Title Page

Title: **Clinical Characteristics and Outcomes of WTC-Associated Sarcoidosis**
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List of Terms and Abbreviations

WTC = World Trade Center

FDNY=Fire Department of the City of New York

Abstract
Clinical Characteristics and Outcomes of WTC-Associated Sarcoidosis
PI: Simon Spivack, MD, MPH

Background: Large numbers of new diagnoses of sarcoidosis (or a granulomatous disorder indistinguishable from sarcoidosis, referred to in this document as World Trade Center (WTC)-associated sarcoidosis) have been demonstrated in all of the major cohorts tracking post-WTC conditions, suggesting that WTC exposure may have played an etiologic role. In particular, there have been 74 new cases in Fire Department of the City of New York (FDNY) firefighters exposed to WTC These cases, many of which arguably were triggered by WTC exposure, provided a unique opportunity to explore the clinical characteristics, genetic correlates, temporal patterns of progression or resolution, and response to treatments of WTC associated sarcoidosis.

The two specific aims of this proposal were to: 1) Characterize the current and past clinical profiles of sarcoidosis among FDNY firefighters who developed sarcoidosis after WTC-exposure, and 2) Compare the frequency of known genetic markers associated with sarcoidosis in WTC-associated sarcoidosis with controls who did not have sarcoidosis.

Methods: For Aim 1 we characterized organ involvement the 15 organs or systems using an organ assessment tool adapted from the WASOG (World Association of Sarcoidosis and other Granulomatous Diseases) Organ assessment instrument and the response to treatment. We also assessed the lung function of among the patients at diagnosis and follow-up.
For Aim 2, we conducted a case-control study with controls matched for race, age, smoking history, and WTC-exposure history. Genetic markers included: HLA alleles, BTNL2 haplotype, Annexin A11 single nucleotide polymorphisms and beryllium-responsive CD4 T cells were also be examined.

Results: In Aim 1 we found radiographic resolution of intrathoracic involvement occurred in 24 (45%). Lung function for nearly all was within normal limits. Extrathoracic involvement increased, most prominently joints (15%) and cardiac (16%). There was no evidence for calcium dysmetabolism. Few had ocular (5%) or skin (2%) involvement. None had beryllium sensitization. Most (76%) did not receive any treatment. Extrathoracic disease was more prevalent in WTC-related sarcoidosis than reported for sarcoidosis patients without WTC-exposure or for other exposure-related granulomatous diseases (beryllium disease and hypersensitivity pneumonitis). Cardiac involvement would have been missed if evaluation stopped after electrocardiogram, 48-hour recordings and echocardiogram. Our results also support the need for advanced cardiac screening in asymptomatic patients with strenuous, stressful, public safety occupations given the potential fatality of a missed diagnosis.

In Aim 2 we found that all samples showed no evidence for beryllium-responsive CD4 T cells. Blood samples with matching controls have been obtained for the genetic markers analyses and are currently being processed.

Conclusions: The results from this proposal show how WTC-exposed rescue/recovery workers with sarcoidosis should be clinically evaluated at diagnosis and during follow-up to maximize worker health and safety. Our study also demonstrates no evidence for beryllium as the cause for the sarcoid granulomatous inflammatory response after WTC-exposure. We are currently doing further genetic variant analyses to determine if: (i) There are predisposing inherited variants for sarcoid in our population, and (ii) There are any genetic x environmental interactions that might explain our findings.

Section 1 of the Final Progress Report
(2 page limit)

Significant or Key Findings
Key findings from Aim 1:
Radiographic resolution of intrathoracic involvement occurred in 24 of the 59 cases seen in follow-up (45%). Lung function for nearly all was within normal limits. Extrathoracic involvement increased; the largest increases were seen in joints (15%) and cardiac (16%). There was no evidence for calcium dysmetabolism. Few had ocular (5%) or skin (2%) involvement. None had beryllium sensitization. Most (76%) did not receive any treatment. Extrathoracic disease was more prevalent in WTC-related sarcoidosis than reported for sarcoidosis patients without WTC-exposure or for other exposure-related granulomatous diseases (beryllium disease and hypersensitivity pneumonitis). Cardiac involvement would have been missed if evaluation stopped after electrocardiogram, 48-hour recordings and echocardiogram.

Key findings from aim 2: Our study also demonstrates no evidence for beryllium as the cause for the sarcoid granulomatous inflammatory response after WTC-exposure. We are currently doing further analyses to determine if there are any genetic environmental interactions that might explain our findings.

Translation of Findings
Our results from Aim 1 show how WTC-exposed rescue/recovery workers with sarcoidosis should be clinically evaluated at diagnosis and during follow up to maximize worker health and safety. The cardiac findings from Aim 1 support the need for advanced cardiac screening in asymptomatic patients with strenuous, stressful, public safety occupations given the potential fatality of a missed diagnosis.

Research Outcomes/Impact
The findings from this study can guide the WTC Health Program approach to diagnosing and treating sarcoidosis in this population both at the time of diagnosis and during follow up, thereby reducing morbidity.

Section 2 of the Final Progress Report

Scientific Report

Aim 1:

Characterize the current and past clinical profiles of sarcoidosis among FDNY firefighters who developed sarcoidosis after WTC-exposure, with regard to involvement of each of the 15 organs or systems tabulated in an organ assessment tool adapted from the WASOG (World Association of Sarcoidosis and other Granulomatous Diseases) Organ assessment instrument.

