Blood Eosinophils and World Trade Center Exposure Predict Surgery in Chronic Rhinosinusitis: A 13.5-Year Longitudinal Study

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Abstract

Rationale: The World Trade Center (WTC) collapse generated caustic airborne particulates that caused chronic rhinosinusitis in exposed fire department of New York (FDNY) firefighters. Surgery was performed when symptoms remained uncontrolled despite medical management.

Objectives: To identify predictors of surgical intervention for chronic rhinosinusitis in firefighters exposed to airborne irritants at the WTC collapse site.

Methods: We assessed in 8,227 firefighters with WTC-exposure between 9/11/2001 (9/11) and 9/25/2001, including WTC-site arrival time, months of rescue/recovery work, and eosinophil concentration measured between 9/11 and 3/10/2003. We assessed the association of serum cytokines and immunoglobulins with eosinophil concentration and surgery for rhinosinusitis in 112 surgical cases and 376 controls with serum available from the first 6 months after exposure to the WTC collapse site.

Measurements and Main Results: Between 9/11 and 3/10/2015, the surgery rate was 0.47 cases per 100 person years. In the first 18 months post 9/11, surgical patients had higher mean blood eosinophil levels than study cohort patients(219±155 vs. 191±134; P <0.0001). Increased surgery risk was associated with increasing blood eosinophil counts (HR 1.12 per 100 cells/uL; 95% CI 1.07 to1.17; P <0.001); arriving at the WTC site 9/11 or 9/12/2001 (HR 1.43; 95% CI 1.04 to 1.99; P=0.03); and working ≥6 months at the WTC-site (HR 1.48; 95% CI 1.14 to 1.93; P<0.01). Median blood eosinophil levels for surgery patients were above levels for the cohort in all 18-month intervals 3/11/2000 through 3/10/2015 using 51,163 measurements representing 97,733 person-years of observation. Increasing age, increasing IL-17A and low IgA in serum

from 2001-2002 predicted blood eosinophil concentration in surgical patients but not in controls (R^2=0.26, p<0.0001 vs. R^2=0.008, p=0.56).

Conclusions: Increasing blood eosinophil concentration predicts surgical intervention for chronic rhinosinusitis, particularly in those with intense acute and prolonged exposure to airborne irritants. WTC-exposed FDNY firefighters who underwent irritant-associated sinus surgery are immunologically different from the cohort. Surgical patients have a higher blood eosinophil levels that is associated with mediators of mucosal immunity.

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Rhinosinusitis is a syndrome producing obstruction to nasal airflow, drip, anosmia, and facial pain. Chronic rhinosinusitis (CRS) is defined as this constellation of symptoms lasting 3 or more months. The prevalence of CRS is between 13% and 17%, with 600,000 sinus surgeries performed in the United States of America during 2006.[1-3] Analysis of ICD9-coded electronic medical records (EMR) from a large private health system estimated a CRS incidence of 1.1 cases per 100 person-years.[4]

In 2012, the current European position paper on rhinosinusitis and nasal polyps recommended that sinus inflammation should be objectively confirmed with by computed tomographic (CT) imaging and/or endoscopy and argued for separation into two distinct entities – chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP)[5]. In spite of high disease burden and associated morbidity, few longitudinal studies have provided data on risk factors for CRS, limiting approaches to model disease outcomes and institute effective prevention.[4,11-13]

Environmental particulate matter exposure is a risk factor for upper and lower airway disease.[14,15] The collapse of the World Trade Center (WTC) on 9/11/2001 (9/11) produced a dust cloud containing alkaline pulverized concrete and other building materials that irritated mucosal surfaces of the aerodigestive system. All individuals present at the WTC site prior to 9/13/2001 sustained intense particulate exposure, which produced upper airway symptoms including nasal congestion and drip in most survivors.[16]

Rainfall 3 days after 9/11 reduced dust levels, and may have played a role in lower levels of persistent aero-digestive symptoms in later arriving FDNY firefighters.[17] Digging activities to recover human remains continued through July 2002, producing chronic particulate

re-exposures. Upper airway filtration of larger particles protects the lower airway, but can produce inflammation of the nose and paranasal sinuses leading to CRS, which has, over time, become a major health concern in WTC-exposed populations.[18-21] We have previously shown that chronic particulate exposure, defined by months of firefighter work at the WTC-site, predicted health care utilization, including sinus surgery.[17]

CRS has multiple inflammatory endotypes.[22] Innate as well as Th2 and Th17-driven eosinophilic responses are observed in specimens from surgically treated CRS patients,[23-26] suggesting separate eosinophilic inflammatory pathways produce CRS. IL-17A is an inflammatory mediator of sinus disease. Eosinophilia is present in WTC-exposed area residents and children with upper and lower respiratory complaints.[19,28]

In a small cross sectional study, high blood eosinophil concentration soon after WTC exposure increased the odds of visualizing sinus polyps on CT imaging, a risk factor for sinus surgery.[29] This preliminary study led to the hypothesis that blood eosinophil concentration early after 9/11 may predict subsequent sinus surgery, a clearly defined disease definition with high morbidity and health care utilization.[17] We therefore tested if increased blood eosinophil levels and associated inflammatory mediators, combined with WTC-exposure are risk factors for surgical-CRS in FDNY firefighters.

