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ONE AIRWAY: BIOMARKERS OF PROTECTION FROM UPPER AND LOWER AIRWAY INJURY AFTER WORLD TRADE CENTER EXPOSURE

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Abstract

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Background—Firefighters exposed to World Trade Center (WTC) dust have developed chronic rhinosinusitis (CRS) and abnormal forced expiratory volume in 1 second (FEV_1). Overlapping but distinct immune responses may be responsible for the clinical manifestations of upper and lower airway injury. We investigated whether a panel of inflammatory cytokines, either associated or not associated with WTC-LI, can predict future chronic rhinosinusitis disease and its severity.

Methods—Serum obtained within six months of 9/11/2001 from 179 WTC exposed firefighters presenting for subspecialty evaluation prior to 3/2008 was assayed for 39 cytokines. The main outcomes were medically managed CRS (N=62) and more severe CRS cases requiring sinus surgery (N=14). We tested biomarker-CRS severity association using ordinal logistic regression analysis.

Results—Increasing serum IL-6, IL-8, GRO and neutrophil concentration reduced the risk of CRS progression. Conversely, increasing TNF-α increased the risk of progression. In a multivariable model adjusted for exposure intensity, increasing IL-6, TNF-α and neutrophil concentration remained significant predictors of progression. Elevated IL-6 levels and neutrophil counts also reduced the risk of abnormal FEV_1 but in contrast to CRS, increased TNF-α did not increase the risk of abnormal FEV_1.

Conclusions—Our study demonstrates both independent and overlapping biomarker associations with upper and lower respiratory injury, and suggests that the innate immune response may play a protective role against CRS and abnormal lung function in those with WTC exposure.

Keywords

one airway; chronic rhinosinusitis; World Trade Center; innate immunity

INTRODUCTION

The World Trade Center (WTC) collapse produced vast quantities of respirable dust affecting Fire Department of New York (FDNY) rescue workers, other exposed workers, lower Manhattan residents and children (1–6). WTC dust was alkaline (pH, 9.2–11.5) and was comprised of metals, radionuclides, ionic species, asbestos, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzodioxines and other potentially hazardous materials. The bulk of WTC particulate matter (PM) was larger than 10μm, which usually is filtered in the nasopharynx (7). However, the body's usual protective barriers were overwhelmed, producing intense dust exposure to both the upper and lower airways. (2).

A high incidence of upper and lower airway respiratory disorders has persisted in WTC exposed firefighters years after 9/11 (8). Chronic rhinosinusitis (CRS) has been the most common manifestation of upper airway injury in this population. Prior to 9/11, only 4.4% of FDNY firefighters reported rhinosinusitis symptoms. By one year after 9/11, self-reported rhinosinusitis symptoms had increased 10-fold (45.1%) and persisted above 30% well into the fifth year after 9/11 (9, 10). Numerous disability claims arising from respiratory disorders such as CRS have had substantial financial ramifications (11).

Shared upper and lower airway immune response is well established in the spectrum of atopic rhinosinusitis and allergic asthma (12–14) and as a cause of chronic cough syndrome (15). CRS in the FDNY firefighter cohort exists both in isolation and in accompaniment with WTC lower airway injury (WTC-LI) (16), portending overlapping but distinct immune pathogenesis of irritant induced upper and lower airway injury. The pathophysiology of CRS after occupational irritant exposure has not been well characterized.

We have previously reported inflammatory biomarkers that are predictive of future abnormal lung function in the FDNY firefighter cohort (17). No biomarker studies have been published that predict the long-term outcome of upper airway disease in this population. We investigated whether a panel of inflammatory cytokines, either associated or not associated with WTC-LI, can predict future chronic rhinosinusitis disease and its severity.