1a. Specifically, determine whether and to what extent granulomatous inflammation in WTC-associated sarcoidosis is limited to intrathoracic involvement, as one might expect from a predominantly inhalation exposure, vs. more widespread systemic involvement.

1b. Characterize the time course of disease progression or resolution over the 5 to 13 years after diagnosis.

Introduction/Background:

Sarcoidosis is a multisystem granulomatous disease.[1-3] The annual incidence varies widely among races/ethnicities: 11/100,000 in U.S. Whites and 36/100,000 in U.S. Blacks.[4,5] In the Fire Department of the City of New York (FDNY), Prezant and coworkers found that between 1985 and 1998, FDNY firefighters had a significantly higher annual incidence of sarcoidosis than FDNY EMS workers and historical controls.[6] The average annual incidence was estimated at 12.9/100,000, significantly greater than in EMS workers (0.0/100,000) and several times the expected rate (2.5 to 7.6/100,000 for white men in the U.S.).[4]

Following the World Trade Center (WTC) attack on 9/11/2001 (9/11), an increase in sarcoidosis was found in WTC-exposed populations[7,8] including FDNY rescue/recovery workers.[9] Between 2002 and 2015, we found an age-adjusted incidence rate of 25/100,000 in male FDNY rescue/recovery workers.[10] By 2015, we identified 74 FDNY firefighters with new post-9/11 sarcoidosis: 65 diagnosed by transbronchial or mediastinal biopsy and 9 by typical clinical or radiologic findings without alternate diagnosis. Possible triggering agents/antigens include particulate matter (calcium carbonate and silica) and fibers (asbestos, fibrous glass, gypsum), organic pollutants (polycyclic aromatic hydrocarbons), gases, combustion byproducts from WTC fires, and metal dusts such as beryllium.[11]

Although its etiology is unknown, sarcoidosis is thought to represent a genetically-primed abnormal immune response to an antigen exposure or inflammatory trigger[1], with both genetic and environmental factors playing a role in disease onset and phenotypic expression, including which organs are involved. Reports have described the clinical presentation at diagnosis, but few have described its clinical course over time.[12-14]

Given the extensive phenotyping of this group at diagnosis, via comprehensive medical evaluations and cohort maintenance through the FDNY WTC Health Program, we recognized an opportunity to describe the clinical course of incident sarcoidosis 15-years after WTC-exposure, during the follow-up period of 2015-2016.

Materials and Methods:

Study population:

All 74 WTC-exposed FDNY firefighters with post-9/11 sarcoidosis were recruited via mailings and phone calls. The Montefiore/Einstein Institutional Review Board approved the study. Participants provided written informed consent.

Clinical criteria for case definition:

All cases were WTC-exposed, and had normal chest radiographs prior to 9/11 (obtained pre-employment and biannually at medical monitoring). For biopsy proven cases, pathology reports were reviewed to verify histologic culture-negative, noncaseating granulomas. For those without biopsy (n=7), charts were reviewed by two pulmonologists and cases were included if chest CT showed bilateral symmetrical mediastinal/hilar adenopathy (>1.5cm), perilymphatic nodules, or fibrosis with bronchial distortion, without alternative etiology.[15]

Evaluation at Diagnosis and Follow-up:

Diagnostic and follow-up evaluations were similar (Table 1) with the following additions at follow-up: serum angiotensin converting enzyme (ACE), serum vitamin D (25-hydroxy and 1, 25 dihydroxy), urinary calcium measurements; and a gadolinium-enhanced cardiac MRI. If joint findings or cardiac findings were suspicious for sarcoidosis involvement, confirmation by a rheumatologist or cardiologist was required. Treatment was recorded at diagnosis and follow-up.

Cardiac studies:

Advanced cardiac imaging was pursued, in absence of symptoms or abnormal screening test, given the potential for a cardiac fatality resulting from a missed diagnosis in firefighters and the relatively low risk of a gadolinium-enhanced cardiac MRI. Electrophysiologic (EP) studies were used for risk-stratification in those patients with abnormal cardiac MRI (delayed gadolinium-enhancement of infero-lateral-basilar segments).[18] Implantable cardiac defibrillator (ICD) placement was guided by traditional primary and secondary prevention as well as consideration for the degree of abnormality on MRI. Cardiac PET scanning was performed when treatment with disease modifying drugs was considered due to a positive EP study or extensive disease on echocardiogram or MRI.

Organ involvement: at time of diagnosis and follow-up:

For each participant, the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) organ assessment tool[19] was used to categorize sarcoidosis involvement of each organ system both at time of diagnosis and at follow-up (2015-2016). With the exception of bone-joints, a finding of “highly probable” or “at least probable” was considered diagnostic for organ involvement. For bone-joints, symptoms of arthralgias (“possible” by WASOG criterion) were upgraded to “at least probable” when there was tenderness on exam in two or more symmetrical joints, negative rheumatology serologies, and response to treatment with disease modifying drugs other than corticosteroids.[20] Indeterminate cardiac MRI results were considered non-diagnostic until a repeat was obtained 6-12 months later. If abnormalities were too subtle to be characterized as cardiac sarcoidosis by both radiologist and cardiologist or were no longer present or unchanged, the MRI was considered negative.