Methods

Study Population

This study included male firefighters who were employed by FDNY on 9/11, first arrived at the WTC-site between 9/11 and 9/24/2001, had an available eosinophil concentration from an FDNY medical monitoring exam between 9/11 and 3/10/2003, and consented to research. The Montefiore Medical Center and New York University institutional review boards approved this study.

Identification and Characterization of Patients with Chronic Rhinosinusitis

We obtained surgical-CRS occurrence and dates from multiple sources including the FDNY-WTC Health Program (FDNY-WTCHP) electronic medical record (EMR), FDNY-WTCHP claims data and the records of a WTC center of excellence otolaryngologist (MRS). When the FDNY-EMR was the only identifier of surgical-CRS, a WTC treatment physician (author MDW) reviewed the FDNY-EMR notes to confirm the date and indication for surgical-CRS.

Otolaryngologists caring for CRS patients were not provided patients' WTC-exposure specifics, job tasks, or FDNY-WTCHP's eosinophil concentrations. CT reports were reviewed by a WTC treatment physician (author DP), noting the symptoms, the presence of upper airway polyps or inflammation. CRS was defined by having sinus symptoms and sinus surgery or sinus CT and findings of inflammation or polyps.

Eosinophil, Exposure and Demographic Data

Eosinophil concentrations were obtained from cell blood counts (CBC) drawn at each WTCHP monitoring exam, scheduled at 12 to 18 month intervals, and sent to a single commercial laboratory. The first eosinophil concentration during each 18-month interval was used in the analysis. We did not use eosinophil measurements from physician encounters for symptom evaluation or treatment. Information documented during FDNY-WTCHP exams included responses from self-administered questionnaires with questions about smoking, self-reported race/ethnicity, WTC-arrival time and months of work.

A never smoker was defined as consistently denying smoking on longitudinal questionnaires. High intensity acute exposure was defined as arrival between the morning of 9/11 and the end of 9/12/2001; lower intensity acute exposure was arrival on or after 9/13/2001. High intensity chronic exposure was defined as six or more months of rescue/recovery work, intermediate intensity was two to five months and lower intensity was one month of work.

Serum Biomarker Cases and Controls

Serum was obtained from the same venipuncture as bloods drawn at first post-9/11 medical monitoring exam and was stored at -80° C. Exclusions for the control population were any physician diagnosis of sinus disease or firefighters who presented for evaluation of respiratory symptoms prior to March 2008.[30] To exclude chronic sinus disease, CRS diagnoses and dates were identified by searching the EMR for ICD9 codes for Chronic Sinusitis, 473.x or Chronic rhinitis or nasopharyngitis 472.0/472.2 or polyps of the nose or sinus 471.x.

Chronic disease was defined as at least two FDNY physician visits with one of these diagnoses at least four weeks apart. Serum IL-17A and IL-6 were assayed with EMD Milipore HSTCMAG28SPMX21, IgA with HGAMMAG-301K and IgE with HGAMMAG-303E. To avoid batch bias equal proportions of cases and controls were included in each batch.

Statistical Analysis

All reported P values are two-sided. Characteristics between the cohort and the surgical-CRS group were assessed using score tests for continuous variables and log-rank tests for categorical variables. Follow-up time for CBC was calculated from the first to the last medical monitoring CBC for each study participant. Follow-up time for surgical-CRS began on 9/11 and ended on the date of surgical-CRS.

For active FDNY members without surgical-CRS, follow-up time ended on 3/10/2015. For retirees without surgical-CRS, follow-up ended on the last FDNY-WTCHP monitoring exam or treatment date. Rates for surgical-CRS included cases occurring after 9/11.

Cox proportional hazards models for multivariable analysis of rates, adjusted for race, were used to assess the effect of WTC-exposure (initial arrival time, and work duration at the site), smoking and eosinophil levels; stratification by smoking status assessed effect modification by smoking. Kaplan Meir curves for single variable assessment of eosinophils in the top quartile, initial arrival time, and work duration at the site on surgical-CRS were produced by setting all other covariates on the Cox model at their mean.

In the biomarkers sub-study, stratified multivariable linear models analyzed predictors of eosinophil concentration in surgical-CRS patients and controls. All data analyses were

performed with SPSS version 22 and replicated using SAS version 9.4.

Results

Characteristics of the Study Cohort, Surgical-CRS and Medical-CRS Patients

Figure 1 shows the parent population of 10,612 FDNY male firefighters who were first present at the WTC-site between 9/11 and September 24, 2001. The final consented study cohort consisted of 8,227 firefighters, the 1,907 with objectively confirmed CRS, the 479 who were treated with surgery within 13.5 years of 9/11 (surgical-CRS) and the 1,428 who were medically managed (medical-CRS) up to March 10 2015.

Table 1 shows the demographic characteristics of all exposed firefighters who consented to research, the study cohort, those with confirmed CRS, enumerating medical-CRS and surgical-CRS subgroups, and the biomarker sub-study subjects without sinus diagnosis (controls) and surgical-CRS patients. The study cohort was similar to all exposed male firefighters:-mostly white, never-smokers and usually arrived at the WTC-site on 9/11 or 9/12/2001. Compared to the study cohort, surgical-CRS patients had higher blood eosinophil concentration, were younger, had a lower percentage of ever-smokers, arrived at the WTC-site earlier, had longer duration of work at the WTC-site and earlier diagnosis of sinus disease.

