

Nested Case–Control Study of Selected Systemic Autoimmune Diseases in World Trade Center Rescue/Recovery Workers

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Objective. To test the a priori hypothesis that acute and chronic work exposures to the World Trade Center (WTC) site on or after September 11, 2001 were associated with risk of new-onset systemic autoimmune diseases.

Methods. A nested case–control study was performed in WTC rescue/recovery workers who had received a rheumatologist-confirmed systemic autoimmune disease diagnosis between September 12, 2001 and September 11, 2013 (n = 59), each of whom was individually matched to 4 randomly selected controls (n = 236) on the basis of year of hire (± 1 year), sex, race, and work assignment (firefighter or emergency medical service). Acute exposure was defined according to the earliest time of arrival (morning of 9/11 versus later) at the WTC site, and chronic exposure was defined as duration (number of months) of WTC site–related work. Rheumatologists were blinded with

regard to each subject's exposure status. The conditional odds ratios (CORs) with 95% confidence intervals (95% CIs) for incident autoimmune disease were derived from exact conditional logistic regression models.

Results. Rheumatoid arthritis was the most common autoimmune diagnosis (37% of subjects), followed by spondyloarthritis (22%), inflammatory myositis (14%), systemic lupus erythematosus (12%), systemic sclerosis (5%), Sjögren's syndrome (5%), antiphospholipid syndrome (3%), and granulomatosis with polyangiitis (Wegener's) (2%). The COR for incident autoimmune disease increased by 13% (COR 1.13, 95% CI 1.02–1.26) for each additional month worked at the WTC site. These odds were independent of the association between high acute exposure (working during the morning of 9/11) and disease outcome, which conveyed an elevated, but not statistically significant, risk (COR 1.85, 95% CI 0.86–3.89).

Conclusion. Prolonged work at the WTC site, independent of acute exposure, was an important predictor of post-9/11 systemic autoimmune diseases. The WTC Health Program should expand surveillance efforts for those with extended exposures, as early detection can facilitate early treatment, which has been shown to minimize organ damage and improve quality of life.

Genetic factors are known to influence the development of autoimmune diseases, although heritability studies using identical twins suggest only low-to-moderate concordance rates (1), depending on the disease, implying that environmental, occupational, or other factors also play an important role in disease development. Compared with the growing body of genetic research, fewer resources have been allocated to studying environmental/occupational exposures. One well-studied environmental exposure is silica, a basic component of soil, sand, granite, and many other minerals,

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which has been associated with rheumatoid arthritis (RA) (2), systemic sclerosis (3,4), systemic lupus erythematosus (5), dermatomyositis (1), Sjögren's syndrome (6), and risk of antineutrophil cytoplasmic antibody-associated vasculitis (7). Autoimmune diseases have also been associated with environmental exposures to metals, ozone, hydrocarbons, organic solvents, pesticides, and particulates, and cigarette smoking has been shown to increase the formation of autoantibodies (8–11). In general, these autoimmune conditions were found to be associated with chronic environmental exposures acquired over years or even decades, presumably in individuals with genetic predispositions.

The terrorist attacks on the World Trade Center (WTC) buildings and the subsequent building collapses and fires on September 11, 2001 exposed rescue/recovery workers and residents to aerosolized WTC dust—an amalgam of pulverized cement, glass fibers, silica, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and polychlorinated furans and dioxins (12). While it is widely known that most of the Fire Department of the City of New York (FDNY) workforce of firefighters and emergency medical service (EMS) workers arrived at the disaster site within days or even hours of the 9/11 attacks, it may be less well known that many continued to work at the site for up to 10 months, potentially experiencing chronic exposures to resuspended particulate matter. Evidence of the effects of these intense WTC work site exposures, both acute and chronic, is abundant, as more than 70% of FDNY workers reported experiencing one or more respiratory and aerodigestive symptoms in the first year post-9/11, which, over time, led to physician-diagnosed chronic conditions, including asthma, chronic bronchitis, rhinosinusitis, gastroesophageal reflux disease, and cancer (13,14). We have also documented dramatic post-9/11 declines in lung function, consistent with the increased incidence of these respiratory conditions (15,16).

