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## Post-9/11 Sarcoidosis in WTC-Exposed Firefighters and Emergency Medical Service Workers

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### Abstract

**Introduction**—The World Trade Center (WTC) disaster released a huge quantity and variety of toxicants into the environment. To-date, studies from each of the three major cohorts of WTC-exposed workers have suggested “greater than expected” numbers of post-9/11 cases in some workers. We undertook this study to estimate the incidence of post-9/11 sarcoidosis in ~13,000 male firefighters and EMS workers enrolled in The Fire Department of the City of New York (FDNY) WTC Health Program; to compare FDNY incidence to rates from unexposed, demographically similar men in the Rochester Epidemiology Project (REP); and, to examine rates by level of WTC exposure.

**Methods**—We calculated incidence of sarcoidosis diagnosed from 9/12/2001 to 9/11/2015, and generated expected sex- and age-specific rates based on REP rates. Standardized incidence ratios (SIR) based on REP rates, and 95% confidence intervals (95% CI) were estimated. Two sensitivity analyses limited cases to those with intra-thoracic symptoms or biopsy confirmation.

**Results**—We identified 68 post-9/11 cases in the FDNY cohort. Overall, FDNY rates were significantly higher than expected rates (SIR= 2.8; 95% CI= 2.2, 3.6). Including only symptomatic cases, the SIR decreased (SIR= 2.2; 95% CI=1.5, 3.0), but remained significantly elevated. SIRs

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ranged from 2.7 (95% CI=2.0, 3.5) in the lower WTC exposure group to 4.2 (95% CI=1.9, 8.0) in the most highly exposed.

**Conclusions**—We found excess incident post-9/11 sarcoidosis in WTC-exposed workers. Continued surveillance, particularly of those most highly exposed, is necessary to identify those with sarcoidosis and to follow them for possible adverse effects including functional impairments and organ damage.

### Keywords

Sarcoidosis; World Trade Center; Fire Department of the City of New York; Rochester Epidemiology Project

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## INTRODUCTION

Epidemiologic evidence suggests that, in genetically susceptible individuals, inhalation of particulate matter may trigger a systemic inflammatory response, [1] which can ultimately result in granuloma formation in any organ.[2] Sarcoidosis, a condition that occurs as part of an exaggerated CD4+ T cell immune response to antigens, is a multisystem granulomatous disease that has been known to occur in response to multiple environmental/occupational exposures.[1, 2] The World Trade Center (WTC) disaster released a huge quantity and variety of toxicants into the environment, potentially affecting between 60,000 – 70,000 rescue/recovery workers[3] and thousands of local residents. To date, two of the three major cohorts of WTC-exposed rescue/recovery workers have reported “greater than expected” numbers of post-9/11 cases of sarcoidosis[3, 4] while the third reported an elevated sarcoidosis risk among specific WTC-exposed workers.[5]

Although findings of more cases than expected are consistent across the three cohorts, excess cases do not clarify an association between WTC exposure and incident sarcoidosis for several reasons. First, there is no agreed-upon baseline rate of sarcoidosis in the US. Published incidence and prevalence rates of sarcoidosis in non-WTC-exposed populations, which are often used as comparison rates for WTC-exposed, are highly variable and population dependent, based on race/ethnicity, geography,[6, 7] socioeconomic status and access to healthcare.[8] The access to care issue is of particular importance in sarcoidosis as a substantial proportion of cases (30–50% by various estimates) are asymptomatic,[9] of which a significant proportion resolve spontaneously over time, leading to an unknown amount of undetected and unreported disease. Second, rates from different populations can only be meaningfully compared when cases have been collected in the same way, i.e., when the method of case ascertainment is similar across groups.[10] For example, populations that are routinely screened for employment or for other reasons using chest x-rays will undoubtedly detect cases of asymptomatic disease that would otherwise have remained undetected, resulting in higher rates from screened populations relative to rates from unscreened groups. For these and other reasons, U.S. prevalence estimates have ranged from 1 to 40 per 100,000 persons, although rates as high as 330 per 100,000 persons have been reported.[11] Reasonable, but possibly outdated incidence data from an early study estimate sarcoidosis rates in systematically screened white male military personnel as 7.2 per 100,000 person-years (1958 – 1969).[12] Recently, age-adjusted incidence for unscreened males

participating in the Rochester Epidemiology Project (REP) during 1946–2013 was reported to be 9.4 per 100,000 person-years,[13] while another study based on health care utilization found incidence rates of 8.1 per 100,000 in whites.[14]

