HHS Public Access

Author manuscript

Am J Ind Med. Author manuscript; available in PMC 2022 February 17.

Published in final edited form as:

Am J Ind Med. 2022 February ; 65(2): 117–131. doi:10.1002/ajim.23313.

Autoimmune conditions in the World Trade Center general responder cohort: A nested case-control and standardized incidence ratio analysis

Henry S. Sacks, PhD, MD[1], **Margaret Smirnoff, RN, FNP, MPH**[1], **Deborah Carson, BSN, MSN, MPH**[1], **Michael L. Cooney, MS**[1], **Moshe Z. Shapiro, MS**[1], **Christopher J. Hahn, MS**[1], **Christopher R. Dasaro, MA**[1], **Cynthia Crowson, PhD**[2], **Ioannis Tassiulas, MD, PhD**[3], **Robert P. Hirten, MD**[3], **Benjamin L. Cohen, MD, MAS, AGAF**[3,4], **Richard S. Haber, MD**[3], **Terry F. Davies, MD**[3], **David M. Simpson, MD, FAAN**[3], **Michael A. Crane, MD**[5], **Denise J. Harrison, MD**[6], **Benjamin J. Luft, MD**[7], **Jacqueline M. Moline, MD, MSc**[8], **Iris G. Udasin, MD**[9], **Andrew C. Todd, PhD**[1], **Nancy L. Sloan, DrPH**[1], **Susan L. Teitelbaum, PhD**[1]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[2]Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

[3]Rheumatology Department, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[4]Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Correspondence: Nancy L. Sloan, DrPH, and Susan L. Teitelbaum, PhD, Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, Box 1057, NY 10029, USA. nancy.sloan@mssm.edu and Susan.Teitelbaum@mssm.edu.
Henry S. Sacks and Margaret Smirnoff are equal first authors.
Nancy L. Sloan and Susan L. Teitelbaum are equal last authors.

AUTHOR CONTRIBUTIONS

Authors' participation is as follows: (a) Susan L. Teitelbaum, Henry S. Sacks, Margaret Smirnoff, Deborah Carson, and Nancy L. Sloan conceived and designed the work; (b) Cynthia Crowson, Michael A. Crane, Denise J. Harrison, Benjamin J. Luft, Jacqueline M. Moline, and Iris G. Udasin participated in data acquisition; Moshe Z. Shapiro, Michael L. Cooney, Christopher J. Hahn, Nancy L. Sloan, and Cynthia Crowson conducted the analysis; and Henry S. Sacks, Moshe Z. Shapiro, Michael L. Cooney, Margaret Smirnoff, Susan L. Teitelbaum, Nancy L. Sloan, Christopher R. Dasaro, and Cynthia Crowson participated in the interpretation of data. All authors participated in drafting or critically revising the work for important intellectual content, in its final approval, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

ETHICS STATEMENT

The work was performed and the WTCHP research has been approved by the Institutional Review Boards (IRB) of the Icahn School of Medicine at Mount Sinai (formerly Mount Sinai School of Medicine), New York, New York and the program's other clinical sites, including New York University Langone Medical Center, New York University School of Medicine, New York, New York; Department of Medicine, Stony Brook University Medical Center, Stony Brook, New York; Department of Occupational Medicine, Epidemiology and Prevention, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; and Environmental and Occupational Health Sciences Institute, Rutgers University, Piscataway, New Jersey. Aggregate data provided by Mayo Clinic College of Medicine, Rochester, MN was exempt from IRB review.

[5]Department of Environmental Medicine and Public Health, World Trade Center Health Program Clinical Center of Excellence, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[6]Department of Medicine, Department of Environmental Medicine, World Trade Center Health Program Clinical Center of Excellence, NYU Langone Medical Center, New York University School of Medicine, New York, New York, USA

[7]Department of Medicine, World Trade Center Health Program Clinical Center of Excellence, Stony Brook University Medical Center, Stony Brook, New York, USA

[8]Department of Occupational Medicine, Epidemiology and Prevention, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, World Trade Center Health Program Clinical Center of Excellence, Hempstead, New York, USA

[9]Department of Environmental and Occupational Medicine, World Trade Center Health Program Clinical Center of Excellence, Environmental and Occupational Health Sciences Institute, Rutgers University Biomedical Sciences, Piscataway, New Jersey, USA

Abstract

Background: The World Trade Center (WTC) general responder cohort (GRC) was exposed to environmental toxins possibly associated with increased risk of developing autoimmune conditions.

Objectives: Two study designs were used to assess incidence and risks of autoimmune conditions in the GRC.

Methods: Three clinically trained professionals established the status of possible GRC cases of autoimmune disorders adhering to diagnostic criteria, supplemented, as needed, by specialists' review of consenting responders' medical records. Nested case-control analyses using conditional logistic regression estimated the risk associated with high WTC exposure (being in the 9/11/2001 dust cloud or ≥median days' response worked) compared with low WTC exposure (all other GRC members'). Four controls were matched to each case on age at case diagnosis (±2 years), sex, race/ethnicity, and year of program enrollment. Sex-specific and sensitivity analyses were performed. GRC age- and sex-adjusted standardized incidence ratios (SIRs) were compared with the Rochester Epidemiology Project (REP). Complete REP inpatient and outpatient medical records were reviewed by specialists. Conditions meeting standardized criteria on ≥2 visits were classified as REP confirmed cases.

Results: Six hundred and twenty-eight responders were diagnosed with autoimmune conditions between 2002 and 2017. In the nested case-control analyses, high WTC exposure was not associated with autoimmune domains and conditions (rheumatologic domain odds ratio [OR] = 1.03, 95% confidence interval [CI] = 0.77, 1.37; rheumatoid arthritis OR = 1.12, 95% CI = 0.70, 1.77). GRC members had lower SIR than REP. Women's risks were generally greater than men's.

Conclusions: The study found no statistically significant increased risk of autoimmune conditions with WTC exposures.

Keywords

autoimmune conditions; environmental exposure; responder/recovery worker; World Trade Center

1 | INTRODUCTION

On 9/11/2001 and during the following months, World Trade Center (WTC) responders were exposed to environmental factors and psychological and physical stress that have been implicated in the development of autoimmune disease.[1–6] The responders' exposures to toxic inorganic and organic matter, body parts, injury, trauma, and physical exertion and experiences have been associated with increased risk of respiratory, gastrointestinal, cardiovascular, and mental health disorders.[7–9] While the exact etiology and pathogenesis of autoimmune disease remains elusive, environmental and genetic factors are known to trigger auto-immunity.[10,11] About 40%–70% of autoimmune conditions may be attributable to environmental factors, including particulate matter, hydrocarbons, burnt fuel, and other substances found at the attack site.[12–15]

Limited evidence supports associations between WTC responders' exposures and increased risk of autoimmune rheumatologic conditions. With 12 years of follow-up, the Fire Department of New York City (FDNY) found an increased odds ratio (OR) of autoimmune rheumatologic conditions among their FDNY WTC responders (FDNYR) who had worked at least 1 day per month for 2 or more months compared with those who had worked less time (OR = 2.40, 95% confidence interval [CI] = 1.16, 5.23). However, exposure to the 9/11 morning toxic dust cloud (OR = 1.85, 95% CI = 0.86, 3.89) or longer duration of WTC work, adjusted for 9/11 dust cloud exposure (OR = 1.80, 95% CI = 0.84, 3.80), were not significantly associated with the development of autoimmune conditions among FDNYR.[16] Similarly, compared with a racially similar WTC-unexposed population from Minnesota in data provided by the Rochester Epidemiology Project (REP), FDNYR had no excess risk of rheumatologic autoimmune conditions (OR = 0.97, 95% CI = 0.77, 1.21).[17] With 11 years of follow-up, the WTC Health Registry, which represents WTC-exposed community members and a subset of WTC responders (19.1% of the General Responders Cohort [GRC] members are also WTC Health Registry participants), found 9/11 dust cloud exposure was associated (relative risk [RR] = 1.86, 95% CI = 1.02, 3.40) with the risk of systemic autoimmune rheumatologic conditions.[18,19] In addition, there was a borderline significant association was found with the duration of work for WTC responders (RR = 1.10, 95% CI = 0.97, 1.24), and with a composite measure of response time worked and dust cloud exposure (RR = 1.86, 95% CI = 0.98, 3.53).[18] The FDNY and WTC Health Registry studies included limited numbers of autoimmune cases, mainly rheumatoid and psoriatic arthritis (FDNY case-control $n = 59$; FDNY external comparison $n = 97$; WTC Health Registry $n = 118$).[16–18]

