equations [Skloot et al., 2009]. As an interstitial lung disease, sarcoidosis is expected to cause this restrictive pattern. However an obstructive pattern can also be seen, as a result of airway deposition of granulomas [Shorr et al., 2001]. None of our cases of sarcoid like granulomatous pulmonary disease were classified as having a purely obstructive pattern. However, among WTC responder firefighters with sarcoid-like granulomatous pulmonary disease new onset airway obstruction was present in 4 of the 26 patients and evidence of restrictive abnormalities was rare [Izbicki et al., 2007]. The implications of the inconsistent spirometry patterns across these studies are unclear but may be related to the effect of specific occupational exposures on disease manifestations. However, it is important to note that in a recent study by Enright et al. [2010] it has been observed that the overall quality of spirometry in WTC program is very good.

Although sarcoidosis can involve any organ, it presents more commonly with pulmonary abnormalities (seen in 90% of sarcoidosis patients), lymphadenopathy (75–90% of sarcoidosis patients), skin and eye involvement (seen in 25% of sarcoidosis patients) or some combination of these findings [ATS, 1999; Crystal, 2004; Iannuzzi et al., 2007]. Izbicki et al. [2007] observed primarily pulmonary abnormalities and lymphadenopathy in the 26 WTC dust-exposed FDNY rescue workers with sarcoid like granulomatous pulmonary disease along with skin, bone and joint involvement in one case, spleen involvement in three cases, renal involvement and pelvic adenopathy in one case and abdomen/pelvic lymphadenopathy in one case. In the ACCESS study of the 736 sarcoidosis patients the lung, skin, lymph node, eye and liver were the most common organs involved [Baughman et al., 2001].

In our study, in addition to the lung (100%), lymph node (84%), and skin (8%) involvement, we also found a higher

percentage of musculoskeletal (26%) (bone/joint and muscle) and cardiac involvement (8%) in our cases with sarcoid like granulomatous pulmonary disease. It has been mentioned in literature that joint involvement is more common than bone and muscle involvement and is seen in about 25–50% of sarcoidosis cases [Crystal, 2004]. Similarly, although clinical evidence of sarcoidosis affecting the heart is uncommon it has been seen in 2–7% of sarcoidosis patients [Deng et al., 2002; Smedema et al., 2007]. Additionally, serious cardiac dysfunction has also been seen in 5–10% of sarcoidosis patients [Newman et al., 1997]. Overall our findings appear to be consistent with previous studies [Newman et al., 1997; Deng et al., 2002; Crystal, 2004; Smedema et al., 2007].

The incidence rates reported in this study would doubled if the additional 39 cases of sarcoid like granulomatous disease as seen in Figure 1 with incomplete medical records or a final diagnosis of granulomatous disease of unknown etiology were included in our study. A final diagnosis of granulomatous pulmonary disease requires an experienced physician to review all medical records, as well as the occupational and exposure history. Granulomatous diseases on biopsy such as hypersensitivity pneumonitis and CBD need to be differentiated before a final diagnosis of sarcoid like granulomatous pulmonary disease is made. When considering CBD, to date there have been no published reports of elevated beryllium levels post-9/11. Urine levels of beryllium were measured in WTC exposed firefighters but were not elevated in those firefighters diagnosed with sarcoid like granulomatous pulmonary disease [Izbicki et al., 2007]. Although this test is not used to diagnose CBD it is still consistent with lack of exposure [Izbicki et al., 2007]. Additionally, beryllium specific T-lymphocyte proliferation was not tested in this study, as CBD was unlikely because beryllium was not a component in the WTC dust exposure [Izbicki et al., 2007]. Future studies need to determine if beryllium or any other exposure may have contributed to responders developing sarcoidosis. It is unlikely that this is CBD or for that matter hypersensitivity pneumonitis, as over 30% of the cases had extrapulmonary manifestations. However, further investigation may be warranted.

CONCLUSION

Incidence rates of sarcoid like granulomatous pulmonary disease appear increased among WTC responders after 9/11/2001 compared with other published background rates. These findings support the hypothesis that a variety of environmental exposures, including those generated by the destruction of the World Trade Center, may cause sarcoidosis or sarcoid like granulomatous pulmonary disease. The fact that similar findings have been reported by two other cohort studies, FDNY and the WTC Registry [Jordan et al., 2008] provide additional evidence in support of this hypothesis. Further scientific study is needed to understand the genetic-environmental interactions that may be responsible for the apparent relationship between WTC exposure and sarcoid like granulomatous disease.