The current study is designed to assess the association between WTC exposure and post-9/11/2001 (9/11) sarcoidosis in 13,098 WTC-exposed Fire Department of the City of New York (FDNY) firefighters and emergency medical service (EMS) workers. To do so, we first determined sarcoidosis incidence in demographically similar individuals (mostly white males) from the REP, which includes all residents of Olmsted County, MN, during a similar time period. We also assessed screening differences between the FDNY and REP populations by performing a sensitivity analysis which limited the analytic group to cases with symptoms of intra-thoracic involvement from each population. The second sensitivity analysis limited the analytic group to biopsy-proven cases from each population to ensure similar case definitions.

The primary study aims were to: 1) Estimate the incidence of sarcoidosis from 9/12/2001 to 9/11/2015 in male, WTC-exposed FDNY rescue/recovery workers; 2) Compare sarcoidosis incidence in our WTC-exposed cohort to incidence rates from demographically similar males from Olmsted County, MN, participating in the REP; and, 3) Examine differences in rates of sarcoidosis by level of WTC exposure.

## **MATERIALS AND METHODS**

### **DATA COLLECTION**

FDNY WTC Health Program performs periodic health evaluations on all active FDNY members, and on WTC-exposed retired members, both firefighters and EMS personnel, every 12–18 months. These monitoring visits include physician examinations and, since 2001, completion of self-administered health questionnaires that collect information about WTC exposure, health behaviors including smoking history and physician-diagnosed sarcoidosis. WTC-exposed members are routinely offered chest radiographs (posterioranterior and lateral views) every 2 years as part of their monitoring exam and chest radiographs or chest CT scans, when clinically indicated, as part of a diagnostic exam for those presenting with symptoms or signs of intra-thoracic involvement.

### **DEFINING WTC EXPOSURE INTENSITY**

WTC exposure is defined from the earliest post-9/11 health questionnaire. We categorized exposure into the following groups: arriving on the morning of 9/11 (arrival group 1; highest level of exposure); arriving after noon of 9/11 (arrival group 2); arriving on 9/12/2001 (arrival group 3); arriving between 9/13/2001 and 9/24/2001 (arrival group 4).[15] Duration of WTC exposure was defined as the number of months a member worked at the WTC-site between 9/11 and 7/25/2002 for at least one day (range 1–10).[16]

### **STUDY POPULATION**

The source population consisted of 14,589 male WTC-exposed firefighters and EMS workers who provided written consent for research. The inclusion criteria for this study

were: (1) having arrived at the disaster site between the morning of September 11, 2001 and September 24, 2001; (2) not having a pre-9/11 diagnosis of sarcoidosis; (3) having a working telephone number; (4) having at least 18 months of service at FDNY; and, (5) having taken at least one post-9/11 health questionnaire. The final study population consisted of 13,098 participants.

## DEFINING A FDNY SARCOIDOSIS POPULATION

Years before 9/11, sarcoidosis was a key interest of the FDNY health care team because of its possible association with firefighting.[17, 18] Post-9/11, FDNY continued to capture electronic medical records for physician diagnoses of sarcoidosis (ICD9 and ICD10 codes) and all chest imaging interpretations for the diagnosis of sarcoidosis or for findings consistent with sarcoidosis (e.g., bilateral hilar/mediastinal adenopathy). Self-administered health questionnaires completed by all FDNY firefighters and EMS workers at their monitoring exams also captured self-reported sarcoidosis. In 2005, the question was refined as follows *“Since 9/11/01 has a doctor or health professional told you that you have any of the following problems?”* The second option on the list is *“Sarcoidosis”*. Once captured, the case was reviewed to confirm the accuracy of the medical record or self-report; to identify whether the case was diagnosed by FDNY physicians during a medical monitoring or diagnostic exam; whether the case was symptomatic at diagnosis based on the presence of intra-thoracic symptoms, signs or abnormal chest imaging; and, whether there was biopsy confirmation. If diagnosed by a non-FDNY physician, pertinent medical records were reviewed to determine the above.