Clinical course:

Organ involvement was considered present based on WASOG criteria at follow-up and whether treatment had occurred. If new organ involvement occurred more than 1-year after diagnosis but before the follow-up study (2015-2016), it was considered a follow-up finding – this included one patient with cardiac involvement and 8 patients with bone/joint involvement for which treatment was initiated prior to our study. For lung involvement, the clinical course was assessed by chest imaging and classified by Scadding stages (0=normal, 1=bilateral hilar adenopathy with normal lung parenchyma; 2=bilateral hilar adenopathy with pulmonary infiltrates; 3=pulmonary infiltrates without hilar adenopathy; 4=pulmonary fibrosis);[21] PFT as percent predicted for age, height and race;[22,23] and, the need for treatment.

Statistics:

Demographic characteristics, clinical characteristics, and pulmonary function metrics were compared by T-test, Fisher Exact test, Wilcoxon-Mann-Whitney test, or Pearson's chi-square test. Analyses were conducted using SAS version 9.4.

Results:

Demographics and clinical characteristics:

The incidence of sarcoidosis between 9/11 and 1/2015 was 25/100,000. Of the 74 WTC-exposed firefighters with post 9/11 sarcoidosis, we successfully recruited 59 (80%). All cases with biopsy proven disease were biopsied within 3-months of presentation. At diagnosis, non-participants were slightly older (P=0.044), but did not significantly differ from study participants in other demographics (Table 2) or organ involvement (Table 3). Follow-up occurred in late 2015 to early 2016, on average 8-years after diagnosis (Interquartile range: 5-11 years).

Clinical Course of Sarcoidosis from Diagnosis to Follow-up:

Of 59 cases, pulmonary symptoms were reported by 32 (54%) at diagnosis and 35 (59%) at follow-up, while evidence of pulmonary disease on imaging was present in 98% at diagnosis and 51% at follow-up. Resolution of intrathoracic involvement (parenchyma and adenopathy) by follow-up occurred in 24 (45%) of 53 cases who had chest CTs at diagnosis and follow-up (Table 3). Pulmonary functions were within normal limits for nearly all, changed little over time, and were not significantly different in those with or without intrathoracic involvement by CT scan at follow-up (Figure 1, all p>0.05).

Extrathoracic involvement increased over time (Table 3), most prominently in joints and cardiac systems, which, at follow-up affected 15% and 16% of the study population, respectively (Figure 2). Several findings at follow-up were noteworthy for not being counted as involvement by WASOG criterion.[19] Thirty-four (58%) patients with chronic rhinosinusitis (symptoms and inflammation on sinus CT but without nasal/sinus biopsy), 2 patients with small fiber neuropathy (considered a para-sarcoidosis syndrome) and minor abnormalities of vitamin D/calcium homeostasis (35 cases with low 25-hydroxy- and normal 1,25-dihydroxy- vitamin D levels) without hypercalcemia or hypercalciuria.

Cardiac involvement:

Our initial protocol at diagnosis found no evidence of cardiac involvement by symptoms, electrocardiogram, electrocardiogram recording or echocardiogram. At follow-up, cardiac MRI was added. Thirty-one (53%) of 59 cases reported symptoms of possible concern (e.g., palpitations, dizziness/syncope), but only for 1 case was cardiac attribution considered likely. Figure 3 shows how many cases would have been missed at follow-up if the evaluation stopped after an earlier unremarkable test. For example, an unremarkable electrocardiogram would have missed 7 cases with abnormal continuous cardiac recording and 6 cases with abnormal cardiac MRI. Abnormal findings included for: electrocardiograms (e.g., right ventricular strain, right bundle branch block or intermittent complete AV block); echocardiogram (left ventricular ejection fraction less than 45%); 48-hour recording (short runs of ectopy usually supraventricular and 4 with variable block [second degree, right bundle branch or intermittent complete AV block]); and cardiac MRI (delayed gadolinium-enhancement of infero-lateral-basilar segments). Eight of the 9 cases with abnormal cardiac MRI underwent an EP study – 2 had inducible ventricular tachycardia, of which one had the low ejection fraction noted on both echocardiogram and MRI, but a negative cardiac PET scan. One case with a negative EP study and normal echocardiogram had extensive scarring on cardiac MRI with a positive cardiac PET scan.

Bone-Joint Involvement:

Eight cases presented with symmetrical polyarticular arthritis involving swelling and tenderness of the small joints, of which 5 also involved large joints. One additional case had asymptomatic vertebral bone involvement. In all cases, serum markers for other autoimmune diseases, in particular rheumatoid factor and anti-CCP antibody, were negative on initial presentation.

Angiotensin Converting Enzyme (ACE):

At follow-up, mean ACE levels were 47 U/L (interquartile range: 32 U/L); 9 (15%) had mildly elevated ACE levels (>67 U/L).