Previous experience with worker cohorts exposed to construction debris has demonstrated that the most serious respiratory outcomes of occupational exposures in the construction trades—fibrosis and neoplasm—do not appear until 10–30 years post-exposure. Only with continued care and surveillance can such emerging health issues of long latency be identified and characterized. The main goal of the WTCMMTP is to continue surveillance of a highly vulnerable cohort in order to identify and address the health issues unique to the responder population. Active screening and monitoring of all WTC responders including periodic chest radiography and spirometry must continue so that the population's medical issues may be optimally addressed by identifying and treating diseases in their earlier stages.

ACKNOWLEDGMENTS

J. Howard, D. Savitz, S. Baron, J. Melius, M. Crane, S. Levin, S.Markowitz, D. Harrison, J. Mercado, N. Sloan, H. Juman-James, all staff and patients of the WTC Worker and Volunteer Medical Screening and Monitoring and Treatment Program, labor, community, and volunteer organizations. This publication and funding was made possible by CDC/NIOSH; Grant Number: under contract 200-2002-00384 and cooperative agreements U1O 0H008232, U10 OH008225, U10 OH008239, U10 OH008275, OH008216 and U10 OH008223.

REFERENCES

American Thoracic society (ATS). 1999. Statement on sarcoidosis, Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee. Am J Respir Crit Care Med 160(2): 736–755.

Banauch GI, Dhala A, Prezant DJ. 2005. Pulmonary disease in rescue workers at the World Trade Center site. Curr Opin Pulm Med 11:160–168.

Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H, , Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, McLennan G, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki B, Weinberger SE, Terrin ML, Knatterud GL, Cherniak R, A Case Control Etiologic study of sarcoidosis (ACCESS) Research Group. 2001. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 164:1885–1889.

Bowers B, Hasni S, Gruber B. 2010. Sarcoidosis in World Trade Center rescue workers presenting with rheumatologic manifestations. J Clin Rheumatol 16(1): 26–27.

Chen LC, Thurston G. 2002. World Trade Center cough. Lancet 360 (Suppl): s37–s38.

Crystal RG. 2004. Sarcoidosis. In: Harrisons principles of internal medicine. 16th edition. Chapter 309. New York, NY: McGraw-Hill Professional, p 2017–2023.

Deng JC, Baughman RP, Lynch JP 2002. Cardiac involvement in sarcoidosis. Semin Respir Crit Care Med 23(6): 513–527.

Drent M, Bomans PH, Van Suylen RJ, Lamers RJ, Bast A, Wouters EF. 2000. Association of man-made mineral fibre exposure and sarcoidlike granulomas. Respir Med 94(8): 815–820.

Enright PL, Skloot GS, Cox-Ganser JM, Udasin IG, Herbert R. 2010. Quality of spirometry performed by 13,599 participants in the World Trade Center Worker and Volunteer Medical Screening Program. Respir Care 55(3): 303–309.

Ferguson GT, Enright PL, Buist AS, Higgins MW. 2000. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 117(4): 1146–1161.

Hankinson JL, Odencranz JR, Fedan KB. 1999. Spirometric reference values from a sample of the General U.S. Population. Am J Respir Crit Care Med 159:179–187.

Hart AC, Stegman MS, Ford B. 2009. ICD-9-CM Professional for Physicians Volumes 1&2. In: International Classification of Diseases 9th Revision. Clinical Modification 6th edition. Salt Lake City, UT: Ingenix.

Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. 1986. The epidemiology of sarcoidosis in Rochester, Minnesota: A population-based study of incidence and survival. Am J Epidemiol 123(5): 840–845.

Herbert R, Moline J, Skloot G, Metzger K, Baron S, Luft B, Markowitz S, Udasin I, Harrison D, Stein D, Todd A, Enright P, Stellman JM, Landrigan PJ, Levin SM. 2006. The World Trade Center Disaster and the Health of Workers: Five-Year Assessment of a Unique Medical Screening Program. Environ Health Perspect 114:1853–1858.

Iannuzzi MC, Rybicki BA, Teirstein AS. 2007. Sarcoidosis. N Engl J Med 357(21): 53–65.

Izbicki G, Chavko R, Banuach GI, Weiden MD, Berger KI, Aldrich TK, Hall C, Kelly KJ, Prezant DJ. 2007. World Trade Center sarcoid like granulomatous pulmonary disease in New York City Fire Department rescue workers. Chest 131(5): 1414–1423.