## CASE CONFIRMATION

We included only confirmed post-9/11 cases of sarcoidosis. We confirmed by history and by review of the medical record, requiring that all cases have physician diagnoses of sarcoidosis. Cases with intra-thoracic involvement were verified by review of pre-and post-hire chest radiographs, which were also used by FDNY to confirm that cases were newly diagnosed post-9/11. Cases with isolated granulomatous inflammations in specific organs (e.g., uveitis) were included after the exclusion of other granulomatous disease diagnoses. Confirmed cases were defined in two ways: *“biopsy-confirmed cases”* were supported by demonstration of non-caseating granulomas and the absence of any known granulomagenic organism or particle on a tissue biopsy, verified by medical record review conducted by either an FDNY pulmonologist or trained clinician. *“Non-biopsy confirmed”* cases were similarly verified by medical records, but did not include a tissue biopsy. *“Symptomatic cases”* were also defined by review of the medical records for indication of intra-thoracic symptoms or signs at the time of the first diagnostic presentation.

## THE ROCHESTER EPIDEMIOLOGY PROJECT

The REP, established in 1966, has medical records from over 700,000 former or current Olmsted County, MN residents. In 2014, Olmsted County had ~111,000 adults over 18 years of age.[19] At that time, about 86% of Olmsted County was white compared to the FDNY cohort which was ~89% white during the study period. REP records include all conditions that come to medical attention in Olmsted County, which includes the Mayo Clinic and Olmsted Medical Center, their outpatient facilities, emergency rooms and inpatient

hospitalizations and from private practitioners, urgent care facilities, and nursing homes. Over 90% of Olmsted County residents are seen by medical providers in any three year period. [20] According to the 2015 US Census, more than 95% of Olmsted County residents under age 65 had health insurance.[21]

REP provided age- and sex-specific sarcoidosis incidence rates during a similar time period (2002–2013) as FDNY case accrual. Given their geographic distance from NYC (~1,300 miles), it is likely that REP participants are entirely non-WTC-exposed. Occupational history for REP participants was not available. For all REP cases, inclusion required physician diagnosis supported by histopathology and/or radiologic features of intra-thoracic sarcoidosis, compatible clinical presentation and exclusion of other granulomatous disease. Isolated granulomatous disease of a specific organ (e.g., uveitis 1 REP case) was included if there was no better alternative diagnosis.[13] REP further designated cases as biopsy proven or non-biopsy proven and symptomatic or non-symptomatic at diagnosis.

## STATISTICAL METHODS

Sarcoidosis incidence was calculated as number of confirmed cases per 100,000 person-years. Person-time (denominator) accrual began on: September 12, 2001 or the FDNY hire date, whichever was later. Follow-up ended on the earliest of the following dates: death, end of the study (9/11/2015), or, for retired members, the last FDNY treatment or FDNY medical monitoring visit. Approximate 95% confidence intervals (CI) were calculated for standardized incidence ratios (SIR) using the Poisson distribution [22] and for direct standardized incidence rates using the modified Gamma approximation method,[23] which assumes a Poisson distribution. FDNY annual incidence rates were directly standardized to the US 2010 adult male population age 18 and over, and were compared to previously published REP incidence rates also standardized to the US 2010 adult male population.[13]

To compare FDNY rates with REP rates in men, the age-specific expected number of cases for the FDNY cohort was generated by applying the REP rates. The observed and expected numbers of cases were compared using 3 definitions of WTC-exposure: (1) arrival group 1 vs. later arrival; (2) long vs. short duration of work at the WTC site (median split < 3.0 months or ≥ 3.0 months); or, (3) by a composite measure of higher (arrival group 1 and ≥ 3.0 months at the site) vs. lower exposure. Exposure not designated as “higher” was labeled “lower”. Standardized incidence ratios (SIR), which are the ratios of the observed number of cases in FDNY to the expected number of cases based on REP rates, were calculated assuming the expected rates are fixed and that the observed number of cases follows a Poisson distribution. An SIR>1 indicates the observed number of cases is higher than expected and SIR<1 indicates the observed number of cases is lower than expected. We also performed two sensitivity analyses. The first generated expected cases and SIRs based on cases with symptoms of intra-thoracic involvement from each site, and the second generated expected cases and SIRs based on only biopsy proven cases from each site.

All analyses were performed using the statistical software SAS (version 9.4; SAS Institute Inc., Cary, N.C., USA). The study was approved by the institutional review board at Montefiore Medical Center.