The full spectrum of the health consequences of exposure to the WTC disaster site remains unknown. The FDNY-WTC Health Program has been following up a cohort of nearly 16,000 firefighters and EMS workers who worked at the WTC site. Clinical observations of systemic autoimmune diseases in these workers (mostly male) triggered a preliminary medical records review. The current nested case-control study was designed to assess whether acute or chronic work exposures to the WTC site on or after 9/11 were associated with incident systemic autoimmune diseases, including systemic lupus erythematosus, antiphospholi-

pid syndrome, systemic sclerosis, inflammatory myositis, Sjögren's syndrome, RA, spondyloarthritis, granulomatosis with polyangiitis (Wegener's), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

SUBJECTS AND METHODS

Data sources. We obtained information on each subject's race, sex, and FDNY hire date from FDNY employee databases. In addition, self-administered health questionnaires were used to obtain information on smoking status, symptoms of posttraumatic stress disorder (PTSD), and acute and chronic WTC site-related exposures. We also obtained case records on rheumatologist-confirmed diagnoses of systemic autoimmune diseases.

Health questionnaires. Cigarette smoking was characterized as "ever" versus "never" by combining current and former smokers into a single "ever" category. Smoking status was identified from each participant's most recent questionnaire. The earliest questionnaire date was 2008, the most recent was 2014, and the median was 2013. Symptoms of PTSD were assessed using the 17-item PTSD Checklist, Civilian Version (17), which, since 2005, is routinely administered as part of the mental health questionnaire. We considered symptoms of PTSD as present if the participant attained a total score of ≥ 44 and reported experiencing symptoms in each of 3 domains (reexperiencing, avoidance, and hyperarousal) (18). PTSD status was identified from each participant's first mental health questionnaire. The earliest questionnaire date was 2006, the most recent was 2014, and the median was 2007.

Exposure ascertainment. Measures of WTC site exposure were defined as acute or chronic. Acute exposure was based on the earliest time of arrival at the WTC site, as reported by each individual on the first post-9/11 health questionnaire, which was administered starting in October 2001. We categorized arrival time into 2 groups: arriving on the morning of 9/11 versus arriving any time thereafter until July 25, 2002 (19), when the site was closed to FDNY workers. Questions about chronic exposure, or duration of work, were added to the monitoring questionnaires in 2002. Members were asked to indicate the months in which they worked at least 1 day at the WTC site. Duration was then measured by summing the number of months a member worked between September 11, 2001 and July 25, 2002 (20). Since all of the study participants had reported working at the WTC site, the minimum exposure duration was 1 month.

Study population. The FDNY-WTC Health Program schedules monitoring evaluations of active and retired individuals from the WTC site-exposed workforce every 12 to 18 months. The monitoring visit includes a physical examination and completion of self-administered physical and mental health questionnaires. In 2005, we amended the physical health questionnaire to include a question about doctor-diagnosed autoimmune disease and, in 2009, created an autoimmune registry to capture potential cases of new-onset systemic autoimmune disease in 2 ways. Most commonly, potential cases are self-reported in the physical health questionnaires, which is specifically addressed by one question: "Since your last FDNY WTC annual medical, has a doctor or health professional told you that you have arthritis or any

autoimmune disease listed below?" Answer choices include "rheumatoid arthritis," "lupus," "polymyositis/dermatomyositis," and "other (for example, psoriatic arthritis or scleroderma)." Individuals are not limited to one response. Additionally, the registry is populated by potential cases of systemic autoimmune disease self-reported by a patient to an FDNY physician either during a medical monitoring examination or during a treatment visit. This information is recorded as part of the patient's medical history.