METHODS

Study Design

All WTC exposed FDNY workers were enrolled in the Medical Monitoring and Treatment Program. FDNY workers (N=1,720) who complained of any respiratory symptoms between October 1, 2011 and March 10, 2008 were systematically sent for subspecialty pulmonary evaluation (SPE). We performed a nested case-cohort study on firefighters using this baseline cohort of 1,720 exposed, symptomatic workers. Study subgroups were derived from the baseline cohort after excluding for patients with prior lung or sinus disease. Figure 1. Chronic rhinosinusitis (CRS) in our study was defined as nasal and/or sinus inflammation, with recurrence of symptoms after re-exposure to irritants (16). The diagnosis of chronic rhinosinusitis was determined by the evaluating physician and was confirmed by sinus CT scan and treated medically with nasal saline lavage, nasal steroids decongestant and proton pump inhibitor (18). The time of CRS diagnosis was abstracted from the FDNY electronic medical record (FDNY-eMR). Of the 179-study patients, whose serum were available for biomarker assay, 76 developed CRS; 62 were medically managed and 14 were refractory to medical management and elected to have sinus surgery. Refractory was defined as requiring at least 3 months of medical management with persistent symptoms, despite reported medication adherence that substantially interfered with the patient's quality of life. Once medical management failed, patients were referred to ENT subspecialty clinic. For our analysis of progression, we confirmed in the FDNY-eMR an ordered progression from no CRS prior to 9/11/01 to post-9/11/01 medically managed sinusitis and, when refractory to medical management, to surgically managed sinusitis. Subjects signed informed consents approved by the institutional review boards of Montefiore Medical Center (#07–09–320) and New York University (#11–00439).

Demographics

Age, race and years of service at FDNY were obtained from the FDNY-WTC-monitoring database. Body mass indices (BMIs) were calculated from height and weight measured at the time of serum draw. Degree of exposure was self-reported at the first FDNY-WTC-monitoring and was categorized using the FDNY-WTC Exposure Intensity Index (Arrival

Time): i. Presented on the morning of 9/11/2001 ii. Arrived between afternoon on 9/11/2001 and 9/12/2001 (17, 19). Those arrived after day-three were excluded from analysis as a result of their low numbers in this sample. Subjects underwent spirometry at the time of serum collection as previously described (17, 19, 20).

Serum Sampling and Analysis

Blood drawn at the first post-9/11 FDNY-WTC monitoring exam was processed as described.[17] Serum was thawed once at 4°C and assayed using a pro-inflammatory panel (39-Plex including EGF, Eotaxin, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, IFN-γ, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, IL-1Rα, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, TGF-α, TNF-α, TNF-β, VEGF, sCD40L, sIL-2Rα, Millipore, Billerica, MA) and Metabolic Hormone Panel (13-Plex including GM-CSF, IFN-γ, IL-10, IL-15, IL-18, IL-2, IL-6, IL-7, IL-8, IP-10, KC-like, MCP-1, TNF-α, Millipore, Billerica, MA) according to manufacturer's instructions (Millipore) and analyzed on a Luminex 200IS (Luminex Corporation).

Statistical Analysis

We tested normality using the Shapiro-Wilk test and Q-Q plots. Jonckheere-Terpstra or Wilcoxon rank-sum tested for group comparisons. The Chi-squared or Fisher's exact tested for inferences on proportions. Ordinal logistic regression analysis with the proportional-odds model tested association between inflammatory biomarkers and progressive sinusitis severity. The approximate likelihood-ratio test of proportionality of odds and the Brant test of parallel lines assumption assessed model appropriateness. Since biomarkers were severely skewed, we log-transformed them before including them as continuous covariates in the model. Logistic regression was used to assess the association between biomarkers and abnormal forced expiratory volume in 1 second (FEV_1 less than lower limit of normal). A two-sided P-value less than 0.05 was considered significant. All analyses were performed with STATA/SE version 12.1 (StataCorp LP, College Station, TX).

RESULTS

Study Design and demographics

The derivation of medical CRS cases, surgical CRS cases and controls with no sinusitis during the study period is described in Figure 1. Demographics of the baseline cohort and all study subgroups are shown in Table 1. Serum obtained for biomarker analysis was drawn on average 2 to 3 months post 9/11. There was no significant difference in the time to serum collection amongst these subgroups (P=0.118). Cases and controls had similar age at 9/11, years of firefighting service, body mass index, racial distribution and WTC exposure intensity. There were no significant differences in spirometric parameters including FEV_1 and FEV_1/FVC in cases versus controls.