## RESULTS

From 9/12/2001 – 9/11/2015, we identified 68 confirmed cases of post-9/11 sarcoidosis, of whom 67 (98.5%) had evidence of intra-thoracic involvement and 1 only had evidence of uveitis (Table 1). The median age at diagnosis was 43.2 (IQR 38.3 – 47.2) years. As has been shown in other studies, cases were also more likely to report never-smoking (72% FDNY vs. 56% REP;  $p = 0.093$ ). Ascertainment of exposure occurred well before diagnosis. The median time between ascertainment of arrival time to the WTC-site from the monitoring questionnaire and diagnosis of sarcoidosis was 5.7 years; the median time between ascertainment of duration of exposure and diagnosis of sarcoidosis was 3.1 years because duration questions were a later addition to our monitoring questionnaire.

Figure 1 graphs the number of post-9/11 cases by year of diagnosis. The highest number of incident diagnoses occurred during years 7–9 (i.e., 7 to 9 years after 9/11 or 2008 – 2010). Overall, the age-adjusted incidence of sarcoidosis was significantly higher in the FDNY cohort: 25.5 (95% CI=19.6, 47.2) vs. 10.2 (95% CI=7.7, 12.7) per 100,000 in the REP (Table 2). FDNY cases were limited to men 30 – 69 years of age whereas the age range for REP included both younger and older men. The median age at diagnosis of FDNY and REP cases was similar: 43.2 years for FDNY and 45.8 years for REP participants ( $p=0.17$ ).

Figure 2 graphs the post-9/11 incidence of sarcoidosis by SIR overall (SIR=2.8; 95% CI=2.2, 3.6) and by various exposure characteristics. We observed 68 cases of sarcoidosis during the study period, which was considerably higher than the expected number ( $n=24.1$ ), based on REP age-adjusted rates. The difference between expected and observed cases was greatest among persons whose composite level of WTC exposure was highest: the higher exposure group had 9 observed cases, which was considerably greater than the expected number ( $n=2.1$ ; SIR=4.2; 95% CI=1.9, 8.0). In the sensitivity analysis that was restricted to cases with intra-thoracic involvement, we included only those who were symptomatic at the time of diagnosis, 53.7% of FDNY cases vs. 74.2% of REP cases. Based on REP symptomatic rates, we expected 16.5 FDNY cases, but observed 36 cases, (SIR=2.2; 95% CI=1.5, 3.0). As anticipated, most likely due to FDNY screening practices, the SIR for asymptomatic cases was even higher, SIR= 4.4 (95% CI=3.0, 6.2) (Observed = 31; Expected = 7.1). In the second sensitivity analysis, considering only biopsy-proven cases (FDNY  $n=63$ , 92.6%), we expected 17.6 FDNY cases, but observed 63 (SIR=3.6; 95% CI=2.7, 4.6).

## DISCUSSION

FDNY rescue/recovery workers experienced an increased risk of sarcoidosis starting soon after 9/11 which persisted, at least through 2013. Comparing demographically similar males, age-adjusted rates of sarcoidosis were significantly higher in the FDNY cohort: 25.5/100,000 vs. 10.2/100,000 in the REP. The REP comparison rates we reported are consistent with rates from a large recent study based in Olmsted County, MN (9.4 per 100,000 men) [13] and 2012 rates from a Midwestern population generated by analyses of health care use (9.5 per 100,000 adults) [14], validating our decision to use the REP as a reference population. By level of WTC exposure, SIRs ranged from 2.7 in the low exposure group to 4.2 in the most highly exposed, although the confidence intervals overlapped, likely



due to small numbers. Since exposure information was collected years before diagnosis, at a median 5.7 years for arrival time and 3.1 years for duration, it is unlikely that recall bias was a factor in the observed association. Accordingly, we believe that the observed dose-response trend in post-9/11 incidence may support an association between WTC exposure and incident sarcoidosis.

Critics of post-9/11 sarcoidosis incidence studies in WTC-exposed responders have raised a number of valid methodologic issues that suggest that observed increases are partially or entirely due to enhanced case finding.[24, 25] To address this point, we undertook two sensitivity analyses. The first limited both REP and FDNY cases to persons with symptomatic intra-thoracic involvement at presentation, as we reasoned that these individuals would likely have received a sarcoidosis diagnosis regardless of screening practices. While the SIR was diminished, we found a two-fold risk for the FDNY cohort in symptomatic individuals, suggesting that the increased incidence in the FDNY population cannot be entirely attributed to detection bias. The second sensitivity analysis included only biopsy-proven FDNY and REP cases, and similarly showed excess cases in the FDNY cohort: SIR 3.6. This is reassuring, as it indicates that our population does, in fact, have sarcoidosis – a sometimes difficult to diagnose disease, and speaks to similar case definitions in both cohorts. While these sensitivity analyses represent our attempt to reduce the impact of routine surveillance, we acknowledge the likelihood that some of our cases, particularly asymptomatic ones, would not have been diagnosed in the community.