According to the National Institutes of Health (NIH) Autoimmune Diseases Coordinating Committee, autoimmune diseases affect 3%–5% of Americans.[20] They are frequently debilitating, lack definitive cure, and might require lifelong medical care. Thus, they impose a heavy emotional and financial burden on patients, their families, and society and on health

costs in the United States. They also disproportionately affect women and minorities.[21,22] Addressing the rising concern about the risks that WTC exposures pose to developing autoimmune conditions, we identified and verified self-reported autoimmune conditions among the WTC general responder cohort (GRC; described elsewhere) to demonstrate the breadth and incidence of autoimmune conditions they experienced and to assess the risks WTC exposure posed to the GRC.[19,23,24]

2 | MATERIALS AND METHODS

2.1 | Study population

The first WTC medical screening program was established in 2002. Today's successor is the CDC/NIOSH WTC Health Program (WTCHP) of which the GRC has five participating Clinical Centers of Excellence in the New York City metropolitan area. GRC WTCHP members are invited to attend comprehensive annual health monitoring visits. Standardized instruments are used to collect socio-demographic status and WTC exposure information at their first visit; self-reported physical and mental health status and use of medication are assessed at each visit. Targeted physical examinations, pulmonary function testing, laboratory tests, and an assessment for social service needs are also conducted at each visit.[23] From July 16, 2002 through December 31, 2017, there were 41,168 GRC members consenting to data aggregation for research; about one-fifth are also members of the WTC Health Registry, while less than 1% were also active firefighters on September 11, 2001.[13]

2.2 | GRC case identification and verification

The WTC GRC autoimmune surveillance project was conducted between January 1, 2017 and December 31, 2019. The project was conducted to identify all potential autoimmune conditions among GRC members since the inception of the WTCHP and to verify their case status. Lists of search terms were refined over time, and multiple searches of conditions, medications, and combinations of both, were produced to identify all likely self-reported autoimmune conditions in the GRC database. The search terms identified 9163 responders, and physician referrals identified an additional 49 responders with possible autoimmune conditions. A clinically trained team, consisting of an internist, a nurse practitioner, and a research coordinator, followed up on the cases with a higher level of evidence of possible autoimmune disease based on self-reported symptoms and disease-specific medications and treatments (n = 2303; Figure 1). Follow-up was not conducted on 1174 responders for the following reasons: pre-9/11 conditions (n = 260); insufficient indication for further investigation (n = 790); no signed medical release form (n = 6); members who did not provide consent for data aggregation for research (n =11); and other reasons (n = 66). Reported sarcoidosis, which has been previously well investigated, and conditions of lesser physiologic consequence were not included in follow-up (n =30).[25] Table 1 presents the autoimmune domains and conditions encountered.

The clinical review team reached out to the remaining 1140 responders by telephone and/or letters to request their written permission for their treating physicians to share their pertinent medical records. Multiple attempts were made to obtain the requested records.

To reach consensus regarding case status, the clinical review team examined the medical records and, when needed, consulted with appropriate specialists, all of whom were blind to the responders' extent of WTC exposure. Standardized criteria from guidance published by specialty organizations and/or peer-reviewed journals were used to classify case status. Five categories of certainty were assigned, ranging from definite to unlikely (Table 2), based on the available supporting evidence (diagnosis by specialist, disease presentation, physical exam, biopsy, diagnostic procedures, non-serologic laboratory tests, serologies, imaging, highly supportive prescription/treatment, surgery/other major treatment procedure, associated conditions and/or meeting the diagnostic criteria of the specialty organization). Cases in one of the three top categories (definite, highly probable, and probable) were considered confirmed. Specialist judgment was necessary for conditions without standardized guidance (e.g., mixed and/or unclassified connective tissue disease), and the categories with few cases (e.g., other rheumatologic, neurologic, and dermatologic conditions, autoimmune gastritis and/or pernicious anemia, lichen planus; Table 1). When disagreement on case certainty occurred, the more conservative (less certain) status was assigned. While pre-9/11 autoimmune conditions were excluded from analysis, responders with a pre-9/11 autoimmune condition in one organ system who developed an unrelated post-9/11 autoimmune condition in another system were included. The earliest year of diagnosis was specified for each confirmed case. Autoimmune conditions were grouped into six domains: rheumatologic, endocrinologic, gastrointestinal, neurologic, dermatologic, and other major conditions. Results are provided for conditions with ≥10 cases; sex-specific results are provided for conditions where both sexes have ≥10 cases.

2.3 | Study design and objectives

Two study designs were used to assess how GRC WTC exposure is associated with the incidence of autoimmune conditions. Nested case-control analyses were used to estimate the risks associated with high compared with low WTC exposures. Additionally, GRC age- and sex-adjusted incidence rates between 2002 and 2017 were calculated. The GRC standardized incidence rates were compared with similar rates for identical conditions observed in an external population, residents of Olmstead County, MN, identified by the REP to calculate standardized incidence ratios (SIRs). Only one GRC member was diagnosed with an autoimmune condition in the remainder (after 9/11) of 2001. Atypically few GRC cases of autoimmune conditions were diagnosed after 2017 ($n = 7$). Therefore, GRC data were limited to 2002 through 2017, when an annual median of 42.5 cases (interquartile range: 34.8, 49.0) was observed. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc.). Point estimates and 95% CIs are presented.

2.4 | Nested case-control comparison of high and low WTC exposures

Nested case-control analyses were performed using all confirmed cases. Incident density sampling was utilized to match randomly four controls to each case on age (for controls, attained age of the matched cases' year) of diagnosis (±2 years), sex, race/ethnicity and, to account for potential selection biases and disease latency, year of enrollment in the GRC (±2 years). Controls could match to more than one case, and cases could serve as controls before their date of first autoimmune condition diagnosis. Multivariable regression was performed using a semipara-metric Cox procedure to produce conditional likelihoods to estimate the

odds of five of the six autoimmune domains (as too few, e.g., <20 cases were identified to analyze the domain of other major autoimmune conditions). The models were adjusted for the following known risk factors for autoimmune conditions: visit 1 body mass index (BMI) category (<25 referent group, 25 to <30 overweight, ≥30 obese), probable posttraumatic stress disorder (PTSD) diagnosis (for cases, before condition diagnosis), and visit 1 smoking status (never smoker referent group, former smoker, current smoker).[10,52–54] The models were also adjusted for occupation on 9/11/2001 as a surrogate measure of past occupational and occupationally associated environmental exposures.[55] All missing values for BMI (n = 23) and smoking status (n = 20) were replaced with non-missing information from the most recent visit before the date of diagnosis of the case or matching case. As with the FDNY nested case-control analyses, to avoid over-control, our analyses do not adjust for co-morbidities that could be associated with both WTC exposure and autoimmune disease.

GRC members reported whether they were exposed to the dust cloud on the morning of September 11, 2001 and how many days they worked on the WTC rescue and recovery effort from September 11, 2001 to July 30, 2002. The total days of WTC work were dichotomized at the median. Of the 41,168 GRC responders, 1390 had missing dust cloud exposure data and 3786 had incomplete data for response time worked. Those with missing dust cloud exposure data were excluded from the analyses that involved dust cloud exposure (in the matched sample n = 17). Those with incomplete duration data, whose minimum and maximum possible values were both above or both below the median (43 days), were respectively classified as >median and ≤median. The 2549 GRC members who still could not be classified were assigned missing values and (in the matched sample n = 37) excluded from analyses that utilized time worked on the WTC response efforts. High WTC exposure was defined as being in the >median number of days in work duration or being in the dust cloud on the morning of 9/11, regardless of work duration. Low WTC exposure was defined as being ≤median number of days in work duration and with no 9/11 dust cloud exposure. Responders missing both dust cloud and duration exposure information were excluded from the analyses comparing high with low WTC exposure (matched sample n = 32). As sex differences are observed in autoimmune conditions, sex-specific analyses were also performed.[56,57] A sensitivity analysis was conducted, limiting cases to diagnoses after 2004, to further account for potential disease latency. Two additional sensitivity analyses were conducted to assess the associations with the separate components of high and low WTC exposure, work duration, and 9/11 dust cloud exposure.