Sinusitis incidence and overlap with abnormal FEV1

Kaplan-Meier estimator was used to assess the cumulative proportion of CRS. The incidence of CRS steadily increased over study period, Figure 2 Panel A. We examined the proportion

of the study cohort with sinusitis alone, abnormal FEV_1 alone or sinusitis with abnormal FEV_1. Fourteen percent (25/179) had both diagnoses, 28% (51/179) had only sinusitis and 20% (35/179) had only abnormal FEV_1, Figure 2 panel B.

Characteristics of Chronic Rhinosinusitis

The median time from 9/11 to CRS diagnosis was between 39 and 40 months in medical and surgical cases. The subspecialty pulmonary evaluation (SPE) spirometery occurred 7 months before the diagnosis of CRS in the medically managed cases and 4 months after the diagnosis of CRS in surgical cases, Table 2. Eighty three percent of CRS cases (63/76) had CT scans available for analysis including 50 medical and 13 surgical CRS cases. The median time from 9/11 to sinus CT scan was 77 months in both medical and surgical cases, respectively (P=0.322). Polypoid pathology on CT scan was more prevalent in surgical than medical cases; 46% (6/13) of surgically and 10% (5/50) of medically managed CRS patients had polypoid sinusitis (P=0.007).

Univariable Ordinal Logistic Regression

Assuming an ordered progression of severity from no sinusitis to medically managed sinusitis to sinusitis requiring surgery, we modeled biomarker ability to predict sinus disease status. We included a panel of 39 cytokines, neutrophil concentration and potential confounders such as age, BMI and exposure intensity in the initial analysis. Interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), growth-regulated oncogene (GRO), neutrophil counts and BMI had a P-value less than 0.2 and were therefore included in the multivariable ordinal logistic model, Table 3.

Multivariable Ordinal Regression Model

After adjustment for exposure intensity, IL-6, TNF-α and neutrophil concentration made it into the final model, Table 4. Increasing IL-6 and neutrophil counts increased the odds of being in the control, non-sinusitis group. With every 1 $\log_{10}$ pg/mL increase in IL-6, the probability of being in the control group increased by 10.6% while the probabilities of being in the medical and surgical sinusitis groups decreased by 7.8% and 2.8%, respectively. Similarly, with every 1,000 cells/μL increase in neutrophil count, the probability of being in the control group increased by 8.8% while the probabilities of being in the medical and surgical sinusitis groups decreased by 6.5% and 2.3%, respectively. Conversely, elevated TNF-α levels increased the odds of having surgically managed sinusitis. Every 1 $\log_{10}$pg/mL increase in TNF-α level resulted in a 20.4% lower probability of being in the control group, 15.1% higher probability of being in the medical sinusitis group and 5.3% higher probability of being in the surgical group.

Biomarkers of Chronic Rhinosinusitis with Polyps

Since surgical patients had a 7.7 fold (95% CI: 1.8–32) increased odds of sinus polyps we investigated biomarkers of polyps in this cohort. We observed that increasing serum eotaxin, interferon-gamma (IFN-γ), interleukin-4 (IL-4), interleukin-13 (IL-13), vascular endothelial growth factor (VEGF), and neutrophil concentration reduced the risk of having CRS with polyps. Conversely, increasing eosinophil concentration increased the risk of CRS with

polyps, Table 5. In a multivariable model adjusted for exposure intensity, each 1 $\log_{10}$pg/mL increase in IFN-γ and IL-4 decreased the odds of having sinus polyps by 96% (95% CI: 0.00–0.99) and 80% (95% CI: 0.06–0.75) respectively. Each 1,000 cells/μL increase of neutrophil count was associated with 96% (95% CI: 0.01–0.48) decrease the odds of sinus polyps while each 10 cells/μL increase of eosinophil count increased the risk of developing polyps by 15% (95%CI: 1.03–1.27), Table 6.