Treatment:

The average number of organs involved decreased by 0.59, from 1.88 to 1.29 organ/patient after an average of 8 years of follow-up. Five (8%) cases were treated with oral corticosteroids for dyspnea with reductions in pulmonary function. Eight cases with joint symptoms underwent a stepwise treatment algorithm to achieve adequate disease control,[2] ultimately with hydroxychloroquine and methotrexate in 1 patient and TNF-α blockers in 7 cases. For the entire study cohort, regardless of why treatment was initiated, the course of pulmonary functions (FVC, FEV1, DLCO, and FRC) were similar in patients who were ever treated with any disease modifying drug as compared to those who were never treated (all $p>0.05$). Among 24 cases who demonstrated resolution of intrathoracic involvement at follow-up, six were treated. Three cases with cardiac sarcoidosis were treated with an ICD – 2 for inducible VT on EP study and 1 for severe scarring on MRI. One of the 3 had a positive cardiac PET scan and was treated with corticosteroids. In the 3 cases with ICDs, none have discharged, and all patients (study participants and non-participants) remain alive (as of 2017).

Discussion:

We described the phenotypic expression of sarcoidosis at diagnosis and follow-up in a relatively homogeneous cohort of WTC-exposed firefighters. Nearly 68% were highly exposed (present on 9/11). Consistent with recent studies in sarcoidosis patients without WTC-exposure,[12,24,25] the median age at diagnosis was 43 years old, nearly every case had intrathoracic involvement (predominantly radiographic Stage I and II, and 45% had resolution of intrathoracic findings. WTC sarcoidosis differed, however, in terms of its extrathoracic manifestations with more joint and cardiac disease, and less hypercalcemia, ocular, and skin involvement than usually found in white male sarcoidosis patients without WTC-exposure. This is interesting as other exposure-related granulomatous diseases (chronic beryllium disease and hypersensitivity pneumonitis) are confined to the lungs while this study shows that WTC sarcoidosis is a multisystem disease.

The ACCESS study found that white patients developed an average of 0.17 new organ involvements over a 2-year follow-up.[13] In the cohort from the Medical University of South Carolina (MUSC), white males developed an average of 0.8 new organ involvements over a 6-year follow-up.[14] In contrast, in our study the average number of organs involved decreased by 0.59, from 1.88 to 1.29 organs/patient after an average of 8-years of follow-up. Organ assessment in our study, however, included extensive cardiac studies that were not performed in the two aforementioned studies. If we excluded asymptomatic patients who were found to have cardiac sarcoidosis, rates of new organ involvement would have decreased by 0.74 from 1.88 to 1.13 organs/patient.

Over 76% (n=45) of our cohort did not receive treatment for sarcoidosis. This is higher than described in the MUSC cohort where nearly 40% did not receive treatment.[14] Our percent treated (34%), however, is similar to the MUSC treated white subset (35%). Treatment occurred due to dyspnea with declining pulmonary function, joint symptoms, or potentially life-threatening cardiac or neurologic involvement.

As far as bone-joints, while our definition for organ involvement did not technically meet WASOG criteria ("possible" upgraded to "at least probable"), the instrument does acknowledge that multiple lesser manifestations may raise the probability of organ involvement. Therefore, it is reasonable to consider the presence of tenderness on exam in two or more symmetrical joints and response to treatment with disease modifying drugs other than corticosteroids alone as positive for bone-joint involvement.

Our study has several limitations and strengths. First, the cohort was comprised of all male firefighters, all but one of whom was white. This homogeneity precludes us from making any conclusions as to the clinical course of disease in WTC-exposed females, non-whites and non-firefighters with sarcoidosis, although our previous findings have proven to be generalizable to other more diverse WTC-exposed cohorts.[7,8] Close monitoring of our cohort did allow us, however, to be certain that all participants: were WTC-exposed; and that sarcoidosis occurred post-exposure since we have pre-employment and pre-exposure medical exams, including chest

radiographs, on all FDNY firefighters. Second, although the vast majority participated, 20% of the base cohort did not participate in follow-up. While these patients were similar at diagnosis, we cannot determine whether their disease was stable or in which direction it evolved. For those who chose to participate, a study strength was the long-term follow-up (mean 8-years).

Another strength was the standardization of the evaluation protocol for organ involvement at diagnosis and follow-up, which was independent of symptoms. This allowed us to more accurately determine the prevalence of cardiac involvement, since all patients had a full assessment, even those who were asymptomatic or had normal electrocardiograms. Of particular significance is the relatively high percent found to have unrecognized cardiac involvement. Clinically evident cardiac sarcoidosis has been noted in only 2 to 7% of sarcoidosis patients with manifestations including conduction abnormalities, ventricular arrhythmias and heart failure, while the rate in asymptomatic patients is unknown.[26,27] Cardiac sarcoidosis was clinically detected in 16% of our cohort at follow-up. We cannot comment on whether cardiac involvement was present at initial diagnostic evaluation because cardiac MRI was only added at follow-up. We believe that our initial diagnostic protocol likely underestimated its frequency, because in 56% of our cases with a positive cardiac MRI at follow-up, the 3 other cardiac studies (electrocardiogram, echocardiogram and continuous electrocardiogram recording) repeated at follow-up remained normal. This finding is in contrast to the study by Mehta and colleagues,[26] which reported a specificity of 87% and sensitivity of 100% for diagnosing cardiac sarcoidosis with at least one abnormal screening test (electrocardiogram, 24-hour recording or echocardiogram) and/or significant cardiac symptoms. Our data suggest that cardiac sarcoidosis may frequently be missed even if these screening tests are all normal (Figure 3). The prognostic significance, however, of a positive cardiac MRI in this setting requires further studies with larger numbers and longer follow-up.