As sarcoidosis has long been viewed as a potential consequence of firefighting, FDNY has previously published two studies of sarcoidosis, one describing 25 pre-9/11 cases (1985–1998) [17] and another describing 26 post-9/11 ones (2001–2006).[5] In the latter study, the incidence rate was highest in the first post-9/11 year (86/100,000), but decreased over the next 4 years to compare favorably with the age-adjusted rate we report: 22/100,000 vs. 25.4/100,000 in the current study. This rate is also similar to the annual incidence of 23.1/100,000 in white males reported by the WTC non-FDNY responder cohort.[4]

Our study has several strengths. First, our REP co-investigators provided age and sex-specific rates from a similar time period for the generation of expected FDNY rates, providing excellent population-based comparison rates for WTC-exposed males. Second, our cohort existed prior to 9/11, minimizing the risk of recruitment bias. Third, all persons in our cohort had the opportunity to report sarcoidosis diagnoses on their monitoring questionnaires or to their FDNY physicians. Reports were screened, reviewed and validated by our clinicians. Fourth, we confirmed by history and chest radiographs from pre-hire, and post hire but pre-9/11, that all our cases were first diagnosed post-9/11. Fifth, nearly all of our cases were biopsy proven. Finally, information about WTC-exposures was collected from questionnaires completed by all cohort members regardless of symptoms and, obtained years prior to the date of diagnosis, arguing against recall bias.

Study limitations include that we lacked an FDNY non-WTC-exposed comparison group. Such a group could have better accounted for the healthy worker effect, which might have minimized the impact of WTC work exposures on sarcoidosis outcomes as observed using REP comparison rates. Nonetheless, we showed that FDNY rates were significantly higher

than rates in a demographically similar group with high rates of health insurance and physician visits. Second, using REP comparison rates, we could not distinguish between the possible effect of firefighting and the possible effect of WTC exposure. Third, REP case accrual included persons diagnosed from 2002–2013, which differed from the time of FDNY case accrual, which began on 9/12/2001 and ended on 9/11/2015. Thus, we do not have comparison rates for the entirety of the follow-up period, although there is no evidence that secular trends substantially affected sarcoidosis incidence in men.[13] Further, missing and mistimed sarcoidosis diagnoses in the two cohorts could have impacted our results. Our primary analyses, however, aggregated FDNY cases diagnosed from 9/12/2001 – 9/11/2015 and Olmsted County cases diagnosed from 2002 – 2013, which was done to minimize the impact of mistimed diagnoses on annual incidence rates, which, for that reason, we do not present. Our results may not be generalizable to other occupational cohorts, as our population was relatively small (~13,000), exclusively male, mostly white and had above-average physical health prior to WTC-exposure. We further acknowledge that our attempt to control for the effect of routine screening may not have fully neutralized its impact, especially as we lack specific information about the frequency of chest x-rays in the REP population. Lastly, we do not know from the REP about possible firefighting and WTC exposures, which, if present, would have increased the risk for sarcoidosis, minimizing the difference between Olmsted County and FDNY rates (i.e., biasing results toward the null). We also note that we lack information from both cohorts about non-WTC-related exposures, both work-related and recreational.

## CONCLUSION

We found excess incident sarcoidosis in FDNY WTC-exposed rescue/recovery workers. Continued surveillance, particularly of those most highly exposed, is necessary to identify those with sarcoidosis and to follow them for possible adverse effects including functional impairment and evidence of organ damage.