Biomarkers of Sinus Disease as Predictors of FEV_1<LLN

We have previously reported biomarkers of inflammation that predict FEV_1 below the lower limit of normal (LLN) in WTC exposed firefighters, and previously reported that macrophage derived chemokine (MDC) and granulocyte macrophage colony stimulating factor (GM-CSF) increased the risk of abnormal FEV_1 years later. We therefore investigated if inflammatory biomarkers of sinus disease predicted abnormal FEV_1 in this cohort. We observed that each 1 $\log_{10}$pg/mL increase in IL-6 decreased the odds of abnormal FEV_1 by 65% (95% CI: 0.19–0.62) and that each 1,000 cells/μL increase of neutrophil count was associated with 40% decrease in the risk of abnormal FEV_1 (95% CI: 0.43–0.83) in a model adjusted for exposure, BMI, age, MDC and GM-CSF. TNF-α levels didn't have statistically significant association with lung function in this cohort.

DISCUSSION

Years after 9/11, a high incidence of both upper and lower airway respiratory disorders has persisted in WTC exposed firefighters (8), with CRS representing both the most common manifestation of upper airway injury in this cohort and a condition of substantial morbidity (11). The FDNY has reported that 80% of previously healthy firefighters complained of rhinosinusitis symptoms the first day after 9/11/2001, 25% during the first year after exposure, and 32% during the next 2–4 years (21). In our study cohort who presented to the subspecialty pulmonary evaluation, 42% of WTC exposed firefighters were diagnosed with CRS, 4 times higher than physician diagnosed sinusitis in the total cohort (N=10,943) (22).

Whereas we have previously reported biomarkers of inflammation predicting abnormal FEV_1 in WTC-exposed firefighters, this is the first study to report a panel of inflammatory biomarkers that predict both future CRS disease and its progression or severity in this population. Specifically, IL-6 and neutrophil concentration were found to be protective against CRS, whereas TNF-α was a risk factor for CRS progression or severity. Interestingly, in this same group of patients using identical blood samples, increased IL-6 levels and neutrophil counts were likewise protective against an abnormal FEV_1. In contrast, TNF-α was not a risk factor for an abnormal FEV_1 post-9/11 (17).

That we found both independent (TNF-α) and overlapping (IL-6, neutrophil counts) biomarker association with irritant-induced upper and lower airway injury suggests shared but distinct immune pathways. Indeed, there appears to be considerable clinical overlap between CRS and lower airway injury as WTC-LI was a common comorbidity of CRS in this cohort. Twenty five out of 79 (32%) previously healthy firefighters who developed CRS also developed obstructive airway dysfunction post-9/11. This finding is consistent with a

prior report that 40% of WTC rescue workers were diagnosed with both CRS and obstructive airway disease post-9/11 (23).

The one-airway or unified airway concept linking the upper and lower airways is already a well recognized and accepted in asthma and allergic rhinitis (12, 13) and in chronic cough syndrome (15). Numerous cross-sectional and retrospective studies have demonstrated that allergic rhinitis is a risk factor for the presence of asthma (24). Potential mechanisms linking these upper and lower airway disease states are the nasobronchial neural reflex (airway hyperreactivity), drainage of pro-inflammatory material from the nose to the lungs (common allergen), loss of protective function of the nose, and inflammatory processes characterized by eosinophilia and local IgE production (14, 25, 26).

Several studies by Braunstahl (27, 28) have shown that stimulation with antigen at one respiratory site can result in expression of inflammatory cytokines at a location distant from the site of stimulation. The activation of Th2 lymphocytes in the nose can lead to the differentiation and activation of immune cells from precursors in the nasal mucosa and bone marrow, leading to recruitment of these newly generated cells throughout the upper and lower airways (14). These findings suggest that there is “inflammatory crosstalk” occurring throughout a “unified” upper and lower airway. However the pathophysiology of CRS and WTC-LI after occupational irritant exposure has not been previously described.