2.5 | GRC incidence and GRC-to-REP comparisons

Incidence rates adjusted to the US Census 2000 distribution for age and sex were calculated for all GRC autoimmune conditions.[58] Person-years were calculated by counting the time each member of the GRC was at risk within each age group from January 1, 2002 through December 31, 2017. Autoimmune case person-years were calculated through their earliest date of (domain-specific) diagnosis. Person-years for GRC members who did not develop an autoimmune condition were censored at their death, last monitoring visit, or study end date (December 31, 2017), whichever was the earliest date. Age was grouped into 18–29, 30–39, 40–49, 50–59, 60–69, and 70–79. The 95% CIs were calculated using a modified gamma distribution.[59]

Recognized for their high-quality systematic review and validation of a broad array of autoimmune conditions in a large United States population between 1966 and 2017, the Olmsted County, Minnesota, REP population was selected as an external comparison group.[60–63] The population-based data resources of the REP medical record linkage system provide essentially complete ascertainment of all individuals in the community regardless of age, sex, race/ethnicity, insurance status, or care delivery setting (inpatient and outpatient). Using the resources of the REP, for each potential case of autoimmune disease, the complete inpatient and outpatient medical records were systematically reviewed by qualified experts they engaged for each condition. Records were obtained across all care providers, including the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes, and private practitioners. Records documenting diagnoses of the same autoimmune condition on at least two occasions that met established diagnostic criteria were classified as confirmed cases, with the earliest date of confirmed diagnosis for each condition used as the date of diagnosis. Data from special studies of some conditions (multiple sclerosis, dermatomyositis/polymyositis, Hashimoto's thyroiditis, Graves' disease, myasthenia gravis, and psoriasis) were reviewed and validated in the same manner. None of the GRC members were residents of Olmstead County or the six contiguous counties between 2002 and 2017, therefore they would not have been included in the REP comparison population. Comparison with the REP population also allowed determination of whether the risk ratios were consistent with those observed by the FDNY.[17]

The REP provided age- and sex-specific counts of cases and time at risk for conditions (identified in Table 2) identical to those observed in the GRC for which the REP had reasonably stable population rates. The date ranges of the REP cases are generally similar to the GRC, mostly between 2001 and 2018. The date range varied, mostly by starting in 1995, for the following conditions: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, ankylosing spondylitis, mixed connective tissue disease, pemphigoid, ulcerative colitis, and by ending in 2009 for ankylosing spondylitis and pemphigoid. However, as some cases have more than one domain-specific condition and as some conditions have distinct observation periods within a domain, REP domain-specific results are limited to the smallest uniform observation periods across conditions, whereas GRC domain-specific results are 2002–2017 across all individual and aggregate outcome.

Person-years for the GRC were calculated as for the incidence rates. Age-specific and sex-specific incidence rates from the REP were calculated using the number of incident cases as the numerator and population counts from the REP census as the denominator.[58] GRC and REP age- and sex-adjusted rates were compared, and 95% rate ratio CIs were calculated using a lognormal distribution for all autoimmune conditions, 5 autoimmune domains (excluding other major), and 21 individual conditions. As diagnostic date was reported only as a year, age and date of diagnosis were estimated from July 1.

2.6 | Ethics and approval

This investigation follows the principles outlined in the 1975 Declaration of Helsinki revised in 2013 and complies with national and institutional committees' ethical standards on human experimentation. The WTC GRC research is approved by the following Institutional Review

Boards (IRBs): the Icahn School of Medicine at Mount Sinai (formerly Mount Sinai School of Medicine), New York, New York, and its program's other clinical sites: New York University Langone Medical Center, New York University School of Medicine, New York, New York; Department of Medicine, Stony Brook University Medical Center, Stony Brook, New York; Department of Occupational Medicine, Epidemiology and Prevention, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; and Environmental and Occupational Health Sciences Institute, Rutgers University, Piscataway, New Jersey. Deidentified SIRs, exempt from IRB approval, were provided by REP.

3 | RESULTS

Of the 1140 GRC members investigated, 406 (35.6%) were excluded from study(Figure 1: Flow Diagram); 82 (7.2%) of these were later determined to have had pre-9/11 disease onset, an alternative diagnosis or etiology, an autoimmune condition not included as part of the surveillance project, or insufficient information to make a determination. We were unable to obtain records for an additional 324 (28.4%) of these responders. Of the remaining 734 for whom medical records were received, 25 responders were classified as possible but not confirmed cases and excluded from analysis, and 73 were classified as having unlikely or no autoimmune disease. Of the remaining 636 confirmed autoimmune cases, 628 were included for the incidence rates and analyses because all analyses excluded eight cases with confirmed autoimmune diagnoses before 2002 or after 2017.

3.1 | General responder cohort characteristics

Most of the GRC total cohort were male (86%), white (65%), nonsmokers (61%), and had above “normal” BMI (86%; Table 3). Over one-half were engaged in protective (New York Police Department [NYPD], non-NYPD law enforcement, firefighters) or military services on September 11, 2001, and 72% were married at the time of their first monitoring visit. The mean age on September 11, 2001 was 39 years (±9 s.d., standard deviations), ranging from 18 to 79 years old. The average age at diagnosis was 47 years (±9 s.d.), ranging from 23 to 74 years old. Twenty-one percent of the entire GRC were exposed to the 9/11 dust cloud. The median days worked among those with complete data was 43 (range: 1–293), with slightly over one-half the GRC autoimmune cases working more than the median. Sixty-two percent of the GRC were considered high exposure: either exposed to the 9/11 toxic dust cloud or had >median WTC work duration (Table 3). The number of monitoring visits for cases (25th, 50th, and 75% percentiles were 5, 8, and 11) was significantly higher than for non-cases (25th, 50th, and 75% percentiles were 3, 5, and 9), indicating more case than non-case program participation.

3.2 | Incidence of autoimmune conditions in the general responder cohort

The study identified 27 autoimmune conditions across six domains: rheumatologic (n = 11), endocrinologic (n = 2), gastrointestinal (n = 3), neurologic (n = 4), dermatologic (n = 3) and other major autoimmune conditions (n = 4; Table 2). Rheumatologic conditions had the highest domain-specific standardized incidence (73.3/100,000 person-years, 95% CI = 56.6, 94.0) and accounted for 44% of the confirmed autoimmune cases, followed by endocrinologic (24%), gastrointestinal (12%), dermatologic (11%), neurologic (10%), and

other major autoimmune conditions (3%). Four percent of cases experienced more than one condition.

Women's standardized incidence of the most common autoimmune domain (rheumatologic 116/100,000 person-years, 95% CI = 84.5, 160) and the most common rheumatologic condition (rheumatoid arthritis 60.5/100,000 person-years, 95% CI = 35.7, 98.8), were greater than men's (rheumatologic domain 28.4/100,000 person-years, 95% CI = 23.6, 34.6; and rheumatoid arthritis 9.6/100,000 person-years, 95% CI = 7.4, 13.4). The women's-to-men's SIR was 4.1 for the rheumatologic domain (including 6.3 for rheumatoid arthritis), 6.8 for the endocrinologic domain, 1.4 for the gastrointestinal domain, 0.77 for the dermatologic domain, and 0.97 for the neurologic domain. Too few cases were observed in the major other domain to estimate the sex ratio.

3.3 | Nested case-control comparison of high and low WTC exposures

None of the domain- or disease-specific odds ratios were significantly increased or decreased, comparing high with low WTC exposure (Table 4). The odds ratio associated with high compared to low WTC exposure for the rheumatologic domain was 1.03 (95% CI = 0.77, 1.37) and was 1.12 (95% CI = 0.70, 1.77) for rheumatoid arthritis, the autoimmune condition with the highest incidence in the GRC and worldwide. The elevated multiple sclerosis odds ratio was borderline significant (OR = 2.43, 95% CI = 0.99, 5.99).

High WTC exposure was not associated with men's or women's odds of rheumatologic conditions (men's OR = 0.98, 95% CI = 0.70, 1.39; women's OR = 1.24, 95% CI = 0.74, 2.09). With limited numbers of cases, women's domain-specific 95% confidence limits were relatively broad.

Three sensitivity analyses were conducted: defining WTC exposure level using only WTC work duration; WTC exposure level using only 9/11 dust cloud exposure; and limiting cases to those diagnosed after 2004. All produced similar results to the total sample results, with all 95% confidence limits including 1.0 (Table 5).