In summary, we describe the clinical course of sarcoidosis in this WTC-exposed firefighter cohort followed for many years. Intrathoracic involvement resolved in 45% of patients. Pulmonary function was normal in nearly all and remained stable in all but one. Stability of pulmonary function was not associated with radiographic stage at diagnosis or follow-up, or with treatment. Extrathoracic disease was more prevalent than reported for sarcoidosis without WTC-exposure or for other exposure-related granulomatous diseases (beryllium disease and hypersensitivity pneumonitis). Treatment was most often instituted for symptomatic joint involvement or potentially life-threatening cardiac or neurologic involvement rather than for lung, ocular or skin involvement. Given the limited number of longitudinal studies of sarcoidosis, we hope these findings will help guide the management of all sarcoidosis patients, including those with WTC-exposure. We believe that our results support the need for advanced cardiac screening in asymptomatic patients with strenuous, high stress, public safety occupations, although additional follow-up is warranted. Firefighting is extremely stressful– operating at workloads equal to or exceeding 12 METs, in high heat and potentially toxic environments leading to maximum heart rates, high catecholamine levels and an increased rate of myocardial infarction.[28-31] And should a firefighter suffer a cardiac event while in this environment, it would

place not only that firefighter, but also other firefighters on that team and civilians being rescued at grave risk.

Aim 2:

Since beryllium was found at the WTC-site and berylliosis is clinically indistinguishable from sarcoidosis, a second aim was to evaluate for beryllium sensitization. Blood beryllium sensitization studies (IFNγEli spot assay and beryllium lymphocyte proliferation test [BeLPT]) were done at the National Jewish Health Center (Denver, Colorado) [16,17] on samples provided by us obtained at the follow-up exam. None had evidence of beryllium sensitization.

Additional studies are underway at our lab (Albert Einstein College of Medicine) to determine if: (i) There are predisposing inherited variants for sarcoid in our population, using a case-control design, and (ii) There are any genetic x environmental interactions that may have predisposed to sarcoidosis or to its clinical phenotype (ex. cardiac sarcoid). We are currently performing deep sequencing of ~45 candidate genes on the Ion Torrent platform. We will be examining all coding sequence and 2kb of the 5' promoters as well, among ~55 sarcoid cases and ~115 sarcoid controls, in this pilot, exploratory study. These data are now coming in, expected completion late fall 2017.

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Table 1. FDNY Sarcoidosis Evaluation Protocol at Diagnosis and Follow-up		
	Examination Description at Diagnosis	Examination Description at Follow-up
Questionnaire	• Occupational, medical, family and sarcoidosis history • Racial/ethnic background • WTC-exposure details • Tobacco use history • Review of systems • Medication use	• Occupational, medical, family, and sarcoidosis history • Racial/ethnic background • WTC-exposure details • Tobacco use history' • Review of systems • Medication use, including current and past treatment for sarcoidosis
General Physical Exam	• Cardiac and pulmonary auscultation • Abdominal palpation • Lymph node, joint, and skin surveys • Cranial nerves, motor and sensory perception assessments	• Cardiac and pulmonary auscultation • Abdominal palpation • Lymph node, joint, and skin surveys • Cranial nerves, motor and sensory perception assessments
Eye exam by an Ophthalmologist	• Examination of eyelids • Palpebral fissures • Conjunctivae for granulomas • Slit lamp and dilated retina exam	• Examination of eyelids • Palpebral fissures • Conjunctivae for granulomas • Slit lamp and dilated retina exam
Chest Imaging	• Chest Radiographs (PA & lateral) or recreated digitally from CT • Non-contrast chest CT	• Chest Radiographs (PA & lateral) or recreated digitally from CT • Non-contrast chest CT
Pulmonary Function	• Spirometry • Lung volumes • Diffusing capacity	• Spirometry • Lung volumes • Diffusing capacity
Oxygen Saturation	• Resting	• Rest & exercise (6-minute walk)
Cardiac Evaluation	• 12 lead electrocardiogram • Transthoracic echocardiogram • 24-hour continuous recording	• 12 lead electrocardiogram • Transthoracic echocardiogram • 48-hour continuous recording • Cardiac MRI with gadolinium
Blood Analyses	• Complete Blood Count (CBC) • Metabolic panel • Creatinine and ionized calcium • Liver Enzymes	• Complete Blood Count (CBC) • Metabolic panel • Creatinine and ionized calcium • Liver Enzymes • Angiotensin Converting Enzyme (ACE) • Vitamin D (25-hydroxy & 1,25 dihydroxy) • Beryllium testing (IFNγElispot assay and beryllium lymphocyte proliferation test [BeLPT])
Urinalyses	• Urinalysis (micro & chemistry)	• Urinalysis (micro & chemistry) • 4-hr collection for creatinine & Ca

Table 2. Comparison of demographics between non-participants and study participants.