The biomarkers associated with CRS and/or WTC-LI identified in this study are known to be important mediators of the innate immune system. This is consistent with studies suggesting that the innate immune response plays an important role in the pathogenesis of CRS as well as obstructive airway disease (29–31). Interestingly, we found neutrophil concentration to be protective of both CRS and abnormal FEV_1. A recent genome-wide association study (GWAS) demonstrated an association between polymorphisms of the neutrophil’s acyloxyacyl hydrolase (AOAH) gene with CRS in two independent populations (32, 33). The AOAH gene, which is known to contribute to the host defense against bacterial LPS, has also been linked to asthma (34, 35). It may appear counter-intuitive that neutrophils, which are conventionally agents of inflammation, were a protective biomarker for CRS and WTC-LI in our study. However, recent investigations have indeed supported the concept that anti-inflammatory cascades can be mediated by neutrophils early in the innate immune response (36, 37).

In our investigation, IL-6 was identified as a protective biomarker for both sinusitis and abnormal FEV_1 as well. Although many IL-6 related gene variants have previously been associated with conditions such as asthma and COPD (38, 39), studies demonstrating association between IL-6 polymorphisms and susceptibility to CRS have been rare. Interestingly, cause-effect studies using transgenic mice have pointed to a dual role for IL-6 in lower airway diseases; 1) enhancing allergic airway inflammation and 2) protecting against airway hyperreactivity/inflammation (40–42).

TNF-α is a cytokine that is thought to play a central role in pathogenesis in CRS (43, 44). In severe CRS, TNF-α synergizes with Th1 and Th2 to induce a chronic inflammatory state (45, 46). Multiple studies showed that single nucleotide polymorphisms (SNPs) in TNF-α

have been associated with nasal polyps (47–49). In our cohort, elevated TNF-α levels were a risk factor for severe sinusitis (typically polypoid on CT) but not WTC-LI. Further investigation is required to assess if TNF-α directly contributes to the inflammatory cascade in WTC-related CRS.

The traditional classification of allergic CRS into CRS with polyps versus without polyps is useful in the general population in whom the presence of polyps is strongly associated with sensitivity to aspirin or nonsteroidal anti-inflammatory drugs. Our cohort is unique in that development of CRS was provoked by massive exposure to combustion byproducts, with pathophysiology that could potentially be different from classical allergic CRS. There is a suggestion that the cytokines that reduced the risk of developing polyps are different from the cytokines that reduced the risk of CRS progression even though increasing blood PMN were protective biomarkers for both conditions. Alternately, increasing eosinophil concentration was a strong risk factor for polyps but not CRS progression. This suggests overlapping but distinct pathways to CRS progression and sinus polyps.

This study has several limitations. This is an exploratory study using a panel of inflammatory cytokines in this longitudinally followed cohort. The findings of this investigation need to be validated in lager studies and animal models. Our FDNY firefighters cohort is unique as they had massive acute exposure to WTC dusts. This limits the generalizability of these finding to other study populations with lower level PM exposure produced by ambient air pollution. However this is at the same time a strength of our paper since we can make a safe assumption that the etiology of sinusitis was WTC dust. We did not have an unexposed control group to compare and therefore we could not determine the direct effect of WTC-PM exposure on serum biomarkers. In addition, there is no good surrogate measure to estimate exposure prior to 9/11 since all individual firefighters would have had different rate of exposure even in each fire runs. Replication of these findings in other longitudinally followed populations with and without PM exposure will be important to demonstrate the generalizability of our findings.

Our study demonstrates distinct but overlapping biomarker association between upper and lower airway injury, and suggests that a common inflammatory pathway may be shared by CRS and lung disease caused by WTC exposure. The potential relationship between irritant-induced CRS and lung injury may underlie preventive and therapeutic strategies for these conditions by modulating inflammation.

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Abbreviations

CRS	chronic rhinosinusitis
FDNY	Fire Department City of New York
FEV_1	forced expiratory volume in 1 second
GRO	growth-regulated oncogene
IL-6	Interleukin-6
IL-8	interleukin-8
LLN	lower limit of normal
MME	medical monitoring entry
NHANES	National Health and Nutrition Examination Survey
PFT	pulmonary function test
PM	particulate matter
PMN	Polymorphonuclear neutrophil
SPE	subspecialty pulmonary evaluation
TNF-α	tumor necrosis factor-alpha
WTC	World Trade Center
WTC-LI	World Trade Center-related lower airway injury