The registry clinician (NJ) contacts every individual in the autoimmune registry considered to potentially have a systemic autoimmune disease. During the study period, there were 738 potential cases of self-reported systemic autoimmune diseases. After a brief telephone call, 522 cases (71%) were determined to be "reporting errors," mostly involving individuals who had osteoarthritis and not RA. Of the 216 possible cases (i.e., not reporting errors), we were unable to contact 59 of these individuals, either by telephone or mail, and 72 were contacted and determined to be "possible cases," but they failed to submit adequate documentation by the study close. The final population consisted of 59 medically confirmed cases of a systemic autoimmune disease, 51 cases of a systemic autoimmune disease originating from the annual monitoring questionnaires, and 8 additional cases of a systemic autoimmune disease originating from the FDNY physician notes.

Medically confirmed cases required diagnostic documentation from the treating physician/rheumatologist. Documentation from the treating rheumatologist had to include the specific systemic autoimmune disease diagnosis and the approximate diagnosis date (month and year). If there was any supporting laboratory work, imaging, pathologic findings, or relevant treatment notes, we asked that it also be sent to the registry clinician for review. Before final confirmation, all cases were re-reviewed by our systemic autoimmune disease case consultation group, which included 2 rheumatologists (JB and BQ) who were blinded with regard to each subject's history of WTC site exposure. Unanimous agreement was required for confirmation. Only confirmed cases were used for the analyses.

The at-risk population consisted of 15,484 WTC site-exposed firefighters and EMS workers. Inclusion criteria were as follows: having completed a monitoring questionnaire during or after 2005, thereby having had the potential to self-report, not having a pre-9/11 systemic autoimmune disease diagnosis, not having an unconfirmed systemic autoimmune disease diagnosis in the autoimmune registry, having known exposure to the WTC site (known time and date of first arrival and number of months worked at the WTC site), having a working telephone number, and having provided written consent for research. After exclusion of subjects who did not meet these criteria, the study population comprised 13,617 subjects (87.9%).

For the current analysis, post-9/11 diagnoses of interest included rheumatologist-confirmed diagnoses of any of the following systemic autoimmune diseases: systemic lupus erythematosus, antiphospholipid syndrome, systemic sclerosis (both diffuse and limited), inflammatory myositis (dermatomyositis, polymyositis, or inclusion-body myositis), Sjögren's syndrome, RA, spondyloarthritis (i.e., psoriatic arthritis and ankylosing spondylitis), granulomatosis with polyangiitis (Wegener's), and eosinophilic granulomatosis with polyangiitis

(Churg-Strauss). All diagnoses met the American College of Rheumatology classification criteria (21–27). In the primary analyses, all systemic autoimmune disease diagnoses were combined as a single outcome of interest. In additional analyses, the systemic autoimmune disease with the greatest incidence, RA, was used as the outcome of interest.

We accrued cases of systemic autoimmune diseases diagnosed between September 12, 2001 and September 11, 2013. After accrual was closed, we randomly selected 4 matched controls for each case using incidence density sampling, based on the following criteria: year of FDNY hire (within 1 year), sex, race, and work assignment (firefighter or EMS). We did not base the matching on age, because, in this cohort, age and year of hire are highly correlated ($r = 0.91$). Potential controls were contacted by the registry clinician to verify their noncase status as of 2 years prior to the diagnosis date of their matched case (28). Consistent with incidence density sampling, controls were eligible to become a case at a later date and could also serve as a control for more than one case.

This study has been approved by the institutional review board at Montefiore Medical Center, Bronx, New York and is in compliance with the Declaration of Helsinki.

Statistical analysis. Preliminary analyses included examination of demographic features and other characteristics, including acute and chronic exposure, by case or control status. Acute exposure (arrival time) was categorized as arriving on the morning of 9/11 versus arriving any time thereafter up to the time of worksite closure. Chronic exposure (duration of work) was treated as a continuous variable (per month) and was also grouped dichotomously into high chronic exposure versus low chronic exposure based on the median number of months worked (the median split). For univariable and multivariable analyses, we constructed exact conditional logistic regression models for determining the odds of incident systemic autoimmune disease, while separate models were constructed to determine the odds of a diagnosis of RA, the most common individual diagnosis. The exact method was appropriate, given our small sample size (29). The primary predictors of interest were acute and chronic WTC site exposure, but based on factors suggested in the literature, we also examined the possible effects of smoking history (ever versus never) (8) and PTSD symptoms (present versus absent) (30) on the systemic autoimmune disease outcome, and separately, on the RA outcome. Conditional odds ratios (CORs) with 95% confidence intervals (95% CIs) were derived from these conditional logistic regression models.