3.4 | GRC-to-REP comparisons

The GRC had significantly lower rheumatologic relative risks than REP (RR = 0.63, 95% CI = 0.48, 0.83) adjusting by age and sex to the US Census 2000, as did the other four autoimmune condition domains (Table 6). For rheumatoid arthritis, the estimate for both sexes combined was not statistically different from the REP comparison groups (RR = 0.91, 95% CI = 0.60, 1.38). This is true for the other most common rheumatologic conditions outcomes (psoriatic arthritis RR = 0.73, 95% CI = 0.47, 1.14; ANCA-associated vasculitis RR = 0.54, 95% CI = 0.27, 1.12; Sjögren's RR = 0.87, 95% CI = 0.42, 1.79; polymyalgia rheumatica RR = 0.14, 95% CI = 0.06, 0.35; scleroderma RR = 0.64, 95% CI = 0.27, 1.52). Only systemic lupus erythematosus showed a possible elevation in risk (RR = 1.38; 95% CI = 0.85, 2.24). The relative risks for Hashimoto's, Graves', ulcerative colitis, multiple sclerosis, and cutaneous psoriasis were all significantly decreased.

For the most common domain, rheumatologic, GRC-to-REP men's (RR = 0.53, 95% CI = 0.46, 0.62) and women's (RR = 0.77, 95% CI = 0.62, 0.95) relative risks also fell below 1.0.

4 | DISCUSSION

With 16 years of GRC follow-up, our investigation identified a broad array and a large number of confirmed autoimmune cases. We did not find that high WTC exposure (being in the dust cloud or ≥median days of WTC work) was significantly associated with increased risk of rheumatologic or other autoimmune conditions.

The matched, covariate-adjusted nested case-control method was a robust approach that equalized the observation time of the cases and controls, thus minimizing potential selection (including non-ascertainment) and recall/reporting biases. The case review team and diagnosing physicians were all blinded to GRC WTC exposure levels, which were linked after autoimmune diagnosis status had been determined, thus limiting potential diagnostic bias. The study conclusion that our WTC exposure measure/surrogate was not associated with any increase in GRC autoimmune diseases is anchored in our nested case-control analyses, because they have greater internal validity than our comparisons with the external REP cohort.

The FDNY and WTC Health Registry found significantly higher rates of autoimmune conditions in three but not in the remaining four of their seven exposure group comparisons.[16,18] Thus, our nested case-control findings are consistent with some but not all of the FDNY and WTC Health Registry results comparing high to low WTC exposure. Differences in exposure metrics may explain the inconsistencies between our results.

One of the current study's strengths was conducting analyses that matched or standardized on age and sex, bolstered in the case-control analysis by further matching and adjustment of confounders. Our analyses included multiple domain- and condition-specific comparisons using two study designs, including sensitivity analyses. Although ours is the largest study of the effects of WTC exposures on autoimmune conditions, the conditions are relatively rare and almost all of the results had broad confidence limits.[21,22,64] Analyzing the data by domain increased the numbers of responders in each category, but may have obscured the differences observed for individual conditions, which might have distinct etiology. For example, the overall rheumatologic domain-relative risks and odds ratios were lower than that observed for the most common condition, rheumatoid arthritis, and for systemic lupus erythematosus.

The main study limitation was the inability to fully follow up the GRC members identified as possible cases, and this limitation might have led to under-estimation of the GRC autoimmune disease incidence and risk. The FDNY was able to confirm 97 of 217 possible cases (45%) Although some medical records were able, they contained inadequate information for one-half (n = 59) of the 120 for whom case status could not be confirmed.[16,17] The WTC Health Registry was able to ascertain case status for 752 of 1041 (72%) possible cases among members who provided medical record request consent, but were unable to obtain this consent from 1001 (49%) of their 2042 participants reporting an autoimmune condition who completed their autoimmune assessment survey forms (for an overall case ascertainment of 752/2042, e.g., 37%).[18]

Over 9000 possible cases (~22%) of the GRC were identified by our search terms and reviewed by a team of clinically trained professionals. Medical records in our study were obtained for 734 of the 1140 (64%) responders selected for medical records follow-up (Figure 1). How non-ascertainment affected the GRC-to-REP comparisons is unknown.

Compared with the case-control design, the internal validity of the GRC-to-REP comparisons faced a number of challenges. The GRC had significantly lower autoimmune rheumatologic risk compared with the REP (RR = 0.63, 95% CI = 0.48, 0.83), unlike the FDNY finding of no difference (RR = 0.97; 95% CI = 0.77, 1.21).[17] Dissimilarities in sample characteristics, diagnostic criteria, or clinical judgment may explain the difference in results.[21] The GRC comparison with REP were age- and sex- standardized, and the REP data are considered the most generalizable to a majority white population in the United States.[65] The incidence of autoimmune conditions is higher in African-Americans and Hispanics than Whites, in the obese than nonobese, and in some occupations.[6,22,55,66,67] If the GRC-to-REP comparison had been standardized for race/ethnicity or BMI the observed relative risks might be expected to decrease. Standardization for occupational exposure and stress might be expected to increase the relative risks.

Other differences in the GRC comparisons with REP may have also influenced those results. While the GRC and REP cases were both identified using stringent standard criteria agreed upon by ≥2 reviewers, differences in the GRC and REP case-ascertainment and confirmation processes might have influenced the observed incidence in unknown ways. The REP domain-specific data were limited to the smallest uniform observation time periods across conditions, while the GRC domain-specific observation periods were not limited to avoid estimate instability. The incidence and prevalence of autoimmune conditions have increased over time, varying by geographic location, race/ethnicity, and sex, although the absolute change is limited as the conditions are relatively rare.[21,22,64] Therefore, comparing dissimilar, but overlapping time periods should not substantially influence the domain-specific estimates.[61,68] Supporting the validity of our findings, the relative risk for rheumatoid arthritis was not significantly different between the GRC and REP cohorts (RR = 0.91, 95% CI = 0.60, 1.38) and was similar to the FDNY-to-REP rheumatoid arthritis relative risk (RR = 0.91, 95% CI = 0.65, 1.24). Although not statistically significant, the GRC-to-REP systemic lupus erythematosus comparison was in the same direction as that observed by the FDNY.[17]

Similar to the WTC Health Registry observation that women had three to five times the risk of rheumatologic conditions as men, GRC women had 4.1 times the incidence of men's rheumatologic conditions.[18] In a review of autoimmune condition prevalence, strong sexual dimorphism was only observed in about half of the 47 female-predominant autoimmune conditions, with the strongest female predominance among the most prevalent autoimmune conditions.[64] Consistent with this observation, the GRC women's incidence was substantially greater than men's in the most common autoimmune domains and similar or less than men's in the less common domains.

Between 2002 and 2017, the crude GRC rheumatoid arthritis incidence of 19.7/100,000 person-years, the most common autoimmune condition and thus likely to have been the most

reliably measured, was fairly comparable to the 2003 North American annual incidence for both sexes (23.7/100,000 person-years), as only 15% of GRC were female whereas approximately half of adults in the United States are women.[10] Given gender dimorphism, as expected, men's GRC incidence of rheumatoid arthritis (9.6, 95% CI = 7.4, 13.4) was lower than women's (60.5, 95% CI = 35.7, 98.8). In contrast, FDNY men's rheumatoid arthritis incidence (19.1/100,000 person-years), was similar to the national average for men and women combined. The FDNY men's incidence of rheumatoid arthritis was twice as high as then men's GRC incidence possibly due to differences in study methods or due to different exposures (e.g., firefighter's lifetime smoke and fire-associated exposures).[10,17,57]

Common to many environmental research studies, surrogate exposure measures were used in the current study. Environmental exposures found in the settled dust and smoke emanating from the attack on the WTC that have been potentially associated with autoimmune conditions[4,13,16–18] were represented by dichotomous variables based on having been in the September 11, 2001 dust cloud, as well as being above or at/below the median duration of WTC work. These surrogate indices of WTC exposure have identified increased incidence rates of respiratory, gastrointestinal, cardiovascular, and mental health disorders.[7–9] Nevertheless, the indirect nature of these variables could obscure responders' individual exposures to the toxic elements contained in WTC dust and smoke, challenging the ability to identify significant associations with autoimmune morbidity.