Compared to the study cohort, medical-CRS patients were similar in age, eosinophil concentration and time to diagnosis of sinus disease, but arrived at the WTC site earlier and had longer duration of work at the WTC site. The biomarker sub-study contained only never smokers; sub-study surgical-CRS patients were similar to all surgical-CRS patients.

Risk Factors for Surgical-CRS

We utilized the longitudinal database of the FDNY-WTCHP to identify external exposures and patient intrinsic characteristics that altered sinus surgery rates when compared to the cohort.

Table 2 shows multiple-predictor Cox regression models predicting surgery adjusted for age, race, and smoking history. Increasing eosinophil concentration (100 cells/□l), earlier WTC-arrival time, and longer work duration at the WTC-site were all associated with higher incidence of surgery (HR, 1.12 95% CI, 1.07 -1.17; P<0.001); (HR, 1.43 95% CI, 1.04 – 1.99; P=0.03); and (HR, 1.48, 95% CI, 1.14 to 1.93; P<0.01, respectively). To better understand the impact of smoking we tested for interaction between smoking and other risk factors and found none.

We then stratified by smoking status and found that increasing eosinophil concentration remained a significant risk factor for surgical-CRS in both never-smokers and ever-smokers (HR 1.12 p<0.001 and 1.13 p=0.001). Early arrival remained significant only in ever-smokers (HR 2.18 1.11-4.29 p=0.023 vs 1.22 0.84-1.77 p=0.29). Further, ever-smokers had higher eosinophils in than never-smokers (213±139 vs. 194±133 p=0.003 for CRS and 240±166 vs. 209±148 p=0.046 for surgical-CRS). Since smoking confounds the association between surgical-CRS hazard and eosinophils, subsequent models excluded ever smokers to eliminate this confounding.

We performed a biomarker sub-study of 488 individuals with serum drawn within 6 months post-WTC exposure comparing risk factors for sinus surgery in 112 surgery patients and 376 controls using IgE concentration as a biomarker for atopic disease. The control group excluded upper and lower respiratory diagnosis that could be associated with atopy. While eosinophil concentration and age remained significant risk factors for surgical-CRS, IgE was not

associated with surgical-CRS (HR. 1.01 95% CI 0.99-1.03 p=0.23). Consistent with our prior study with different cases and controls[29], IL-6 reduced hazard of surgical-CRS (HR 0.84 95% CI 0.72.-0.97 p=0.021).

With the cohort as the reference, we used Kaplan Meier analysis to illustrate the effect of risk factors on surgical-CRS. As opposed to the Cox models that used eosinophils as a continuous variable, the Kaplan Meier analysis used the top quartile of eosinophils (240 cells/μl) in the cohort to demonstrate the effect of higher eosinophils.

Figure 2 shows cumulative incidence plots for surgical-CRS as a function of blood eosinophil concentration, WTC-arrival time, and WTC-site work duration. Higher levels of eosinophils were associated with higher rates of surgical-CRS($P<0.001$), as were earlier arrival times ($P<0.01$) and WTC-site work duration ($P<0.001$).

Predictors of Eosinophil Concentration

Biological differences between the surgical-CRS patients and the study cohort could explain the impact of eosinophil concentration on surgery rates. To gain insight into immunological pathways associated with elevated eosinophil concentration in surgical-CRS patients we performed multi-variable linear regression with eosinophil concentration 1.6 to 6.3 months post 9/11 as the outcome and inflammatory biomarkers measured in serum from the same venipuncture as the eosinophil concentration as the predictor.

Table 3 shows two multi-variable linear regressions with post 9/11 eosinophil concentration as the outcome. IL-17A is strongly correlated with eosinophil concentration in surgical-CRS patients but not in controls (standardized beta 0.428, $p<0.0001$ vs. standardized

beta -0.06 p=0.23) . Similarly, age and low serum IgA positively correlate with eosinophil concentration only in surgical-CRS patients. Alternately, surgical-CRS patients had a trend for higher eosinophil concentration soon after exposure, with decline over time (28.6±16.7 cells per month decline p=0.093).

In the control group, there was no impact of time post exposure on eosinophil concentration (5±5 cells per month increase p=0.32). Age, IL-17A, low IgA and time post exposure explained 26% of the observed variance in surgical-CRS patients' eosinophil concentration (R^2=0.26 p<0.0001). These four variables had no association with eosinophils in controls (R^2=0.008, p=0.56).

Longitudinal Eosinophil Concentration in the Study Cohort and Surgical-CRS

Examination of eosinophil concentration and biomarkers obtained soon after WTC exposure suggests biological differences between surgical-CRS patients and other subgroups in the study cohort. The FDNY-WTCHP has pre-exposure data as well as compressive longitudinal data on eosinophil concentration. We therefore explored if differences in surgical-CRS patients' concentration existed before exposure or extended beyond the initial insult.

Figure 3 shows median eosinophil concentrations from 3/10/2000 to 3/10/2015 representing 97,733 person years of follow up, in 18-month intervals. The surgical-CRS patients had higher eosinophil than the study cohort at every time interval including pre-9/11. Analyzing results from a subset of 2,444 who had bloods drawn 18 months pre-9/11, first 18 months post-9/11 and during the 36 months between 3/11/2003 and 3/10/2006, we found that the pre-9/11 eosinophils were 126 cells/µl (IQR 78-198), increased to 160 cells/µl (IQR 108-244) in the first

18 months post-9/11, and then declined to 144 cells/µl (IQR 90-216) in the following 36 post-9/11 months (P<0.001 for both comparisons).