To adjust for possible disease latency, we performed a sensitivity analysis using an exact conditional logistic model in which we removed the 5 strata (cases and matched controls) with cases that had been diagnosed within 2 years of 9/11. Similarly, for the model predicting RA, we carried out a sensitivity analysis in which we removed the 3 strata with cases that had been diagnosed within 2 years of 9/11.

All analyses were performed using SAS statistical software (version 9.4). *P* values less than or equal to 0.05 were considered statistically significant.

RESULTS

Overall, we confirmed 59 cases of systemic autoimmune diseases. The most common individual diagnosis

Table 1. Distribution and year of systemic autoimmune disease diagnoses in the case cohort (n = 59)*

Type of systemic autoimmune disease	
Rheumatoid arthritis	22 (37.3)
Spondyloarthritis	13 (22.0)
Psoriatic arthritis	11 (18.6)
Reactive arthritis	1 (1.7)
Spondyloarthritis (axial and peripheral, without ankylosis)	1 (1.7)
Inflammatory myositis	8 (13.6)
Polymyositis	6 (10.2)
Dermatomyositis	2 (3.4)
Systemic lupus erythematosus	7 (11.9)
Systemic sclerosis (scleroderma)	3 (5.1)
Sjögren's syndrome	3 (5.1)
Antiphospholipid syndrome	2 (3.4)
Granulomatosis with polyangiitis (Wegener's)	1 (1.7)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	0 (0.0)
Year of diagnosis	
2002–2004	10 (16.9)
2005–2007	19 (32.2)
2008–2010	17 (28.8)
2011–2013†	13 (22.0)

* Values are the number (%) of subjects. Due to rounding, percentages do not add up to 100%.

† Case ascertainment may be incomplete for this time period.

was RA (22 cases [37.3%]). The number of diagnoses increased after 2004, peaking between 2005 and 2010 (Table 1). Most cases (56 [94.9%] of 59) occurred in men. Characteristics of the cases and controls are displayed in Table 2.

Ascertainment of exposure, both acute and chronic, usually occurred well before diagnosis. The median time between ascertainment of time of arrival at the WTC site, as obtained from the monitoring questionnaire, and diagnosis of a systemic autoimmune disease was 5 years. The median time between ascertainment of duration of work exposure, as obtained from the monitoring questionnaire, and diagnosis of a systemic autoimmune disease was 3 years, because duration-related questions were a later addition to our monitoring program. In all final models, cases of systemic autoimmune disease were significantly more likely than controls to have reported prolonged work exposure to the WTC site (Table 3).

Using duration of work exposure as a continuous variable, the COR for incident systemic autoimmune disease was 1.13 (95% CI 1.02–1.26), representing a 13% increase in odds for each month worked at the WTC site. As a dichotomous variable (median split at 2 months' duration), the COR for duration of exposure was 2.40 (95% CI 1.16–5.23). Results were similar in models in which we removed all cases reported by EMS workers (n = 5) and their matched controls (n = 20) (data not shown).