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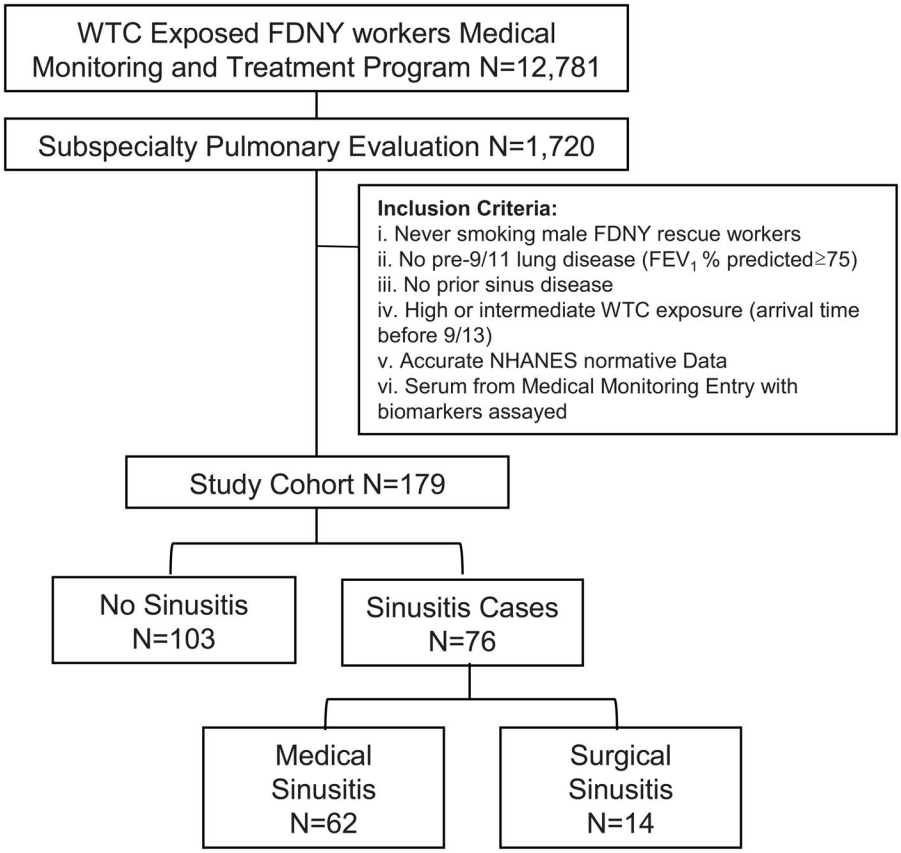

Figure 1.

Study design. WTC=World Trade Center; FDNY=Fire Department City of New York; FEV_1 = forced expiratory volume in 1 second; NHANES=National Health and Nutrition Examination Survey