Jordan HT, Cone J, Thorpe L. 2008. Sarcoidosis diagnosed after September 11, 2001 among persons exposed to 9/11/2001 World Trade Center disaster. Presented at the136th APHA Annual Meeting and Expo October 25–29, 2008. San Diego, California. Abstract retrieved on June 23, 2009 from: http://apha.confex.com/apha/136am/webprogram/Paper182085.html.

Judson MA, Baughman RP, Teirstein AS, Terrin ML, Yeager H, 1999. Defining organ involvement in sarcoidosis: The ACCESS proposed instrument. ACCESS Research Group. A case control etiologic study of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 16(1): 75–86.

Judson MA, Thompson W, Rabin DL, Steimel J, Knattereud GL, Lackland DT, Rose C, Rand CS, Baughman RP, Teirstein AS, ACESS Research Group. 2003. The diagnostic pathway to sarcoidosis. Chest 123(2): 406–412.

Judson MA, Hirst K, Iyenger SK, Rybicki BA, El-Ghormli L, Baughman RP, Donohue JF, Elston RC, Kavuru MS, Moller DR, Newman LS, Rabin DL, Rossman MD, Teirstein AS, Iannuzzi MC, SAGA Study Consortium. 2006. Comparison of sarcoidosis phenotypes among affected African-American siblings. Chest 130:855–862.

Kaplan EL, Meier P. 1958. Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481.

Landrigan PJ, Lioy P, Thurston G, Berkowitz G, Chen LC, Chillrud SN, Gavett SH, Georgopoulos PG, Geyh AS, Levin S, Perera F, Rappaport SM, Small C, NIEHS World Trade Center Working Group. 2004. Health and environmental consequences of the World Trade Center disaster. Enviorn Health Perspect 112(6): 731–739.

Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenberg J, Buckley B, Turpin B, Zhong M, Cohen MD, Prophete C, Yang I, Stiles R, Chee G, Johnson W, Porcja R, Alimokhtari S, Hale RC, Weschler C, Chen LC. 2002. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. Environ Health Perspect 110(7): 703–714.

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. 2005. Standardisation of spirometry. Eur Respir J 26(2): 319–338.

Newman LS, Rose CS, Maier LA. 1997. Sarcoidosis. N Engl J Med 336(17): 1224–1234.

Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, Terrin ML, Weinberger SE, Moller DR, McLennan G, Hunninghake G, DePalo L, Baughman RP, Iannuzzi MC, Judson MA, Knatterud GL, Thompson BW, Teirstein AS, Yeager H, , Johns CJ, Rabin DJ, Rybicki BA, Cherniack R, ACCESS Research Group. 2004. A case control etiologic study of sarcoidosis: Environmental and occupational risk factors. Am J Respir Crit Care Med 170(12): 1324–1330.

Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson R, Johnson DC, MacIntyre N, Mckay R, Miller MR, Navajas D, Pedersen OF, Wanger J. 2005. Interpretative strategies for lung function tests. Eur Respir J 26(5): 948–968.

Prezant DJ, Weiden M, Banauch GI, McGuiness G, Rom WN, Aldrich TK, Kelly KJ. 2002. Cough and bronchial responsiveness in firefighters at the World Trade Center Site. N Engl J Med 347(11): 806–815.

Rybicki BA, Major M, Popovich, J , Maliarik MJ, Iannuzzi MC. 1997. Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am J Epidemiol 145(3): 234–241.

Savitz DA, Oxman RT, Metzger KB, Wallenstein S, Stein D, Moline J, Herbert R. 2008. Epidemiologic research on man-made disasters: Strategies and implications of cohort definition for World Trade Center worker and volunteer surveillance program. Mt Sinai J Med 75(2): 77–87.

Shorr AF, Torrington KG, Hnatiuk OW. 2001. Endobronchial involvement and airway hyperreactivity in patients with sarcoidosis. Chest 120(3): 881–886.

Skloot GS, Schechter CB, Herbert R, Moline JM, Levin SM, Crowley LE, Luft BJ, Udasin IG, Enright PL. 2009. Longitudinal assessment of spirometry in the World Trade Center Medical Monitoring Program. Chest 135(2): 492–498.

Smedema JP, Snoep G, van Kroonenburgh MP, van Genus RJ, Cheriex EC, Gorgels AP, Crijns HJ. 2007. The additional value of gadolinium-enhanced MRI to standard assessment for cardiac involvement in patients with pulmonary sarcoidosis. Chest 128(3): 1629–1637.

Thomas KW, Hunninghake GW. 2003. Sarcoidosis. JAMA 289(24): 3300–3303.