In the sensitivity analysis adjusting for potential disease latency, we removed 5 strata with cases diagnosed within 2 years of 9/11. The effect of duration of exposure (as a continuous variable) on the risk of a

Table 2. Characteristics of systemic autoimmune disease cases and nondisease controls*

	Cases (n = 59)	Controls (n = 236)	Total (n = 295)
Race			
White	56 (94.9)	224 (94.9)	280
Hispanic	3 (5.1)	12 (5.1)	15
African American	0 (0.0)	0 (0.0)	0
Asian	0 (0.0)	0 (0.0)	0
Other	0 (0.0)	0 (0.0)	0
Sex			
Male	56 (94.9)	224 (94.9)	280
Female	3 (5.1)	12 (5.1)	15
Work assignment			
Firefighter	54 (91.5)	216 (91.5)	270
EMS	5 (8.5)	20 (8.5)	25
Age, median (range) years			
At hire	26.9 (21–36.1)	26.5 (19–36.3)	
At diagnosis of case	50.4 (28.4–69.4)	50.2 (26.8–71.6)	
On September 11, 2013	57.2 (36.7–75.9)	56.4 (34.3–78.0)	
Chronic exposure			
High (≥ 2 months on site)	43 (72.9)	132 (55.9)	175
Low (1 month on site)	16 (27.1)	104 (44.1)	120
Acute exposure			
Morning arrival on September 11, 2001	16 (27.1)	41 (17.4)	57
Later arrival	43 (72.9)	195 (82.6)	238

* Except where indicated otherwise, values are the number (%) of subjects. EMS = emergency medical service.

Table 3. Final exact conditional logistic regression models assessing associations between the duration of WTC site exposure and risk of any systemic autoimmune diseases*

Model	Risk of systemic autoimmune diseases	
	Duration as continuous variable (per month)	Duration as dichotomous variable (median split)
Primary model		
Duration of WTC site work	1.13 (1.02–1.26)	2.40 (1.16–5.23)
Secondary models		
Tobacco history		
Duration of WTC site work	1.14 (1.02–1.27)	2.42 (1.17–5.28)
Cigarette smoking history (ever vs. never)	1.16 (0.62–2.20)	1.13 (0.60–2.12)
PTSD		
Duration of WTC site work	1.13 (1.02–1.25)	2.38 (1.15–5.20)
PTSD symptoms (presence vs. absence)	1.40 (0.58–3.14)	1.47 (0.61–3.30)
Sensitivity analysis		
Duration of WTC site work†	1.17 (1.05–1.31)	3.11 (1.40–7.51)

* Values are the exact conditional odds ratio (95% confidence interval). WTC = World Trade Center; PTSD = posttraumatic stress disorder.

† For sensitivity analyses, 5 strata with cases diagnosed between September 12, 2001 and September 11, 2003 (within 2 years of 9/11) were removed. A total of 54 strata remained in the model.

systemic autoimmune disease increased to 17% per month (COR 1.17, 95% CI 1.05–1.31), and similarly increased when we used a median split for duration of work at the site (COR 3.11, 95% CI 1.40–7.51) (Table 3).

We also examined the effects of acute exposure to the WTC site and found that individuals subsequently diagnosed as having a systemic autoimmune disease were somewhat more likely to have arrived at the WTC site during the morning of 9/11, although the effect of early arrival was not statistically significant in either the univariable models (COR 1.85, 95% CI 0.86–3.89) or multivariable models. In a model with a term controlling for duration of exposure, the effect of arriving at the WTC site during the morning of 9/11 was similar to that in the model without adjustment for duration (COR 1.80, 95% CI 0.84–3.80). In the model including both chronic exposure (duration of work exposure as a continuous variable) and acute exposure (time of arrival at the WTC worksite), the COR was 1.13 (95% CI 1.02–1.26) for each additional month worked at the site. There was no interaction between acute exposure and duration of exposure.

Neither of the other potential correlates (smoking status [ever versus never] or PTSD symptoms [presence versus absence]) was associated with new-onset systemic autoimmune diseases in this cohort. Models

using RA as the outcome showed that the CORs for associations with acute and chronic exposures, smoking, and PTSD symptoms were similar to those found in the model combining all systemic autoimmune diseases as the outcome, although no factors attained statistical significance at the 0.05 level (data not shown), perhaps due to low power.