Pooling the FDNY, non-GRC WTC Health Registry and GRC rheumatologic data would provide larger and more stable estimates of the effects of WTC exposure. Although the age at autoimmune condition diagnosis was generally similar or greater than that observed internationally, given the evolving nature of autoimmune conditions, a reassessment of the influence of WTC exposure in the future might be merited to better account for disease latency.[27,39,40,42–44,50,69]

ACKNOWLEDGMENTS

The authors wish to thank Htut Naing Soe, MD, MPH and Kalyan Chilukuri, MD, MPH for their participation in case review. The authors thank the staff of the World Trade Center (WTC) Worker and Volunteer Medical Screening, Medical Monitoring and Treatment, and Health Programs; the labor, community and volunteer organization stakeholders; and the WTC rescue and recovery workers, who gave of themselves so readily in response to the WTC attacks and to whom the WTC Health Program is dedicated. The relevant data are available within the manuscript. This study was supported by the Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (cooperative agreements and contracts 200-2002-00384, U10-OH008216/23/25/32/39/75, 200-2011-39356/61/77/84/85/88, and 200-2017-93325).

Funding information

National Institute for Occupational Safety and Health, Grant/Award Numbers: 200-2017-93325, 200-2002-00384, 200-2011-39356/61/77/84/85/88, U10-OH008216/23/25/32/39/75

DISCLAIMER

The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the National Institute for Occupational Safety and Health.

DATA AVAILABILITY STATEMENT

The relevant data are available within the manuscript.

REFERENCES

1. Smith DA, Germolec DR. Introduction to immun autoimmunity. Environ Health Perspect. 1999;107(Suppl 5): S661–6S665.
2. Powell JJ, Van de Water J, Gershwin ME. Evidence for the role of environmental agents in the initiation or progression of autoimmune conditions. Environ Health Perspect. 1999;107(Suppl 5):S667–S672.
3. Schmidt CW. Environmental factors in autoimmune disease. Environ Health Persp. 2011;119(6):A249–A253.
4. Lioy PJ, Weisel CP, Millette JR, et al. Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC 11 September 2001. Environ Health Perspect. 2002;110(7):703–714. [PubMed: 12117648]
5. Howard J Development of the Inventory of 9/11 Agents: NIOSH; 2018. https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf
6. Stojanovich L, Marisavljevich D. Stress as a trigger of autoimmune disease. Autoimmun Rev 2008;7(3):209–213. [PubMed: 18190880]
7. Gargano LM, Caramanica K, Sisco S, Brackbill RM, Stellman SD. Exposure to the World Trade Center Disaster and 9/11-related posttraumatic stress disorder and household disaster preparedness. Disaster Med Public 2015;9(6):625–633.
8. Sloan NL, Shapiro MZ, Sabra A, et al. Cardiovascular disease in the World Trade Center health program general responder cohort. Am J Ind Med. 2021;64(2):97–107. [PubMed: 33315266]
9. Wisnivesky JP, Teitelbaum SL, Todd AC, et al. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. Lancet. 2011;378(9794):888–897. [PubMed: 21890053]
10. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev. 2003;2(3):119–125. [PubMed: 12848952]
11. Floreani A, Leung PSC, Gershwin ME. Environmental basis of autoimmunity. Clin Rev Allerg Immuol. 2016;50(3):287–300.
12. Zhao CN, Xu Z, Wu GC, et al. Emerging role of air pollution in autoimmune diseases. Autoimmun Rev 2019;18(6):607–614. [PubMed: 30959217]
13. Miller FW, Alfredsson L, Costenbader KH, et al. Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. J Autoimmun. 2012;39(4):259–271. [PubMed: 22739348]
14. Ritz SA. Air pollution as a potential contributor to the ‘epidemic’ of autoimmune disease. Med Hypotheses. 2010;74(1):110–117. [PubMed: 19665849]
15. Selmi C, Lu Q, Humble MC. Heritability versus the role of the environment in autoimmunity. J Autoimmun. 2012;39(4):249–252. [PubMed: 22980030]
16. Webber MP, Moir W, Zeig-Owens R, et al. Nested case-control study of selected systemic autoimmune diseases in World Trade Center rescue/recovery workers. Arthritis Rheumatol. 2015;67(5): 1369–1376. [PubMed: 25779102]
17. Webber MP, Moir W, Crowson CS, et al. Post-September 11, 2001, incidence of systemic autoimmune diseases in World Trade Centerexposed firefighters and emergency medical service workers. Mayo Clin Proc. 2016;91(1):23–32. [PubMed: 26682920]
18. Miller-Archie SA, Izmirly PM, Berman JR, et al. Systemic autoimmune disease among adults exposed to the September 11, 2001 terrorist attack. Arthritis & Rheumatol. 2020;72(5):849–859.
19. New York City. 9/11 Health. Rescue and Recovery Workers: City of New York; 2019. https://www1.nyc.gov/site/911health/enrollees/rescue-recovery-workers.page

20. Committee NTADC. Progress in Autoimmune Diseases Research. NIH Publication No. 05–5140. 2005: U.S. Department of Health and Human Services; 2005. cited 2019. https://www.niaid.nih.gov/sites/default/files/adccfinal.pdf
21. Lerner AJM, Mattias T. The world incidence and prevalence of autoimmune diseases is increasing. Int J Celiac Dis. 2015;3(4):151–155.
22. Roberts MH, Erdei E. Comparative United States autoimmune disease rates for 2010–2016 by sex, geographic region, and race. Autoimmun Rev 2020;19(1):102423. [PubMed: 31733367]
23. Dasaro CR, Holden WL, Berman KD, et al. Cohort profile: World Trade Center health program general responder cohort. Int J Epidemiol 2017;46(2):e9. [PubMed: 26094072]
24. Moline JM, Herbert R, Levin S, et al. WTC medical monitoring and treatment program: comprehensive health care response in aftermath of disaster. Mt Sinai J Med. 2008;75(2):67–75. [PubMed: 18500708]
25. Hena KM, Murphy S, Zhang Y, Shao Y, Kazeros A, Reibman J. Clinical evaluation of sarcoidosis in community members with World Trade Center dust exposure. Int J Environ Res Public Health. 2019;16(7).
26. Kay JUS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology. 2012;51:vi5–vi9. [PubMed: 23221588]
27. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665–2673. [PubMed: 16871531]
28. Aringer M, Costenbader K, Daikh D, et al. European league against rheumatism/American college of rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78(9): 1151–1159. [PubMed: 31383717]
29. Pepmueller PH. Undifferentiated connective tissue disease, mixed connective tissue disease, and overlap syndromes in rheumatology. Mo Med. 2016;113(2):136–140. [PubMed: 27311225]
30. Tanaka Y, Kuwana M, Fujii T, et al. Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases. Mod Rheumatol 2019;31(1):29–33.
31. Rudwaleit M, van de Heijde D, Landewe R. The development of assessment of SpondyloArthritis international society classification criteria for axial spondyloarthritis (part II): validation and final selection (vol 68, pg 777, 2009). Ann Rheum Dis. 2019;78(6).
32. Akgul O, Ozgocmen S. Classification criteria for spondyloarthropathies. World J Orthop. 2011;2(12):107–115. [PubMed: 22474629]
33. Robson JC, Grayson PC, Ponte C, et al. Draft classification criteria for the ANCA associated vasculitides. Am Rheum Dis 2018:60–61.
34. Hunder GG, Bloch DA, Michel BA, et al. The American-College-of-Rheumatology 1990 criteria for the classification of giant-cell arteritis. Arthritis Rheum. 1990;33(8):1122–1128. [PubMed: 2202311]
35. Nesher G The diagnosis and classification of giant cell arteritis. J Autoimmun. 2014;48–49:73–75.
36. Shiboski CH, Shiboski SC, Seror R, et al. American College of Rheumatology/European League against rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2016;69(1):35–45. [PubMed: 27785888]
37. Dasgupta B, Cimmino MA, Maradit-Kremers H, et al. Provisional classification criteria for polymyalgia rheumatica: a European League against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012;71(4):484–492. [PubMed: 22388996]
38. van den Hoogen F, Khanna D, Fransen J, et al. Classification criteria for systemic sclerosis: an ACR-EULAR collaborative initiative. Arthritis Rheum. 2013;65(11):2737–2747. [PubMed: 24122180]
39. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2): 295–306. [PubMed: 16420554]

40. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13:391–397. [PubMed: 24434360]
41. Menconi F, Marcocci C, Marinò M. Diagnosis and classification of Graves' disease. Autoimmun Rev 2014;13:398–402. [PubMed: 24424182]
42. Bernstein CN, Eliakim A, Fedail S, et al. World Gastroenterology Organisation global guidelines inflammatory bowel disease: update August 2015. J Clin Gastroenterol. 2016;50(10):803–818. [PubMed: 27741097]
43. Laass M Diagnosis and classification of Crohn's disease. Autoimmun Rev. 2014;13:467–471. [PubMed: 24424189]
44. Conrad K, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. Autoimmun Rev 2014;13(4–5):463–466. [PubMed: 24424198]
45. Bizzaro N, Antico A. Diagnosis and classification of pernicious anemia. Autoimmun Rev 2014;13(4–5):565–568. [PubMed: 24424200]
46. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50(1):121–127. [PubMed: 11456302]
47. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–173. [PubMed: 29275977]
48. Koski CL, Baumgarten M, Magder LS, et al. Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. J Neurol Sci. 2009;277(1–2):1–8. [PubMed: 19091330]
49. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards (Reprinted from Neurology, vol 55, pg 16–23, 2000). Ann Thorac Surg 2000;70(1):327–334. [PubMed: 10921745]
50. Kuhn A, Meuth AM, Bein D, et al. Revised cutaneous lupus erythematosus disease area and severity index (RCLASI): a modified outcome instrument for cutaneous lupus erythematosus. Br J Dermatol. 2010;163(1):83–92. [PubMed: 20394621]
51. Kuhn A, Landmann A. The classification and diagnosis of cutaneous lupus erythematosus. J Autoimmun. 2014;48–49:14–19.
52. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol. 1997;84(3):223–243. [PubMed: 9281381]
53. Song H, Fang F, Tomasson G, et al. Association of stress-related disorders with subsequent autoimmune disease. JAMA. 2018; 319(23):2388–2400. [PubMed: 29922828]
54. Parks CG, Conrad K, Cooper GS. Occupational exposure to crystalline silica and autoimmune disease. Environ Health Persp. 1999;107: 793–802.
55. Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. Int Immunopharmacol. 2002;2(2–3):303–313. [PubMed: 11811933]
56. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2019;56(3):308–321. [PubMed: 28963611]
57. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347–369. [PubMed: 24793874]
58. Bureau USC. Decennial Census 2000 Sex by Age [49] Table P012: United States Census Bureau; 2000. https://data.census.gov/cedsci/table?q=age%20sex&y=2000&d=DEC%20Summary%20File%201&tid=DECENNIALSF12000.P012&moe=true&tp=false&hidePreview=false
59. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. Stat Methods Med Res. 2006;15(6):547–569. [PubMed: 17260923]
60. Andersen LK, Davis MDP. The epidemiology of skin and skin-related diseases: a review of population-based studies performed by using the Rochester Epidemiology Project. Mayo Clin Proc. 2013;88(12): 1462–1467. [PubMed: 24290120]
61. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58(1):15–25. [PubMed: 18163481]

62. Kremers HM, Myasoedova E, Crowson CS, Savova G, Gabriel SE, Matteson EL. The Rochester Epidemiology Project: exploiting the capabilities for population-based research in rheumatic diseases. Rheumatology. 2011;50(1):6–15. [PubMed: 20627969]

63. St Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. Int J Epidemiol. 2012;41(6):1614–1624. [PubMed: 23159830]

64. Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmun Rev. 2012;11(10):754–765. [PubMed: 22387972]

65. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004–2014. Rheumatol Int 2017;37(9):1551–1557. [PubMed: 28455559]

66. Committee. NIoHTADC. Progress in Autoimmune Diseases Research. Diseases NIoAaI, editor. Bethesda: U.S. Department of Health and Human Services; 2005.

67. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev. 2014; 13(9):981–1000. [PubMed: 25092612]

68. Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011;63(3):633–639. [PubMed: 21360492]

69. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases?. Autoimmune Dis 2012:2012.

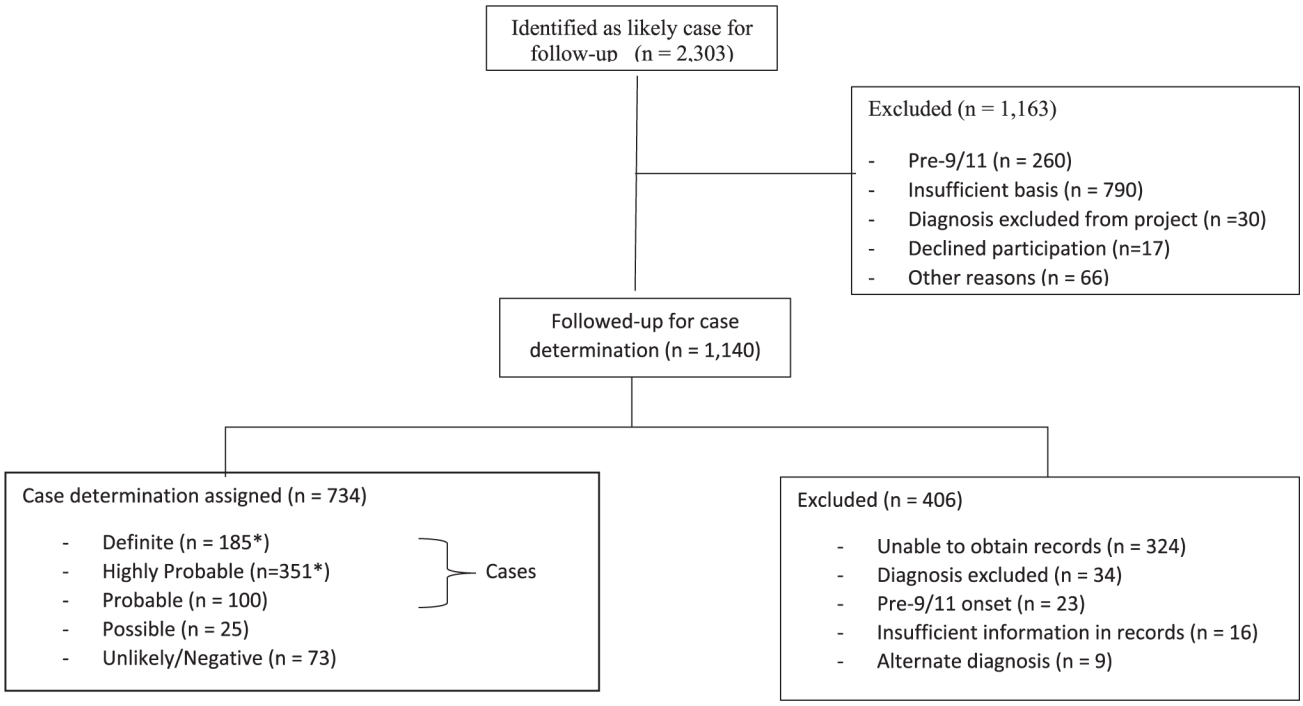

FIGURE 1.

Flow diagram of autoimmune case determination among WTC general responders. *Two definite and six highly probable cases diagnosed in 2001, 2018, or 2019 excluded from analyses

TABLE 1

Crude and standardized WTC Health Program General Responder Cohort autoimmune incidence rates/ 100,000 person years and diagnostic criteria references