In the 158 surgery patients with values in all time intervals, the pre-9/11 eosinophils were 149 cells/µl (IQR 84-238), increased to 179 cells/µl (IQR 120-251) in the first 18 months post-9/11 and then declined to 162(IQR 96-243) cells/µl in the following 36 months post-9/11 (P<0.001 and P=0.001, respectively).

Discussion

We present 13.5-years of post-9/11 longitudinal follow-up for 8,227 firefighters who sustained intense, caustic dust exposure from the WTC towers collapse and participated in subsequent rescue/recovery operations. Those who proceeded to sinus surgery had elevated blood eosinophil concentration prior to exposure. Further, only those who underwent sinus surgery had an association between IL-17A or low IgA and eosinophil concentration after exposure.

These data are consistent with immunological differences between those who proceed to sinus surgery and the rest of the cohort that are evident years before disease presentation. Since both acute and chronic exposure to the WTC-site were significant risk factors for surgical-CRS, there is a need for usable and effective respiratory protection during long-term rescue or recovery work at future disasters. As this is often difficult to achieve, blood eosinophils obtained before or immediately post-exposure could identify those who might benefit the most from early monitoring and targeted treatment. Blood eosinophil concentration is a widely

available, well-studied biomarker of upper and lower respiratory disease that is inexpensive, externally valid and currently collected in many longitudinal cohorts.[18,27,28]

Those firefighters who would underwent sinus surgery had higher blood eosinophil levels than the study cohort throughout the study period, including pre-9/11 suggesting that an elevated eosinophil set point is intrinsic to this vulnerable group. Surprisingly, those with medical-CRS had eosinophil concentration similar to the cohort and significantly below the surgical-CRS patients.

Eosinophil blood levels increased after 9/11. The acute increase likely reflects the systemic response to acute innate inflammation. However, blood eosinophil concentration declined after the first post exposure 18 month interval and trended to the pre-exposure equilibrium after several years.

Exposed firefighters with elevated blood eosinophil concentrations had an 8.4% cumulative incidence of sinus surgery over 13.5 years compared with 5.9% for those with eosinophil levels in the bottom three quarters of the distribution, This resulted in a 45% increased risk of surgical-CRS in the multi-variable Cox regression model using data from the whole study cohort. Only 20/479 (4%) of the surgical-CRS cases had eosinophil concentrations above 500 cell/uL in the first 18 months after exposure, indicating that a vast majority of those who proceeded to non-resolving upper airway inflammation had normal early eosinophil concentrations.

The biomarkers component of this investigation did not identify an association between IgE and surgical-CRS. This is different from FDNY exposed firefighters with lower airways diagnosis where IgE is a significant risk factor [31]. The biomarker data suggests atopy was

not a large contributor to surgical-CRS in this cohort.

Consistent with our prior observations and recent reports, increasing IL-6 reduced surgical-CRS hazard.[29,32] Importantly, increasing IL-17A and age along with low IgA concentration were associated with eosinophils only in surgical-CRS patients but not controls. IL-17A is expressed by excised nasal polyp tissue and correlate with tissue eosinophil.[24,33,34] Low IgA concentration is a known risk factor for sinus disease.[35] Further research is needed to define the underlying mechanism of the differences in mucosal immunity between the surgical-CRS patients and those who do not proceed to surgery.

Increasing acute and chronic particulate exposure are strong risk factors for surgical-CRS , demonstrating a link between surgical-CRS and work at the WTC site. The upper airway protects the lungs by adsorbing “large” particles from inhaled air. This filtering role renders the upper airway vulnerable to caustic dust exposure.

Compared with arrival at the WTC site on or after 9/13, those who arrived 9/11 or 9/12 had a 45% increased risk of surgical-CRS. This results in a 6.6% cumulative incidence of surgical-CRS over 13.5 years in the early arrival group compared with 4.6% in the late arrival group. Compared with working at the site for one month, those who engaged in WTC-rescue or recovery work for 6 or more months had a 48% increased risk of surgical-CRS. This results in an 8.7% cumulative incidence of surgical-CRS over 13.5 years in the prolonged exposure group compared to 4.9% in the briefer exposure group.

The combined effect of early acute injury followed by chronic persistent exposure predisposes these workers to non-resolving inflammation and surgical-CRS years later. The impact of early arrival is most pronounced in smokers, a subgroup with pre-existing upper

airway inflammation.

Limitations

There are several limitations to this study. FDNY firefighters may not be representative of the larger population of non-FDNY WTC-exposed individuals. First, the FDNY study cohort is overwhelmingly male, previously healthy and experienced a massive particulate exposure. This analysis identified risk factors for the most common pathway(s) to surgical-CRS and likely missed risk factors for less common pathways to disease in this population.

It is likely that atopy is an under-represented pathway to sinus disease in this population. Asthma precludes work as a firefighter and most of the WTC-exposed patients had irritant-induced symptoms with no biomarker evidence of atopy within 18 months of exposure and little clinical evidence of an allergic component at presentation. Low levels of atopy are especially likely in the biomarker control population that excluded both upper and lower airway diseases to increase the likelihood of identifying atopy in the surgical-CRS patients. Never the less, a wide-range of findings in the FDNY cohort has been replicated in other WTC-exposed cohorts.