	Non-participants (n = 15)	**Study participants (n = 59)**
WTC-Exposure		
Arrival on the morning of 9/11	3 (20%)	13 (22%)
Arrival in the afternoon of 9/11	9 (60%)	27 (46%)
Arrival on 9/12	1 (7%)	15 (25%)
Arrival from 9/13 – 9/24	2 (13%)	4 (7%)
Age at sarcoidosis diagnosis, years, – median (IQR)	46 years (41 - 55)	43 years (38 - 47)
Gender		
Male	15 (100%)	59 (100%)
Race & ethnicity		
White	12 (80%)	58 (98%)
African American	0 (0%)	1 (2%)
Hispanic	2 (13%)	0 (0%)
Asian	1 (7%)	0 (0%)
Smoking status at the time of sarcoidosis diagnosis		
Current	0 (0%)	1 (2%)
Former	5 (33%)	9 (15%)
Never	10 (67%)	49 (83%)
Sarcoidosis Treatment Medications[a]		
Ever Treatment	5 (33%)	14 (24%)
Corticosteroids	5 (33%)	13 (22%)
Hydroxychloroquine / Methotrexate	2 (13%)	9 (15%)
TNF-α blockers	1 (7%)	6 (10%)

[a] Medications filled under the FDNY WTC Health Program. All comparisons between non-participants and participants were not statistically significant except age (p=0.044)

Table 3. Organ involvement for non-participants (at diagnosis) and study participants (at diagnosis and follow-up).

	Non-participants (n = 15)	**Study participants (n = 59)**	
Organ involvement	At diagnosis[a]	At diagnosis[b]	Follow-up[b]
Intrathoracic involvement by CT	13 (87%)	55 (98%)	29 (51%)
Radiographic Stage 1	0 (%)	8 (15%)	6 (21%)
Radiographic Stage 2	12 (92%)	43(78%)	19 (66%)
Radiographic Stage 3	1 (8%)	4 (7%)	4 (14%)
Radiographic Stage 4	0 (0%)	0 (0%)	0 (0%)
Cardiac	0 (0%)	0 (0%)	9 (16%)
Eyes	1 (8%)	3 (5%)	3 (5%)
ENT	0 (0%)	0 (0%)	1 (2%)
Bone-Joints	2 (13%)	4 (7%)	9 (15%)
Skin	1 (7%)	1 (2%)	1 (2%)
Nervous System	0 (0%)	0 (0%)	1 (2%)
Liver	1 (7%)	1 (2%)	1 (2%)
Spleen	0 (0%)	3 (5%)	3 (5%)
Kidney	0 (0%)	1 (2%)	0 (0%)
Calcium	0 (0%)	0 (0%)	0 (0%)
Extrathoracic lymph nodes	1 (2%)	0 (0%)	0 (0%)

FOOTNOTE Table 3:Involvement based on WASOG criteria.

[a]Non-participants had complete data at diagnosis with the following exceptions:Skin (N=14); Eye (N=13); Spleen (N=7); Bone-Joint (N=9); Cardiac (N=12); Nervous System (N=5); Extrathoracic lymph nodes (N=3)

[b] In the study cohort with follow-up, all cases had complete data at diagnosis and follow-up with the following exceptions:Chest CT at diagnosis (N=56), at follow-up (N=57) and at both (N=53); Eye at follow-up (N=58); Spleen at follow-up (N=57); Cardiac at follow-up (N=57); ENT (ear/nose/throat) at follow-up (N=57).

All comparisons between non-participants and participants were not statistically significant.

Figure 1. Pulmonary Function at Diagnosis and Follow-up

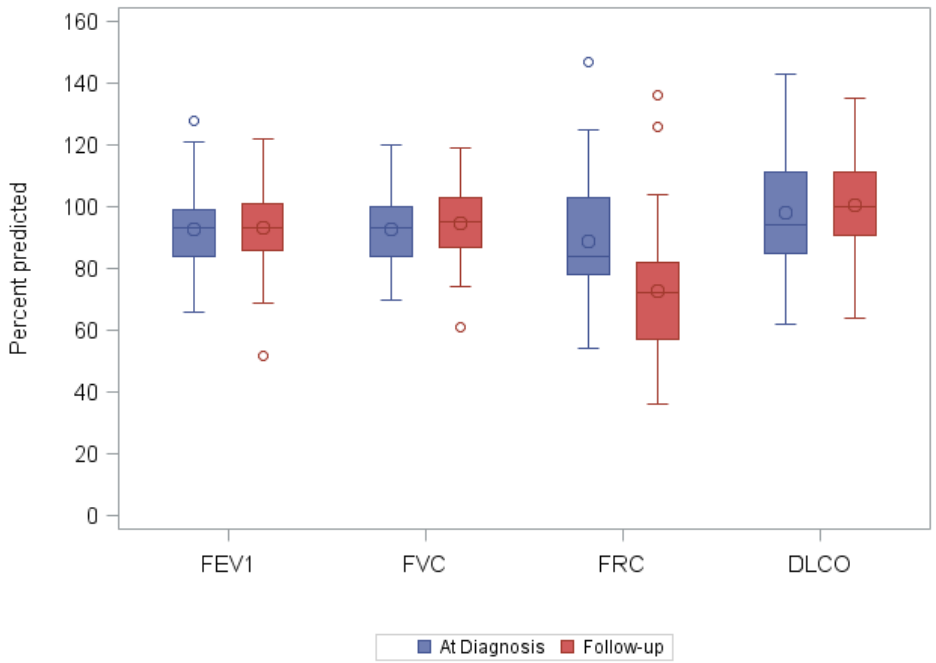

Figure 1 Legend: Average percent predicted pulmonary function among cases who had complete pulmonary data at diagnosis and follow-up: FVC and FEV1 (N=57); DLCO (N=41); FRC (N=30). All 59 cases had complete data at follow-up. Differences in pulmonary function metrics between diagnosis and follow-up were not statistically significant.