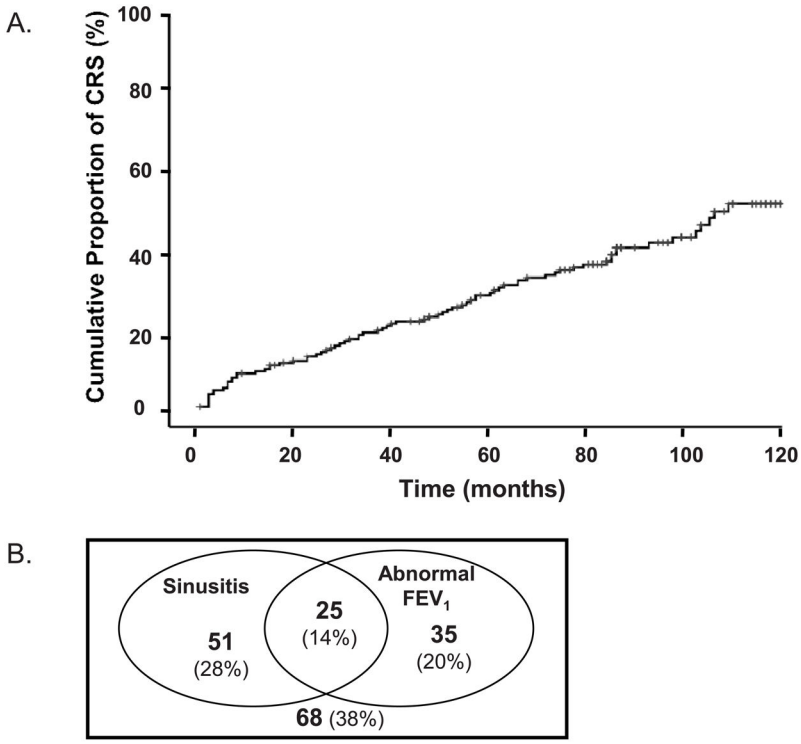

Figure 2.

A. Kaplan-Meier estimator was used to assess the cumulative proportion of CRS. The incidence of CRS steadily increased over study period. **B.** We examined the proportion of the study cohort with sinusitis alone, abnormal FEV_1 alone or sinusitis with abnormal FEV_1. Fourteen percent (25/179) had both diagnoses, 28% (51/179) had only sinusitis and 20% (35/179) had only abnormal FEV_1.

Table 1

Demographics

		Control	Medical Cases	Surgical Cases	P-value[ll]
Number of subjects		103	62	14	
Age at 9/11[*]		41 (36–45)	41 (36–44)	42 (38–46)	0.880
Years of Service at 9/11[*]		15 (8–18)	13 (6–17)	12 (9–16)	0.135
Race[†]	Caucasian	99 (96)	62 (98)	14 (100)	0.550
	African American	4 (4)	1 (2)	0 (0)	
Intensity of WTC Exposure[†]	High[‡]	20 (19)	13 (21)	4 (29)	0.775
	Intermediate[§]	83 (81)	50 (79)	10 (71)	
Time to[*]	Serum Collection, months	2.6 (2.2–3.7)	2.6 (2.0–3.2)	2.3 (1.8–2.9)	0.118
	Spirometry, months	35.7 (23–55)	31.7 (24–55)	43.8 (30–55)	0.550
Spirometry[*]	FEV_1, % Predicted	87 (74–99)	85 (73–95)	101 (88–107)	0.608
	FEV_1/FVC, %	76 (70–80)	76 (70–82)	77 (75–81)	0.263

Definition of abbreviations: WTC = World Trade Center, FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity

[*] Values Expressed as Median (IQR).

[†] Values Expressed as N (%).

[‡] Arrival at WTC 9/11 Morning,

[§] Arrival at WTC between noon of 9/11 and midnight of 9/12.

[ll] Significance assessed by Jonckheere-Terpstra test or Chi-squared test between Medical Cases, Surgical Cases and Controls.

Table 2

Characteristics of Chronic Sinusitis in FDNY cohort

	Medical Cases	Surgical Cases	P-value‡
Time to SPE, months*	31.7 (24–55)	43.8 (30–55)	0.319
Time to sinusitis diagnosis, months*	39 (13–65)	40 (23–79)	0.634
Time to sinus CT scan, months*§	77 (52–98)	77 (57–104)	0.616
Polyps†§	5 (10)	6 (46)	0.007

Definition of abbreviations: SPE = subspecialty pulmonary evaluation; CT = computed tomography.

*Values Expressed as Median (IQR).

†Values Expressed as N (%).

‡Significance assessed by Wilcoxon rank-sum test and Fishers Exact test between medical cases and surgical cases.

§CT scans available: Medical Cases N=50; Surgical Cases N=13

Table 3

Predictive Biomarkers and Univariable Ordinal Logistic Regression Predicting Sinus Disease Severity