DISCUSSION

This study examining the incidence of post-9/11 systemic autoimmune diseases in WTC rescue/recovery workers is the first to demonstrate a strong independent effect of prolonged work at the WTC disaster site on the incidence of systemic autoimmune diseases. The effect of chronic exposure increased by ~13% for each month worked at the WTC site. Based on this model, for those who worked the full 10 months compared with those who worked for 1 month, we estimate the COR for incident systemic autoimmune disease as 3.09 (95% CI 1.21–7.94). When we modeled duration of exposure using a median split, those who worked at least 2 months at the site incurred a risk more than double that of workers who worked fewer than 2 months. These results are consistent with non-WTC-related studies of chronic occupational exposures and disease outcomes. For example, silicosis usually takes at least 10 years after exposure to develop, but may develop sooner after a large exposure (31). To the best of our knowledge, previous studies have demonstrated an association of acute and chronic WTC site exposures with respiratory conditions such as asthma (20,32,33) and PTSD (34–36), but not with the new onset of systemic autoimmune diseases, other than sarcoidosis (37–39).

The cause or causes of systemic autoimmune diseases are unknown and likely multifactorial. One common hypothesis postulates that a series of events are responsible for the initiation of an autoimmune reaction. Genetic susceptibility may be the crucial first factor. Next, an antigenic event such as an infection or environmental exposure occurs, and then, through various immunologic–inflammatory–oxidative pathways, an autoimmune response occurs, ultimately leading to clinical symptoms and disease. Just as genetic susceptibility may involve multiple genetic risk factors, the triggering event may also involve multiple environmental factors or multiple factors at different periods or in a specific time sequence (8).

The systemic autoimmune diseases included in this study have diverse immunogenetic inflammatory mechanisms, but they all can lead to uncontrolled inflammation, pain, disability, and, often, tissue destruction

(40,41). Many components of adaptive and innate immunity come into play in each of these diseases and any attempt to group them by pathophysiology seems problematic. More work is needed to correctly define the dominant pathways for each disease. We excluded sarcoidosis, since we have previously reported that the incidence of sarcoidosis, primarily involving intrathoracic disease, increased after WTC site exposure in FDNY firefighters and EMS workers (38). A high point prevalence was similarly reported in 2 other WTC site-exposed cohorts (37,42), and 2 case series described WTC workers with sarcoid arthropathies (43,44). We included diagnoses of granulomatosis with polyangiitis (Wegener's) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in our analyses, but no cases of the latter were found. In the future, as we begin to understand more about the different parts of the immune system that contribute to these various diseases, further subgroupings may be possible. Until then, however, attempts to force categorization may not only be premature, but also misleading, because they will fail to capture the complexity of the underlying disease mechanisms.

We are confident in the results of the current study for several reasons. First, our cohort existed prior to 9/11, eliminating recruitment bias. Second, although self-reported physician diagnoses usually started the documentation process, all individuals in the cohort had the opportunity to report diagnoses on their monitoring questionnaires, which were then confirmed by our rheumatology case consultation review panel. Third, it is unlikely that members of our cohort had unrecognized pre-9/11 systemic autoimmune diseases, because the physical demands of firefighting and EMS work would have made concealment difficult. Fourth, we examined possible lack of bioplausibility by carrying out sensitivity analyses, removing those diagnosed within 2 years of 9/11, and found similar results, despite lower statistical power. Fifth, we believe that our control subjects were truly nondiseased, as they were selected on the basis of the absence of self-reported and physician diagnoses of systemic autoimmune diseases in our electronic medical records database. Each control was then contacted to confirm his or her nondisease status as of 2 years prior to the case diagnosis date, which thereby rules out the possibility of misclassification of disease outcomes in the control population. Finally, information about WTC site exposures was collected from questionnaires completed by all cohort members regardless of symptoms. In most cases, this information was obtained years prior to the date of diagnosis, which is evidence against the possibility of

recall bias, or differential recall of WTC site exposure among affected individuals.