Second, this study was designed to assess early predictors of surgical-CRS risk, so subsequent events such as repeated irritant exposures or treatment prior to surgery were not studied. Third, the data represent risk factors obtained prior to disease reducing the potential for “reverse causation,” but none of the eosinophil or other biomarker data implies a causal relationship to disease. The longitudinal eosinophil analysis and biomarker data suggest surgical-CRS patients are biologically different in one or more of the innumerable pathways

impacting blood eosinophil concentration when compared to the cohort or biomarker controls. Association of increased IL-17A and reduced IgA levels with eosinophils could be a result of the early immune response in those predisposed to non-resolving inflammation or could cause non-resolving inflammation resulting in surgical-CRS.

In spite of these limitations, the FDNY-WTCHP is a valuable resource for understanding irritant-induced diseases like CRS in the occupation setting where there is little available data.[39,40]

Conclusions and Targets for Future Research

Acute and chronic WTC exposure were risks for non-resolving upper airway inflammation with recurrent CRS responding poorly to medical management that ultimately was treated with surgery years later. Increasing eosinophils served as a biomarker for a population that had increased vulnerability to upper airway injury after WTC exposure. The finding that increasing eosinophils was associated with increased rates of surgical-CRS supports earlier observations linking eosinophilia with sinusitis in WTC-exposed children.[18] Finally, surgical-CRS patients are likely predisposed to exaggerated inflammation and/or poor counter-regulatory responses to inflammation. [23-26]

In future disasters, improved respiratory protection during the rescue/recovery phase may be effective in reducing the hazard of difficult-to-treat CRS. Pathway(s) to non-resolving inflammation are induced and/or sustained by repeated irritant exposures over months. Targeting these inflammatory pathway(s) for intervention early in the disease evolution may yield more effective therapies.

Further research is required to identify additional biomarkers of disease associated with above-average blood eosinophil concentration and develop more effective treatments for CRS patients with persistent symptoms, despite currently available medical management.

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Figure Legends

Figure 1. Study Population of Firefighters Who Participated in the World Trade Center (WTC) Study. Shown are the number of male firefighters who were employed by the Fire Department of New York City (FDNY) on September 11, 2001 who were present at the WTC between September 11 and September 24, 2001; are included in the study group; and the number who had physician diagnosed chronic rhinosinusitis; and, the number who underwent sinus surgery from September 11, 2001 to March 10, 2015.

Figure 2. Cumulative Incidence of surgical-CRS from September 11, 2001 to March 10 2015 in Firefighters Who Worked at the World Trade Center Site during the First 2 Weeks after 9/11 by: Level of blood eosinophil concentration (Panel A), WTC-site arrival time (Panel B) and WTC-site work duration (Panel C). Panel A shows the cumulative incidence of surgical-CRS after the cohort is stratified by blood eosinophil concentration above and below 240 cells/µl, the top quartile in the 18 months post-9/11. Panel B shows the cumulative incidence of surgical-CRS after the cohort is stratified by initial WTC- site arrival time, either within the first two days of 9/11 or after 9/12/2001. Panel C shows the cumulative incidence of surgical-CRS after the cohort is stratified by months of WTC-rescue/recovery work, 1 month, 2-5 months and 6 or more months.

Figure 3. Blood Eosinophil concentration in Firefighters Who Worked at the World Trade Center Site during the First 2 Weeks after 9/11 According to Surgical-CRS Status. Shown are the median

eosinophil concentrations from March 10, 2000 to March 10, 2015, in 18-month intervals. The blue dots show data for Fire Department of New York City Firefighters who worked at the World Trade Center site during the first 2 weeks after the attack of September 11, 2001 (9/11) and who had eosinophil measurement between September 11, 2001 and March 10, 2003. The red triangles show data from the group who had surgical-CRS by the end of the study. The number of measurements contributing to the values in each interval are shown below each data point. The top row of values show in red represents the number of eosinophil measurements in the surgical-CRS group. The bottom row of values show in blue represents the number of eosinophil measurements in the study cohort.

Table 1: Study group Demographics

	WTC Exposed Firefighters	Study Cohort	CRS	Medical CRS	Surgical CRS	Biomarker sub-study	
						Controls	CRS-surgery
	N=10,426	N=8,227	N=1,907	N=1,428	N=479	N=376	N=112
Age on 9/11, Mean±SD	40.3±7.4	40.0±7.4*	38.9±6.6	39.1±6.7 °	38.3±6.2	40.5±8.0	39.1±5.5
Race, N (%)							
Caucasian	9,788 (93.9)	7,721 (93.9)	1,816 (95.2)	1,355 (94.9)	461 (96.2)	351 (93.4)	107 (95.5)
African American	264 (2.5)	204 (2.5)	26 (1.4)	22 (1.5)	4 (0.8)	8 (2.1)	0
Hispanic	344 (3.3)	279 (3.4)	59 (3.1)	46 (3.2)	13 (2.7)	16 (4.3)	5 (4.5)
Other	30 (0.3)	23 (0.3)	6 (0.3)	5 (0.4)	1 (0.2)	1 (0.3)	0
Ever smokers, N (%)	3,932 (37.7)	3,028 (36.8)¶	635 (33.3)	488 (34.2)	147 (30.7)	0	0
WTC arrival time, N (%)							
9/11-9/12	9,137 (87.6)	7,190 (87.4)	1,742 (91.4)	1,303 (91.3)	439 (91.6)	348 (92.5)	104 (92.9)
After 9/12	1,289 (12.4)	1,037 (12.6)¶	165 (8.6)	125 (8.7)	40 (8.4)	28 (7.5)	8 (7.1)
WTC work duration, N (%)¶							
1 month	2,963 (28.4)	2,407 (29.3)	431 (22.6)	332 (23.3)	99 (20.7)	129 (34.3)	31 (27.7)
2-5 months	4,939 (47.4)	3,860 (46.9)	887 (46.5)	664 (46.5)	223 (46.6)	149 (39.6)	44 (39.3)
≥ 6 months	2,524 (24.2)	1,960 (23.8)¶	589 (30.9)	432 (30.2)	157 (32.8)	98 (26.1)	37 (33.0)
Eosinophil /mL 18 mo post-9/11	N/A	191±134*	200±135	194±128⊙	219±155	174±108	218±159
Yrs to 1st sinus diagnosis	7.6±3.6	7.6±3.6	7.8±3.6	8.1±3.6⊙	6.7±3.3	N/A	6.9±3.4
Yrs to CRS surgery	8.7±2.8	8.7±2.9	8.7±2.9	N/A	8.7±2.9	N/A	8.7±2.9