Autoimmune Domains and Conditions (Criteria Reference)	N[a]	Crude rate (per 100,000)	Standardized rate[b] (95% CI) (per 100,000)
Rheumatologic [c]	274	49.2	73.3 (56.6, 94.0)
Rheumatoid arthritis RA[26,d]	110	19.7	35.6 (22.6, 53.3)
Psoriatic arthritis PsA[27,d]	44	7.9	5.0 (3.2, 12.0)
Systemic lupus erythromatosis SLE[28,d]	26	4.7	8.3 (5.0, 16.2)
Connective tissue diseases[29,30,e]	25	4.5	12.4 (5.5, 24.6)
Spondylarthropathies[31,32,d,f]	22	3.9	2.7 (1.4, 9.8)
Vasculitis[33–35,d,g]	16	2.9	1.6 (0.8, 8.9)
Sjögren's[36,d]	12	2.1	4.9 (2.2, 13.0)
Polymyalgia rheumatica PMR[37,d]	12	2.1	2.7 (0.8, 10.4)
Scleroderma[38,d]	10	1.8	1.6 (0.6, 9.1)
Antiphospholipid syndrome APLS[39,d]	NP[a]	NP[a]	0.9 (0.3, 8.4)
Other (Myositis polymyositis relapsing polychondritis)[39,d,e,h]	NP[a]	NP[a]	0.4 (0.0, 8.2)
Endocrinologic Conditions [c]	154	27.6	48.9 (35.1, 66.9)
Hashimoto's[40,d]	103	18.5	36.9 (23.9, 54.6)
Graves'[41,d]	52	9.3	12.0 (8.2, 19.9)
Gastrointestinal Conditions [c]	74	13.3	13.9 (9.3, 22.6)
Crohn's[42,43,d]	36	6.4	7.8 (4.4, 16.0)
Ulcerative colitis UC[42,44,d]	30	5.4	3.7 (2.0, 10.9)
Autoimmune gastritis and/or pernicious anemia[45,e,h]	NP[a]	NP[a]	2.4 (0.7, 10.2)
Neurologic Conditions [c]	65	11.6	13.1 (8.7, 21.6)
Multiple sclerosis[46,47,d]	47	8.4	9.1 (5.6, 17.1)
Chronic inflammatory demyelinating polyneuropathy[48,h]	12	2.1	3.5 (1.3, 11.3)
Myasthenia gravis[49,d]	4[a]	0.7[a]	0.4 (0.1, 8.1)
Other[e,h]	2[a]	0.4[a]	0.1 (0.0, 8.0)
Dermatologic Conditions [c]	71	12.7	8.0 (5.5, 15.1)
Cutaneous psoriasis[d,i]	58	10.4	5.6 (3.6, 12.6)
Cutaneous lupus[50,51,d]	NP[a]	NP[a]	2.1 (0.8, 9.5)
Other[d,h]	NP[a]	NP[a]	0.3 (0.1, 8.1)
Other Major Conditions [c,h]	19	3.4	2.9 (1.1, 10.4)

Autoimmune Domains and Conditions (Criteria Reference)	N[a]	Crude rate (per 100,000)	Standardized rate[b] (95% CI) (per 100,000)
Renal[d,h]	NP[a]	NP[a]	1.2 (0.2, 8.9)
Hematologic[d,h]	NP[a]	NP[a]	0.4 (0.1, 8.1)
Hepatic[d,h]	NP[a]	NP[a]	0.5 (0.1, 8.2)
Ocular[h]	NP[a]	NP[a]	0.8 (0.0, 8.6)

[a] Numbers not presented (NP) due to small numbers.

[b] Age- and sex-adjusted to the U.S. Census 2000, ages 18–79 (N = 199,943,140).

[c] Cases are not mutually exclusive; 14 responders had multiple conditions within a domain, and 26 had multiple conditions across distinct domains.

[d] Diagnosis by specialist.

[e] Subset of mixed connective tissue disease included in REP comparison.

[f] Subset of mixed ankylosing spondylitis included in REP comparison.

[g] Subset of mixed ANCA associated vasculitis and giant cell arteritis included in REP comparison.

[h] Not included in GRC-Rochester Epidemiology Project (REP) comparison as no parallel REP data for the condition.

[i] Diagnosis by monitoring program clinical review team.

TABLE 2

Clinical criteria used to classify autoimmune conditions

Definite	Guidance documents explicitly describe the presence of specific elements, often summarized in a checklist, binary or numerical format, that can yield a definite determination. A condition confirmed by biopsy is also considered a gold-standard, definite determination.
Highly probable	Guidance documents have a range of possible presentations with fewer explicitly described diagnostic criteria, for which a highly probable determination is most appropriate.
Probable	Medical records do not include all required elements of the classification criteria but have sufficient data to presume diagnosis. Elements of information that must be present include: specialist physician confirms diagnosis; member is on appropriate, specific medication; history of appropriate testing has been given, although results may not be available, and member articulates a cogent history.
Possible	Medical record evidence suggests an autoimmune condition; however, confirmatory data are insufficient to qualify according to classification criteria, i.e., a key laboratory result not available, treatment information unknown, symptom burden inconclusive. This may be because the definition of the clinical condition is evolving, and determination may change in the future.
Unlikely or negative	Insufficient evidence to support an autoimmune condition diagnosis; the diagnosis is considered ruled-out.
Pre 9/11	Determination was made that symptoms or conditions predate 9/11, even if diagnosis is reported as post-9/11.
Unable to determine	Insufficient information is available to either support or rule out the diagnosis. This includes instances of a credible history given by the member, but corroborating medical records are not available. These instances are not considered ruled-out, and their determination status may change if more information becomes available.

Note: Confirmation of diagnoses was based on standard classification criteria of the relevant professional organizations and published consensus guidelines or, as necessary, on expert review (Table 1). The standard diagnostic criteria are reproducible and peer-reviewed.

TABLE 3

WTC general responder cohort (GRC) and Rochester Epidemiology Project (REP) sample characteristics for all autoimmune conditions

	GRC total cohort	GRC autoimmune cases	REP autoimmune cases
	n **(%)**	***n*** **(%)**	***n*** **(%)**
Age (years) [a,b]	41,168	628	3862
18–29	6071 (14.8)	11 (1.8)	531 (13.7)
30–39	17,965 (43.6)	128 (20.4)	646 (16.7)
40–49	12,297 (29.9)	238 (37.9)	771 (20.0)
50–59	4170 (10.1)	190 (30.3)	687 (17.8)
60–79	665 (1.6)	61 (9.7)	950 (24.6)
Sex	41,168	628	3862
Female	5631 (13.7)	191 (30.4)	2627 (68.0)
Male	35,537 (86.3)	437 (69.6)	1235 (32.0)
Race/ethnicity	41,168	628	3862
White not Hispanic	26,880 (65.3)	452 (72.0)	3372 (87.3)
Black, not Hispanic	4527 (11.0)	44 (7.0)	98 (2.5)
Hispanic	8036 (19.5)	108 (17.2)	83 (2.1)
Other, not reported or not Hispanic	1725 (4.2)	24 (3.9)	309 (8.0)
Cigarette smoking at first visit [c]	40,963	627	3761
Never	24,926 (60.9)	349 (55.7)	1664 (44.2)
Former	10,477 (25.6)	205 (32.7)	2097 (55.8)
Current	5560 (13.6)	73 (11.6)	
Body mass index kg/m^2 at first visit [c]	40,943	628	3664
<25 normal	5708 (13.9)	104 (16.5)	1270 (34.7)
25 to <30 overweight	17,070 (41.7)	250 (39.8)	1218 (33.2)
≥30 obese	18,165 (44.4)	274 (43.6)	1176 (32.1)
Occupation on 9/11/2001	40,425	618	
Protective services/military	20,862 (51.6)	353 (57.1)	
Construction occupations	7436 (18.4)	79 (12.8)	
Electric, telecom, and other installation/repair	2715 (6.7)	53 (8.6)	
Transportation and material moving	2148 (5.3)	20 (3.2)	

	GRC total cohort	GRC autoimmune cases	REP autoimmune cases
	***n* (%)**	***n* (%)**	***n* (%)**
Other jobs	5304 (13.1)	87 (14.1)	
Unknown/unemployed/retired	1960 (4.8)	26 (4.2)	
Marital status at first visit [c]	39,029	605	
Single	5766 (14.8)	87 (14.4)	
Married or partnered	27,905 (71.5)	448 (74.1)	
Separated or divorced/widowed	5358 (13.8)	70 (11.6)	
WTC dust cloud exposure	39,778	611	
On 9/11 in dust cloud	8289 (20.8)	135 (22.1)	
Not in 9/11 dust cloud	31,489 (79.2)	476 (77.9)	
WTC work duration exposure	38,619	591	
≥Median days worked (>43 days)	20,139 (52.2)	308 (52.1)	
<Median days worked (<43 days)	18,480 (47.9)	283 (47.9)	
Composite WTC exposure	38,617	596	
High exposure (in dust cloud or ≥median days worked in response)	23,792 (61.6)	378 (63.4)	
Low exposure (not in 9/11 dust cloud & <median days worked in response)	14,825 (38.4)	218 (36.6)	
Year of WTCHP/GRC enrollment	41,161	628	
≤2007	21,948 (53.3)	324 (51.6)	
2008–2013	10,362 (25.2)	172 (27.4)	
≥2014	8851 (21.5)	132 (21.0)	
Minimum, maximum number of GRC monitoring visits	1, 16	1, 16	
25th percentile number of GRC monitoring visits	3	5	
50th percentile number of GRC monitoring visits	5	8	
75th percentile number of GRC monitoring visits	9	11	

Note: GRC data observation period 2002–2017.