Our findings have important clinical implications for the estimated 409,000 WTC site-exposed workers and residents (45), of whom ~120,000 have already enrolled in WTC Health Programs at the FDNY, the WTC Responder Health Consortium, or the WTC Health Registry at the New York City Department of Health and Mental Hygiene. Autoimmune diseases in North American and European populations have been thought to predominantly affect women (>75% of cases). Since the FDNY workers are predominantly men (96%), and the other WTC worker populations are also predominantly composed of men (78% at the WTC Health Registry [46] and 87% at the WTC Health Program Consortium [47]), our findings are unexpected and highlight the need for increased clinician awareness of the possibility of these, and perhaps other, autoimmune disorders in their WTC site-exposed male patients.

Our findings also reveal the lack of comparison rates of autoimmune disorders in various non-WTC site-exposed populations, specifically in men. Population-based prevalence studies have been inconsistent in their methods and have reported varying results. For example, 2 meta-analyses indirectly estimated population rates of autoimmune disorders by comprehensively reviewing the published literature and applying rates in samples to the US population (48,49), although neither included estimates by sex. In 1997, Jacobson et al reported the total population prevalence of 19 autoimmune diseases in the US as 1 in 31 (or 3.2%) (49). In 2009, Cooper et al estimated the total population prevalence of 29 autoimmune diseases, which differed from the diseases included in the Jacobson study, as 7.6–9.4% (50). Both studies estimated the incidence of autoimmune diseases as <0.5% per year (48,49). Incidence rates as estimated from other populations, both in the US and abroad, however, may not be applicable to specific populations such as our cohort, which is composed mostly of healthy white men. Our nested case-control study takes on added significance for this very reason.

A limitation of our study is that it involved a relatively small sample size with a largely white, male population. However, since we matched cases and controls on the basis of these characteristics, this limitation should not have affected our primary goal of estimating the association between WTC site exposure (whether acute or chronic) and systemic autoimmune diseases. Each case was randomly matched to 4 controls based on sex, race, work assignment, and hire year, so that cases and controls had similar levels of training, access to personal protective equipment, and work exposures

throughout their careers. We did not match on the basis of age, as in previous studies we found that matching on year of hire was sufficient to control for age, a decision supported by the median age of the cases and controls at the conclusion of the study (median 57.2 years versus 56.4 years). Thus, we are confident that our findings are not the result of confounding by smoking status, PTSD, or other known factors, but rather describe the effects of acute and chronic work exposure to the WTC site.

We cannot, however, rule out the possibility that confounding by unknown and unmeasured factors could have influenced our study results. For example, our duration variable does not differentiate between those with 1 day of exposure and those with many days of exposure in a given month. We also note that in the mid-portion of this study period, the number of cases diagnosed increased. We cannot determine whether this was attributable to a biologic effect or to increased awareness. Regardless, these factors should have had a similar impact on our controls. In addition, case ascertainment may have been incomplete after 2010, as there was a time lag of ~2 years between receiving a systemic autoimmune disease diagnosis and having the opportunity to self-report the diagnosis on the medical monitoring questionnaire. Finally, other study limitations include the lack of information about family history of systemic autoimmune diseases and about non-WTC site-related exposures, both work-related and recreational.

Systemic autoimmune diseases are relatively rare, but their adverse effects in terms of disability and activity limitation are great. This is the first study of WTC site-related systemic autoimmune diseases. We found a strong association between prolonged work at the WTC disaster site, such that the odds of systemic autoimmune diseases increased by ~13% for each month at the site, or more than 3-fold for those who worked at the site for the full 10 months' duration. Accordingly, we suggest enhanced surveillance of WTC site-exposed worker and resident cohorts to further assess our findings and to provide early access to care. The stakes are high because enhanced surveillance can lead to early detection and treatment of systemic autoimmune diseases, which has been shown to improve quality of life and reduce or delay organ damage, including amelioration of erosive joint destruction, kidney failure, pulmonary fibrosis, and hypertension (40,41).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Webber had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Webber, Moir, Zeig-Owens, Glaser, Jaber, Hall, Prezant.

Acquisition of data. Glaser, Jaber, Loupasakis, Kelly, Prezant.

Analysis and interpretation of data. Webber, Moir, Zeig-Owens, Hall, Berman, Qayyum, Loupasakis.

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