¶p< 0.001 log rank test; *p< 0.0001 score test between Study Cohort and surgical CRS °p< 0.05 and ⊙p<0.001 between medical CRS and surgical CRS, t test

Table 2: Cox proportional hazards predicting CRS surgery

	Full Cohort (N=8,227)			Smoking Stratified Model						Biomarker Sub-Study (N=488)		
				Never Smoker (N=5,199)			Ever Smoker (N=3,028)					
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Increasing Eos per 100 cell/μl	1.12	1.07-1.17	<0.001	1.12	1.06-1.19	<0.001	1.13	1.05-1.22	0.001	1.23	1.08-1.41	0.003
Early WTC Site Arrival	1.43	1.04-1.99	0.03	1.22	0.84-1.77	0.29	2.18	1.11-4.29	0.023	0.88	0.42-1.82	0.73
WTC Site Work Duration												
1 Month	Ref			Ref			Ref			Ref		
2-5 Months	1.09	0.85-1.40	0.49	0.94	0.70-1.27	0.69	1.49	0.94-2.36	0.088	0.89	0.53-1.48	0.65
≥ 6 Months	1.48	1.14-1.93	0.003	1.42	1.05-1.94	0.024	1.58	0.95-2.61	0.077	1.18	0.70-1.98	0.54
Age (years)	0.98	0.97-0.99	0.003	0.99	0.97-1.00	0.12	0.97	0.95-0.99	0.007	0.98	0.95-1.01	0.16
Ever Smoker	0.80	0.65-0.97	0.022									
Increasing IL-6 pg/mL										0.84	0.72-0.97	0.02
Increasing IgE ng/mL										1.01	0.99-1.03	0.23

Table 3: Linear models predicting eosinophils cells/µL in post-9/11 blood⌘

	CRS Surgery (N=112) §				No sinus disease (N=376) *			
	B	Std Err	Std B	p	B	Std Err	Std B	p
Age (years)	6.67	2.42	0.23	0.007	-0.18	0.71	-0.01	0.80
IL-17A pg/mL	1.15	0.22	0.43	<0.001¶	-0.27	0.23	-0.06	0.23
IgA ≤ 300 ng/mL	-108.45	40.28	-0.23	0.008	3.85	16.28	0.01	0.81
Months to exam	-28.60	16.72	-0.15	0.09	5.42	5.48	0.05	0.32

⌘From 1.5 to 6 months post 9/11, §Model R^2=0.26 p<0.0001, ¶p after Bonferroni correction, *Model R^2=0.008, p= 0.56