[a] Age on 9/11 for total cohort.

[b] Age at diagnosis for autoimmune cases.

[c] First visit may be after diagnosis with an autoimmune condition.

TABLE 4

Nested case-control analysis of WTC exposure and odds ratio of autoimmune condition diagnosed 2002–2017 among the WTC general responder cohort[a]

	In 9/11 dust cloud or >median number of days of WTC work versus not in 9/11 dust cloud and ≤median number of days of WTC work								
	Both sexes			Men			Women		
Autoimmune domains	**Odds ratio (95% CIs)**	***n* cases**	***n* controls**	**Odds ratio (95% CIs)**	***n* cases**	***n* controls**	**Odds ratio (95% CIs)**	***n* cases**	***n* controls**
Rheumatologic	1.03 (0.77, 1.37)	263	1048	0.98 (0.70, 1.39)	172	688	1.24 (0.74, 2.09)	91	360
Rheumatoid arthritis	1.12 (0.70, 1.77)	105	420	0.96 (0.54, 1.69)	65	260	1.28 (0.53, 3.10)	40	160
Psoriatic arthritis	0.52 (0.23, 1.15)	41	162	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Systemic lupus erythematosus	1.12 (0.44, 2.87)	26	104	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Connective tissue diseases	1.78 (0.59, 5.35)	24	96	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Spondylarthropathies	0.65 (0.18, 2.31)	21	84	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Vasculitis	0.40 (0.09, 1.72)	16	64	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Sjögren's	5.33 (0.71, 40.23)	12	48	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Polymyalgia rheumatica	1.79 (0.38, 8.42)	11	42	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Scleroderma	3.78 (0.47, 30.16)	10	40	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Endocrinologic	0.88 (0.60, 1.29)	149	593	0.99 (0.58, 1.71)	80	320	0.76 (0.44, 1.32)	69	273
Hashimoto's	1.03 (0.65, 1.66)	101	401	1.59 (0.80, 3.19)	55	220	0.69 (0.34, 1.42)	46	181
Graves'	1.44 (0.72, 2.87)	49	196	1.39 (0.54, 3.59)	26	104	2.12 (0.56, 7.95)	23	92
Gastrointestinal	1.60 (0.87, 2.95)	72	285	1.24 (0.62, 2.47)	58	232	2.69 (0.36, 9.96)	14	53
Crohn's	1.04 (0.44, 2.42)	34	136	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Ulcerative colitis	2.13 (0.68, 6.66)	30	120	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Neurologic	1.64 (0.87, 3.12)	59	236	1.33 (0.64, 2.77)	45	180	2.78 (0.35, 22.13)	14	56
Multiple sclerosis	2.43 (0.99, 5.99)	43	172	2.12 (0.77, 5.87)	33	132	NP[b]	10	40
Chronic inflammatory demyelinating polyneuropathy	1.16 (0.14, 9.51)	12	48	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Dermatologic	1.1 (0.62, 1.96)	65	260	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]
Cutaneous psoriasis	0.99 (0.51, 1.93)	53	212	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]	NP[b]

[a] Adjusted for BMI, occupation on September 11, 2001, race, cigarette smoking status, and prior PTSD.

[b] Not presented (NP) due to small numbers ($n \leq 10$) in both sexes or in either male or female sex or model did not converge.

TABLE 5

Sensitivity analysis: Nested case-control analyses of WTC exposure and odds ratio of autoimmune conditions among the WTC general responder cohort[a]

	Autoimmune condition diagnosis period 2002–2017						Autoimmune condition diagnosis period 2005–2017		
	In 9/11 dust cloud versus not in 9/11 dust cloud exposure			>median versus ≤median duration of WTC work duration			In 9/11 dust cloud or >median duration of WTC work duration versus not in 9/11 dust cloud and ≤median work duration		
Autoimmune domains	**Odds ratio(95% CIs)**	***n* cases**	***n* controls**	**Odds ratio (95% CIs)**	***n* cases**	***n* controls**	**Odds ratio (95% CIs)**	***n* cases**	***n* controls**
Rheumatologic	1.11 (0.79, 1.56)	267	1066	1.01 (0.77, 1.34)	261	1040	1.01 (0.75, 1.37)	232	924
Endocrinologic	1.05 (0.68, 1.65)	152	605	1.06 (0.73, 1.56)	146	581	1.02 (0.68, 1.53)	135	537
Gastrointestinal	0.99 (0.50, 1.95)	72	285	1.16 (0.65, 2.06)	71	281	1.12 (0.58, 2.15)	59	233
Neurologic	1.54 (0.80, 2.98)	61	244	1.17 (0.65, 2.09)	60	240	1.10 (0.57, 2.14)	52	208
Dermatologic	1.20 (0.62, 2.33)	69	276	1.24 (0.70, 2.21)	65	260	1.33 (0.70, 2.52)	56	224

[a]Adjusted for body mass index, occupation on September 11, 2001, race, cigarette smoking status, and prior posttraumatic stress disorder.

TABLE 6

WTC general responder cohort and Rochester Epidemiology Project Relative Risks[a]

		GRC[b]		REP		
Domain	**RR (95% CI)[b]**	**Person-years[b]**	***n* cases[b]**	**Person-years**	***n* cases**	**REP data period**
Rheumatologic [c]	0.63 (0.48, 0.83)	557,218	235	902,872	816[c]	2001–2009
Rheumatoid arthritis	0.91 (0.60, 1.38)	558,127	110	1,445,791	561	2001–2014
Psoriatic arthritis	0.73 (0.47, 1.14)	558,524	44	1,787,029	120	2001–2014
Systemic lupus erythematosus	1.38 (0.85, 2.24)	558,685	26	1,903,698	115	2001–2018
Mixed connective tissue disease	NP[d]	NP[d]	NP[d]	NP[d]	NP[d]	1995–2014
Ankylosing spondylitis	NP[d]	NP[d]	NP[d]	NP[d]	NP[d]	1995–2009
ANCA-associated vasculitis	0.54 (0.27, 1.12)	558,762	16	1,997,007	49	1996–2015
Giant cell arteritis	NP[d]	NP[d]	NP[d]	NP[d]	NP[d]	2001–2018
Sjögren's	0.87 (0.42, 1.79	558,773	12	1,649,760	93	2000–2015
Polymyalgia rheumatica	0.14 (0.06, 0.35)	558,792	12	1,445,791	257	2001–2014
Scleroderma	0.64 (0.27, 1.52)	558,739	10	2,425,941	62	1995–2018
Endocrinologic [c]	0.29 (0.21, 0.40)	557,783	154	1,879,359	3171[c]	2000–2017
Hashimoto's	0.52 (0.35, 0.77)	558,143	103	1,879,359	1342	2000–2017
Graves'	0.12 (0.08, 0.16)	558,489	52	1,879,359	1946	2000–2017
Gastrointestinal [c]	0.42 (0.28, 0.62)	558,329	66	1,116,402	308[c]	2001–2011
Crohn's	0.64 (0.38, 1.10)	558,559	36	1,116,402	137	2001–2011
Ulcerative colitis	0.24 (0.14, 0.42)	558,620	30	1,116,402	171	2001–2011
Neurologic [c]	0.46 (0.30, 0.70)	558,454	51	1,879,359	392[c]	2000–2017
Multiple sclerosis	0.50 (0.32, 0.77)	558,471	47	1,879,359	345	2000–2017
Dermatologic [c]	0.07 (0.05, 0.10)	558,337	67	1,879,359	2034[c]	2000–2017
Cutaneous psoriasis	0.05 (0.04, 0.08)	558,374	58	1,879,359	1933	2000–2017

[a] Age- and sex-adjusted to the US Census 2000, ages 18–79.

[b] GRC data observation period 2002–2017.

[c] Condition-specific case and person-year numbers are not additive across conditions as some cases have >1 domain-specific condition and as REP data observation periods vary by condition, with REP domain-specific results limited to the smallest uniform observation periods across conditions in each domain. Domain case numbers are different from those presented in Table 1 for conditions for which REP did not have parallel data.

[d] Not presented as case $n < 10$. Conditions with total case count <10 (antiphospholipid syndrome REP observation period 2000–2015 and other rheumatologic conditions REP observation period 2000–2017) not presented.

Am J Ind Med. Author manuscript; available in PMC 2022 February 17.