Predictor	Controls*	Medical Cases*	Surgical Cases*	Crude OR (95%CI)†	P-value
IL-6 (log_{10} pg/mL)	5.7 (1.7–17.7)	2.6 (0.7–12.2)	4.8 (3.1–13.6)	0.72 (0.48–1.09)	0.118
IL-8 (log_{10} pg/mL)	16.4 (11.7–35.0)	12.6 (9.4–22.7)	11.8 (9.0–21.8)	0.41 (0.19–0.90)	0.023
TNF-α (log_{10} pg/mL)	4.0 (2.6–5.5)	4.3 (2.8–5.8)	5.0 (2.3–8.7)	1.93 (1.00–3.80)	0.044
GRO (log_{10} pg/mL)	732 (487–973)	641 (474–871)	620 (506–952)	0.41 (0.11–1.50)	0.174
BMI, kg/m^2	27.9 (26–31)	29.1 (26–31)	29.8 (28–32)	1.05 (1.03–1.14)	0.163
PMN count, $\times 10^3$	3.8 (3.0–4.5)	3.6 (2.8–4.2)	3.3 (2.6–3.9)	0.73 (0.57–0.94)	0.011

Definition of abbreviations: OR = odds ratio; PMN = polymorphonuclear neutrophils; 95%CI = 95% confidence interval.

*Values Expressed as Median (IQR).

†Analysis was done between Medical Cases, Surgical Cases and Controls.

Table 4

Multivariable Ordinal Logistic Regression: Final Model Predicting Sinus Disease Severity Using Stepwise Approach

Predictor	OR (95%CI)*	P-value
IL-6 (log_{10} pg/mL)	0.65 (0.42–1.00)	0.049
TNF-α (log_{10} pg/mL)	2.31 (1.15–4.65)	0.018
PMN count, $\times 10^3$	0.69 (0.53–0.91)	0.008

Definition of abbreviations: OR = odds ratio; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-alpha; PMN = polymorphonuclear neutrophils; 95%CI = 95% confidence interval.

*Adjusted for exposure intensity. Omnibus test $\chi 2(4) = 15.30$, P=0.004. Approximate likelihood-ratio test of proportionality of odds P=0.424. Brant Test of Parallel Lines P=0.347.

Table 5

Predictive Biomarkers and Univariable Logistic Regression Predicting CRS with Polyps

Predictor	CRS without polyps* N=52	CRS with polyps* N=11	Crude OR (95%CI)†	P-value
Eotaxin (log_{10} pg/mL)	125 (93–172)	79 (65–432)	0.04 (0.00–1.49)	0.082
IFN-γ (log_{10} pg/mL)	8.1 (4.8–20.1)	7.6 (3.3–9.3)	0.15 (0.02–1.32)	0.087
IL-4 (log_{10} pg/mL)	3.2 (0.5–9.1)	0.5 (0.1–2.2)	0.52 (0.26–1.03)	0.062
IL-13 (log_{10} pg/mL)	3.0 (0.5–18.7)	1.4 (0.5–6.9)	0.51 (0.21–1.27)	0.148
VEGF (log_{10} pg/mL)	144 (88–247)	64 (48–94)	0.08 (0.01–0.70)	0.022
PMN count, $\times 10^3$	3.6 (2.9–4.2)	2.9 (2.5–3.4)	0.41 (0.18–0.94)	0.036
Eosinophil count, ×10	16 (11–23)	25 (18–43)	1.04 (1–1.09)	0.058

Definition of abbreviations: OR = odds ratio; IFN-γ = interferon-gamma; IL-4 = interleukin-4; IL-13 = interleukin-13;VEGF = vascular endothelial growth factor; PMN = polymorphonuclear neutrophils; 95%CI = 95% confidence interval.

* Values Expressed as Median (IQR).

Table 6

Multivariable Logistic Regression: Final Model Predicting CRS with Polyps

Predictor	OR (95%CI)*	P-value
IFN-γ (log_{10} pg/mL)	0.04 (0.00–0.99)	0.050
IL-4 (log_{10} pg/mL)	0.20 (0.06–0.75)	0.016
PMN count, $\times 10^3$	0.06 (0.01–0.48)	0.008
Eosinophil count, ×10	1.15 (1.03–1.27)	0.009

Definition of abbreviations: OR = odds ratio; IL-4 = interleukin-4; IFN-γ = interferon-gamma; PMN = polymorphonuclear neutrophils; 95%CI = 95% confidence interval.

*Adjusted for exposure intensity. Omnibus test $\chi 2(5) = 26.87$, $P<0.001$. Approximate likelihood-ratio test of proportionality of odds P=0.737