Figure 1

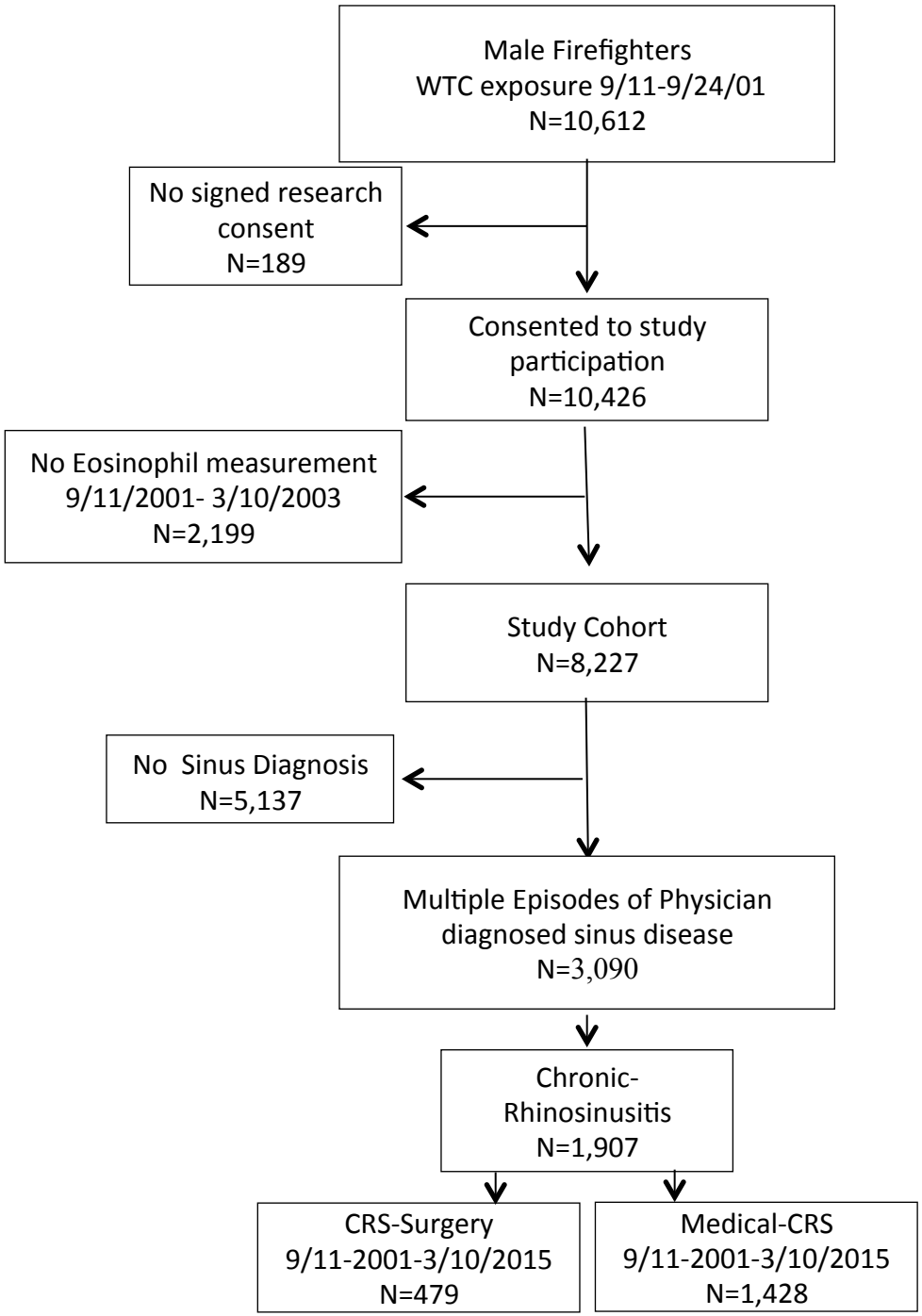

Male Firefighters
WTC exposure 9/11-9/24/01
N=10,612
No signed research consent
N=189
Consented to study participation
N=10,426
No Eosinophil measurement
9/11/2001- 3/10/2003
N=2,199
Study Cohort
N=8,227
No Sinus Diagnosis
N=5,137
Multiple Episodes of Physician diagnosed sinus disease
N=3,090
Chronic-Rhinosinusitis
N=1,907
CRS-Surgery
9/11-2001-3/10/2015
N=479
Medical-CRS
9/11-2001-3/10/2015
N=1,428