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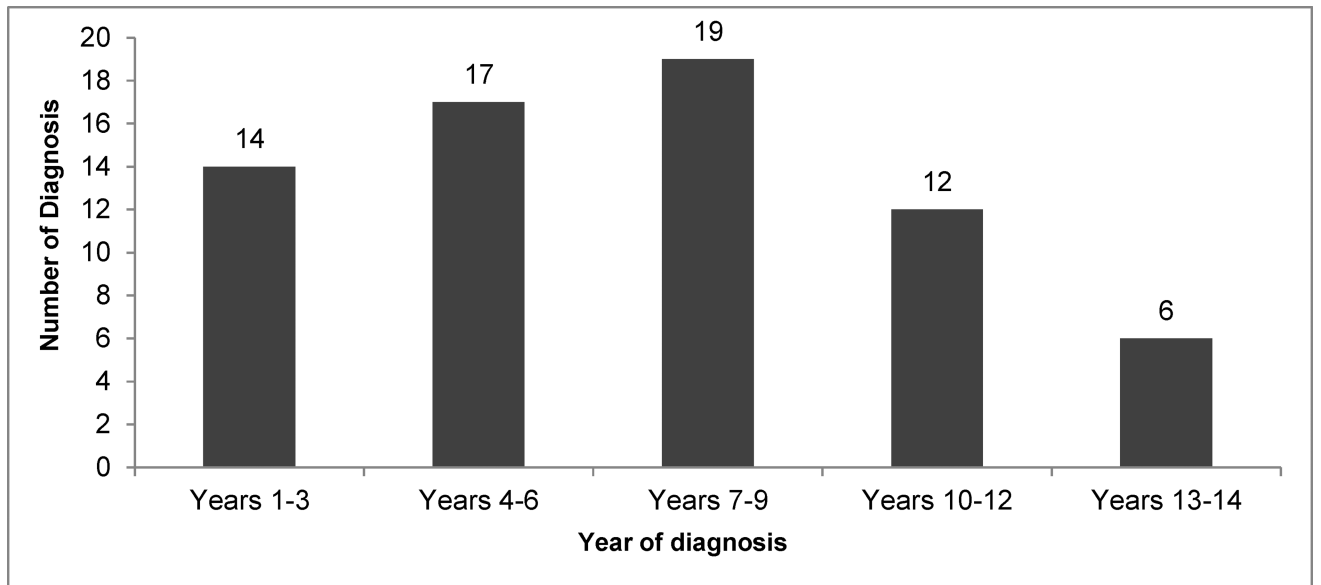
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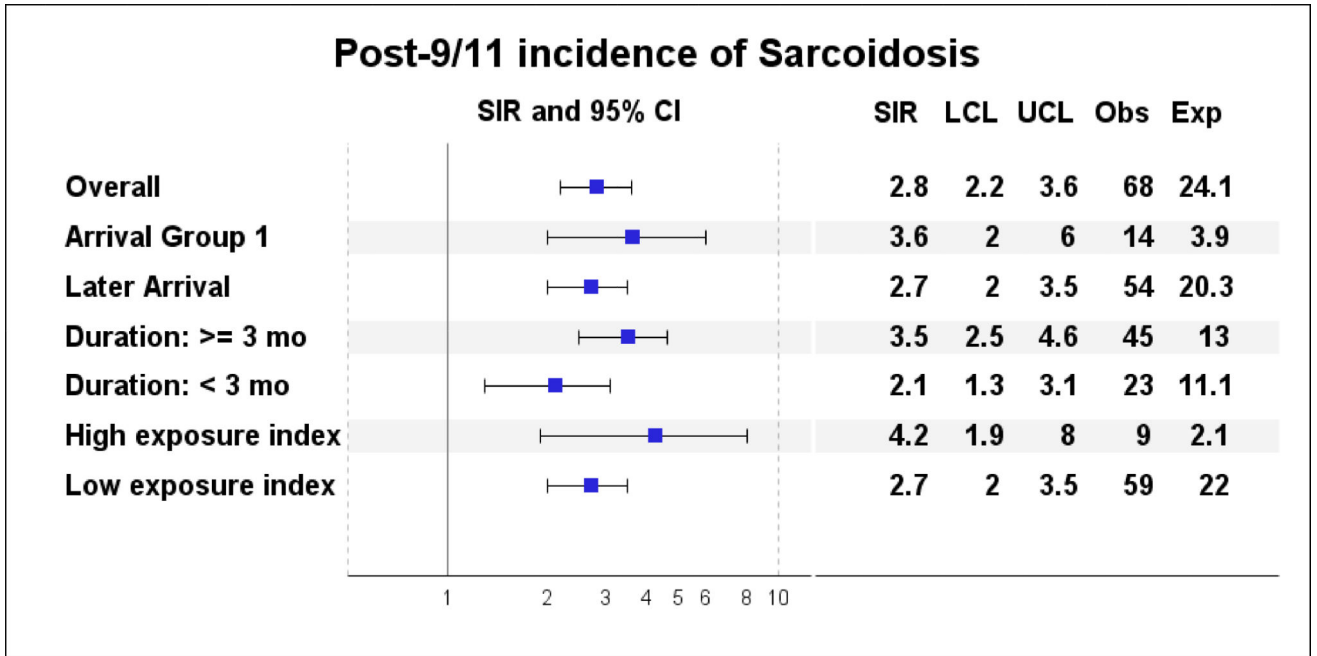
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**Research highlights**