Figure 2: Clinical course of sarcoidosis organ involvement at diagnosis and follow-up

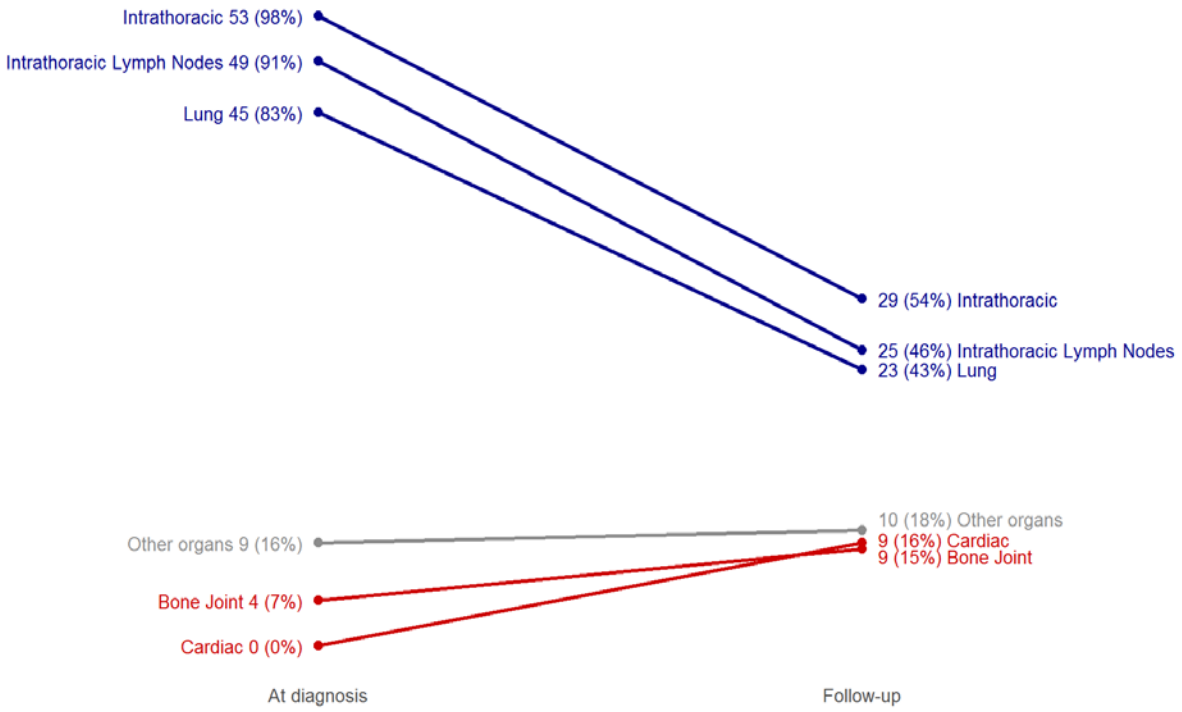

Figure 2 Legend: Other organs include: Eye, Spleen, Skin, Liver, Kidney, ENT, Calcium. All 59 cases had complete data at both diagnosis and follow-up for all organs with the following exceptions: Chest CT (N=54); Eye (N=58); Spleen (N=57); Cardiac (N=57); ENT (N=57).Serum calcium assessed at diagnosis and serum calcium and Vit D levels assessed at follow-up.

Figure 3. Cardiac assessments at follow-up exam for sarcoidosis cases

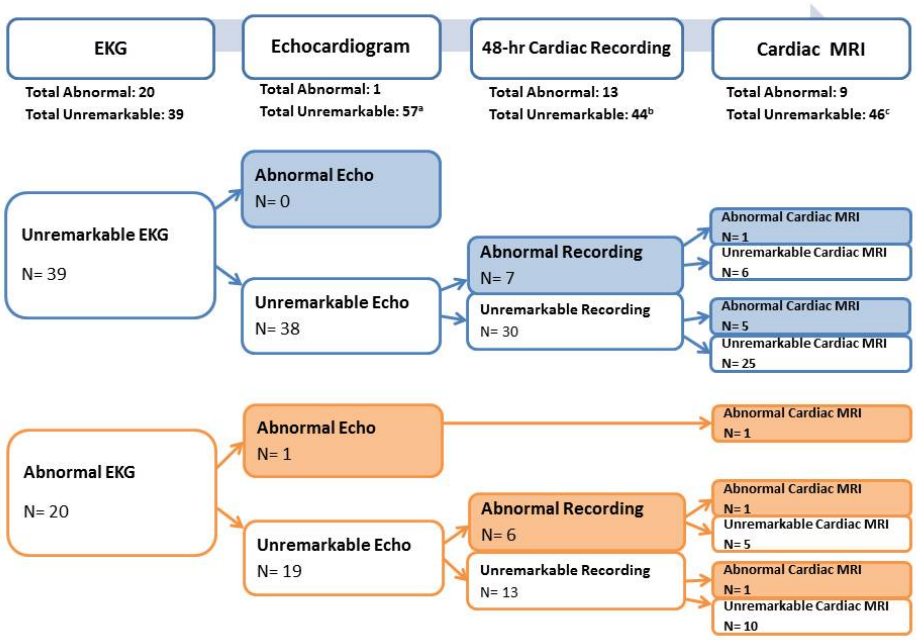

Figure 3 Legend:

[a] One participant missing an echocardiogram

[b] Two participants missing cardiac recordings. One participant missing an echocardiogram, had an unremarkable 48-hr cardiac recording (not shown) and a missing cardiac MRI

[c] Four participants missing cardiac MRIs

Cardiac evaluation at follow-up demonstrating how many cases would have been missed if the evaluation stopped after an earlier test was unremarkable. For example, an unremarkable electrocardiogram would have missed 7 cases with abnormal continuous cardiac recording and 6 cases with abnormal cardiac MRI. The same would have occurred if the evaluation stopped after both an unremarkable electrocardiogram and echocardiogram. An abnormal electrocardiogram with an unremarkable echocardiogram, would have missed 6 cases with abnormal continuous cardiac recording and 2 cases with abnormal cardiac MRI.

Aim 2:
Compare the frequency of known genetic markers associated with sarcoidosis (e.g. HLA alleles, BTNL2 haplotype, Annexin A11 single nucleotide polymorphisms) in WTC-associated sarcoidosis with the frequencies in a 2:1 matched control group---WTC-exposed firefighters, matched for race, age, smoking history, WTC-exposure history, but who did not develop sarcoidosis. Beryllium-responsive CD4 T cells will also be examined in each case-control trio.

Publications
Notes:
CHEST manuscript under review
CHEST and ATS abstracts

Cumulative Inclusion Enrollment Table

See demographic table 2

Inclusion of gender and minority study subjects

See demographic table 2

Inclusion of Children

Not applicable. FDNY respondents (source population) are all adults

Materials available for other investigators

Bio-informatics data available

Additional notes about the final report can be found here:
https://www.cdc.gov/niosh/oep/pdfs/awardcloseoutguidance-august2016.pdf

EQUIPMENT INVENTORY LIST AUTHORIZATION/PURCHASE

Report Date: 6/30/2017
Project Title: Clinical characteristics and outcomes of WTC- associated Sarcoidosis

Grant Number: 1U01OH010993-02
Project Period: 9/10/2015 to 6/30/2017

Grantee Name: Simon Spivack
Grants Management Officer: Mary Pat Shanahan

Project Officer: Travis Kubale
Grants Specialist: Jenise A. Yawn

Description of Item (i.e., pH Meter)	Mfr.[1] (i.e., Fischer)	Serial Number	Quantity	Condition	Location	Purchase Cost	Date Received
Ophthalmology Equipment - Avia Tonopen for intraocular Pressure measurement.	LOMBART	N/A	1	Excellent	FDNY Bureau of Health Services Brooklyn NY	3799	9/14/2015
Used Topcon SL-2E Slit Lamp, Electric Table, Volk 20 D large Aspheric Lens, Keller All Pupil II Headband Dimmer Control Smart Pack, Keeler Roller Back up case 10inch Snellen Eye Test Chart Lorgnette pinhole Occluder	Lombart	N/A	1	Excellent	FDNY Bureau of Health Services Brooklyn NY	6949.45	9/14/2015

Property Administrator & PO Disposition Recommendation and Instructions:

Description of Item (copy from above)	Disposition	Address[1]
Click here to enter text.	Choose an item. Click here to enter text.	Attn: Click here to enter text. Centers for Disease Control & Prevention Peachtree Distribution Center 3719 North Peachtree Road, #100 Chamblee, GA 30341
Click here to enter text.	Choose an item. Click here to enter text.	
Click here to enter text.	Choose an item. Click here to enter text.	
Click here to enter text.	Choose an item. Click here to enter text.	

1The CDC Warehouse is the central receiving point for the delivery of all non-hazardous and non-perishable supplies and equipment, CDC – AM – 2004-03, update 2010

Form Approved Through 10/31/2018
OMB No. 0925-0002

Department of Health and Human Services

Final Invention Statement and Certification

(For Grant or Award)

DHHS Grant or Award No.
1U01OH010993-01

A. We hereby certify that, to the best of our knowledge and belief, all inventions are listed below which were conceived and/or first actually reduced to practice during the course of work under the above-referenced DHHS grant or award for the period

9/10/2015 (*original effective date*) through 6/30/17 (*date of termination*).

B. Inventions (Note: If no inventions have been made under the grant or award, insert the word *"NONE"* under

NAME OF INVENTOR	TITLE OF INVENTION	DATE REPORTED TO DHHS
Dr. Simon Spivack	NONE	
(Use continuation sheet if necessary)		

C. Signature — This block ***must*** be signed by an official authorized to sign on behalf of the institution.

Title
Director Office of Grant Support

Typed Name
Dhanonjoy C Saha, Ph.D.

Signature
DCSaha

Date
2/13/17

Name and Mailing Address of Institution