Figure 2

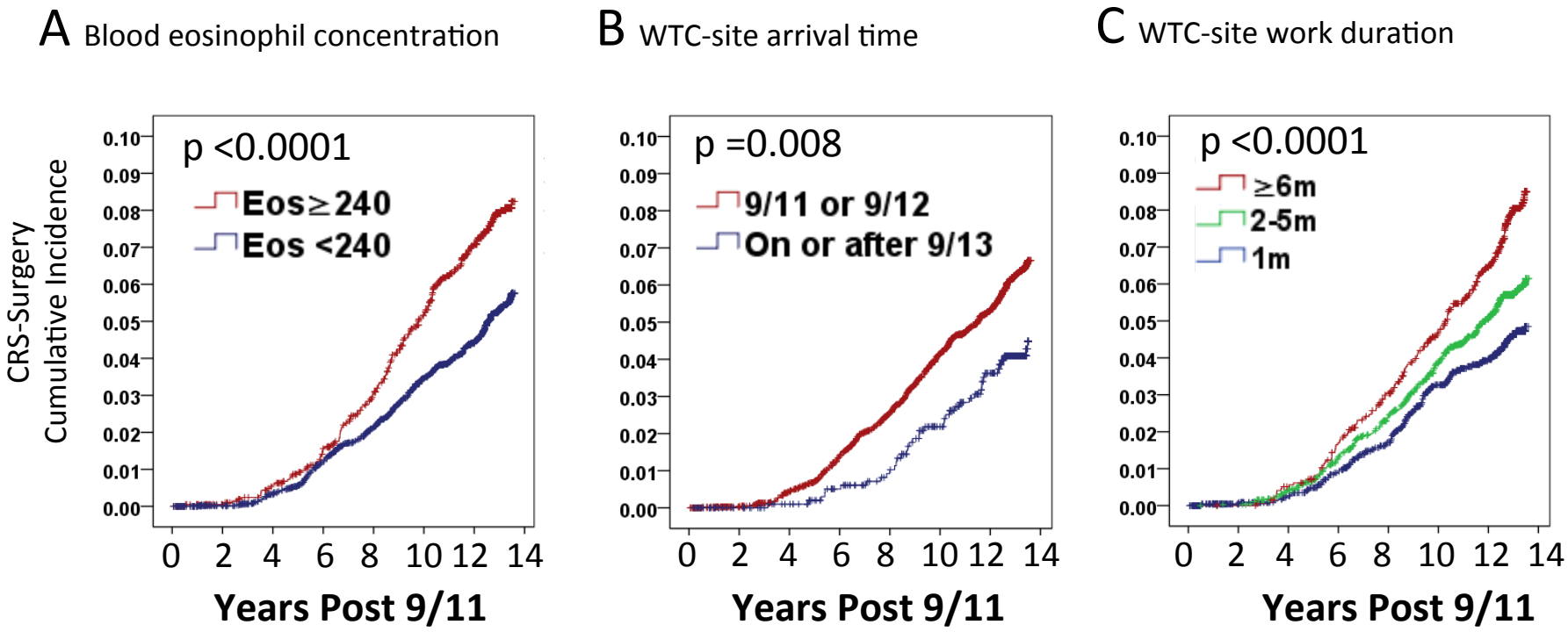
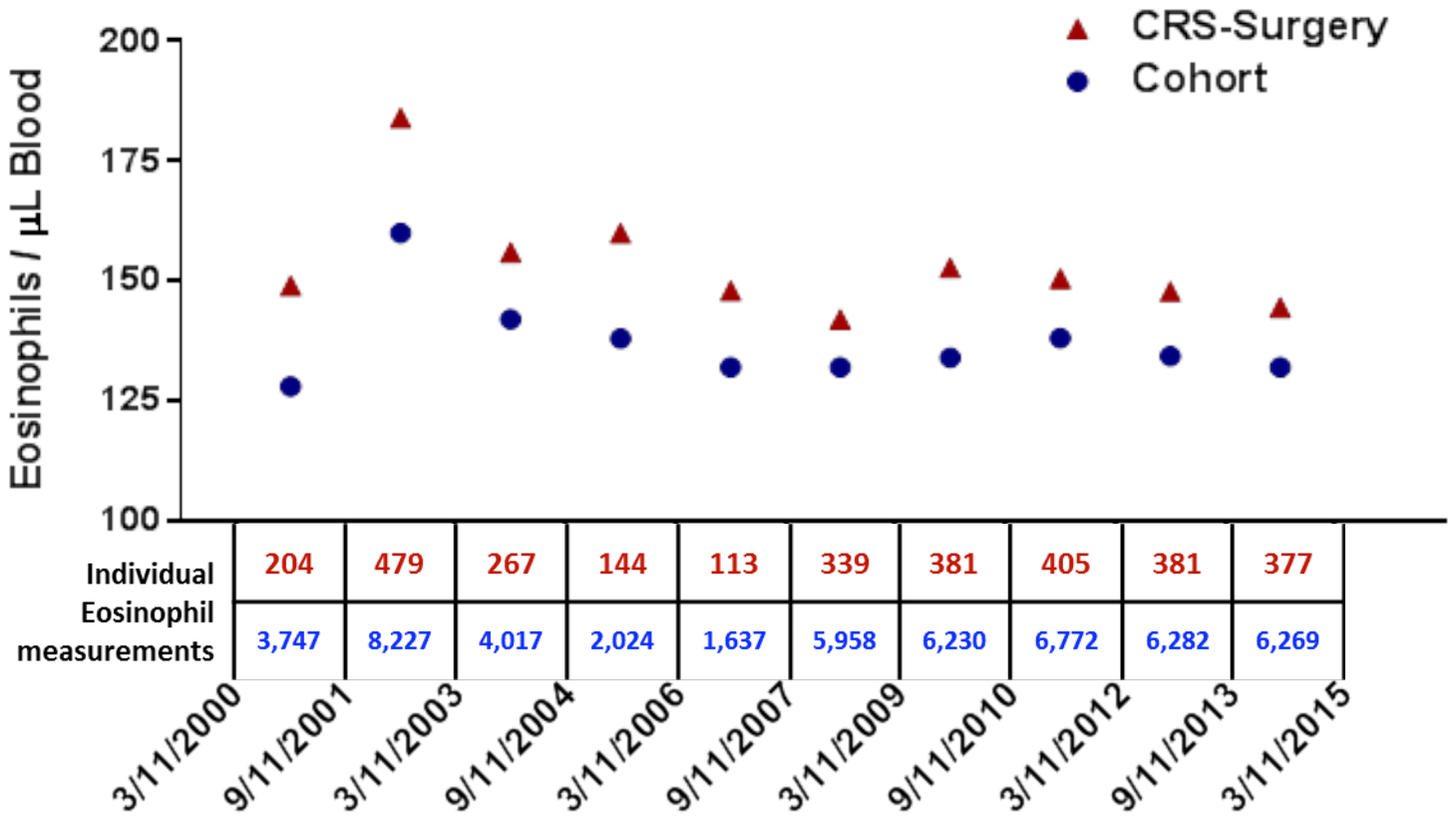

A Blood eosinophil concentration
B WTC-site arrival time
C WTC-site work duration
CRS-Surgery Cumulative Incidence
p <0.0001
Eos≥240
Eos <240
p =0.008
9/11 or 9/12
On or after 9/13
p <0.0001
≥6m
2-5m
1m
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.10
0 2 4 6 8 10 12 14
Years Post 9/11

Figure 3


CRS-Surgery
Cohort
Eosinophils / µL Blood
200
175
150
125
100
Individual Eosinophil measurements
204 479 267 144 113 339 381 405 381 377
3,747 8,227 4,017 2,024 1,637 5,958 6,230 6,772 6,282 6,269
3/11/2000
9/11/2001
3/11/2003
9/11/2004
3/11/2006
9/11/2007
3/11/2009
9/11/2010
3/11/2012
9/11/2013
3/11/2015