- We found 68 post-9/11 sarcoidosis cases in the FDNY WTC-exposed cohort (N=13,098)
- FDNY sarcoidosis incidence rates were significantly higher than expected (SIR=2.8)
- Significantly elevated rates were observed among workers at all WTC exposure levels



**Figure 1.**  
Sarcoidosis Cases in FDNY study population over Time  
Footnote: Years in 9/11 years (i.e., Year 1 corresponds to 9/12/2001 – 9/11/2002)



**Figure 2.** SIRs Overall and by WTC Exposure Level  
 Abbreviations: SIR = Standardized Incidence Ratio; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit; Obs = Observed; Exp = Expected; Mo = Months Reference rates were obtained from REP’s sarcoidosis incidence rates from 2002 – 2013.

**Table 1**

Demographic and other characteristics of the FDNY study population by sarcoidosis diagnosis

Characteristics	With post-9/11 Sarcoidosis		Without Sarcoidosis	
	N	%	N	%
<b>Total</b>	68	100	13,030	100
<b>Race</b>				
White	62	91.2	11,626	89.8
Nonwhite	6	8.8	1,404	10.8
<b>Class</b>				
Firefighter	66	97.1	11,707	89.8
EMS worker	2	2.9	1,323	10.2
<b>Age at diagnosis – years</b>				
Median [IQR range]	43.2 [38.3–47.2]		N/A	
<b>Age at 9/11 – years</b>				
Median [IQR range]	37.4 [33.7 – 40.1]		40 [33.8–46.0]	
<b>WTC Arrival Group</b>				
Arrival morning of 9/11	14	20.6	2,073	15.9
Arrival afternoon of 9/11	30	44.1	6,280	48.2
Arrival on 9/12/2001	17	25.0	2,453	18.8
Arrival any day between 9/13/2001 and 9/24/2001	7	10.3	2,224	17.1
<b>WTC Work duration – months</b>				
Median [IQR range]	4.0 [2.0– 6.5]		3.0 [1.0–5.0]	
<b>Current smoking status</b>				
Never smoker	49	72.1	7,586	58.2
Ever smoker	19	27.9	5,444	41.8
<b>Biopsy-confirmed</b>	63	92.7	N/A	N/A
<b>Intra-thoracic involvement of sarcoidosis<sup>a</sup></b>	67	98.5	N/A	N/A
<b>Symptomatic of intrathoracic involvement at time of diagnosis<sup>b</sup></b>	36	53.7	N/A	N/A

<sup>a</sup>N=1 case had isolated uveitis<sup>b</sup>Percentage of N=67 sarcoidosis cases with intra-thoracic involvement

Abbreviations: FDNY, Fire Department of the City of New York; WTC, World Trade Center



**Table 2**

Age-specific rates of sarcoidosis in males

<b>Comparison of Sarcoidosis Incidence Rates per 100,000 between Male FDNY and REP</b>				
	<b>FDNY</b>		<b>REP<sup>a</sup></b>	
<b>Age Group</b>	<b>No.</b>	<b>Rate</b>	<b>No.</b>	<b>Rate</b>
18 to 29 years	0	0	3	2.3
30 to 39 years	19	57.9	18	14.9
40 to 49 years	35	53.0	19	15.8
50 to 59 years	13	25.2	15	14.1
60 to 69 years	1	6.0	4	6.3
70 to 79 years	0	0	4	10.5
80 to 110 years	0	0	0	0
Age-adjusted rate <sup>b</sup>	25.5 (19.6 – 47.2)		10.2 (7.7 – 12.7)	

<sup>a</sup>Rates for 2002–2013<sup>b</sup>Rates adjusted to the 2010 US adult male population

Abbreviations: FDNY, Fire Department of the City of New York; REP, Rochester Epidemiology Project

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