Journal of Asthma, 2013; 50(1): 25–32

ISSN: 0277-0903 print/1532-4303 online
DOI: 10.3109/02770903.2012.743149

informa
healthcare

BIOMARKERS

Elevated Peripheral Eosinophils Are Associated with New-Onset and Persistent Wheeze and Airflow Obstruction in World Trade Center-Exposed Individuals

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Background. Exposure to World Trade Center (WTC) dust and fumes is associated with the onset of asthma-like respiratory symptoms in rescue and recovery workers and exposed community members. Eosinophilic inflammation with increased lung and peripheral eosinophils has been described in subpopulations with asthma. We hypothesized that persistent asthma-like symptoms in WTC-exposed individuals would be associated with systemic inflammation characterized by peripheral eosinophils. *Methods*. The WTC Environmental Health Center (WTC EHC) is a treatment program for local residents, local workers, and cleanup workers with presumed WTC-related symptoms. Patients undergo a standardized evaluation including questionnaires and complete blood count. Between September 2005 and March 2009, 2462 individuals enrolled in the program and were available for analysis. Individuals with preexisting respiratory symptoms or lung disease diagnoses prior to September 2001 and current or significant tobacco use were excluded, *Results.* One thousand five hundred and seventeen individuals met the inclusion criteria. Patients had a mean age of 47 years, were mostly female (51%), and had a diverse race/ethnicity. Respiratory symptoms that developed after WTC dust/fume exposure and remained persistent included dyspnea on exertion (68%), cough (57%), chest tightness (47%), and wheeze (33%). A larger percentage of patients with wheeze had elevated peripheral eosinophils compared with those without wheeze (21% vs. 13%, $p < .0001$). Individuals with elevated peripheral eosinophils were more likely to have airflow obstruction on spirometry (16% vs. 7%, $p = .0003$). *Conclusion*. Peripheral eosinophils were associated with wheeze and airflow obstruction in a diverse WTC-exposed population. These data suggest that eosinophils may participate in lung inflammation in this population with symptoms consistent with WTC-related asthma.

Keywords asthma, eosinophil, spirometry, World Trade Center

INTRODUCTION

The destruction of the World Trade Center (WTC) towers on September 11, 2001 resulted in the massive release of dust, gas, and fumes with potential environmental and occupational exposures for thousands of individuals. Adverse health effects from these exposures are well described for rescue and recovery workers with work-related exposure, as well as for community members including local workers in the WTC towers and in surrounding commercial spaces, and residents of the surrounding buildings (1–11). Community members, including over 360,000 local workers and over 57,000 residents in south of Canal Street in lower Manhattan, alone have been estimated to have had potential dust and fume exposure (12). Exposure to the dust cloud from the collapsing buildings on September 11, 2001 and exposure to resuspended dusts and ongoing fumes have been shown to be associated with new-onset lower respiratory tract symptoms (LRSs) in local community members (13, 14).

Most studies of WTC-exposed populations demonstrate the presence of new-onset and persistent LRSs of cough, wheeze, dyspnea on exertion (DOE), and chest tightness. These symptoms have been found to persist at least 5 years after exposure (7, 8, 10, 13, 15). Most patients in screening or treatment programs for rescue workers or community members with potential for WTC dust/fume exposures have been described to have normal spirometry, with only one-third displaying abnormalities on screening spirometry (3, 15). Airflow obstruction was identified in only a minority of individuals in these studies; a low forced vital capacity (FVC) was a more common abnormality (3, 15, 16). In a recent study of WTC-exposed community members, those with LRS had an increase in abnormal spirometry and oscillometry measurements compared with those without LRS symptoms; these lung function abnormalities were associated with WTC dust/fume exposure (17). Many rescue workers and responders, as well as community members with LRS, have persistent hyperresponsiveness (1, 2, 9). Thus, most patients have been given a diagnosis of reactive airways dysfunction, irritant-induced asthma, or asthma. However, not all patients clearly fit the diagnosis of asthma, and in some patients, sarcoidosis and other interstitial lung diseases have also been described, suggesting a variety of pathologic processes in WTC-exposed patients (18–20).

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Few studies have examined biological processes involved in WTC-related LRS. Rom et al. (21) reported a case of acute eosinophilic pneumonia in a firefighter with symptoms that developed soon after the event. Fireman et al. (22) reported an increase in both sputum eosinophils and neutrophils in WTC-exposed firefighters that persisted 1 year after the event. Elevated blood levels of proinflammatory cytokines, including granulocyte macrophage-colony stimulating factor (GM-CSF), have been identified in the blood samples obtained from the firefighters soon after the event (23). Blood or peripheral eosinophils have been suggested as a biomarker for phenotypes of asthma (24).

The WTC Environmental Health Center (WTC EHC) is a treatment program for self-referred community members (residents and individuals who worked in the area surrounding the WTC) as well as for individuals involved in the cleanup of the surrounding area (cleanup workers). These individuals undergo a standardized WTC dust/fume exposure and clinical evaluation including a complete blood count. Because eosinophilic inflammation is associated with some patients with asthma, and sputum eosinophilia has been described in the WTC-exposed firefighters, we hypothesized that new-onset and persistent LRS in patients enrolled in the WTC EHC would be associated with an eosinophilic process reflected by elevated blood eosinophils.

Materials and Methods

Subjects

Patients were enrolled in the Bellevue WTC EHC as described (15). In brief, patients were self-referred in response to program information distributed by community-based organizations and local news and advertisements. Enrollment criteria included exposure to WTC dust, gas, or fumes as a local worker, resident, or cleanup worker in southern Manhattan on or in the months after September 11, 2001 and the presence of a physical symptom that occurred or was exacerbated after September 11, 2001. Patients who enrolled over the 42-month period from September 2005 to March 2009 were included in the analysis.

Exclusion criteria for the main analysis included the existence of respiratory symptoms or disease prior to September 11, 2001 and active or significant past smoking history ($\geq$5 pack-years). The study was approved by the New York University School of Medicine Institutional Review Board, and all patients who were analyzed signed consent.

Procedures

On enrollment in the program, the patients were administered a multidimensional questionnaire that queried demographics and exposure to WTC dust via occupation, work or residence, and symptoms, including the symptoms of severity and temporal relationship relative to September 11, 2001. A physical examination and blood test, including automated complete blood cell counts, were performed. All individuals were initially referred for spirometry, which was performed in accordance with the American Thoracic Society/European Respiratory Society standards using a SensorMedics spirometer (Yorba Linda, CA, USA) (25). For over 30% of patients, the blood collection and spirometry were performed on the same day they underwent the initial evaluation. Spirometry testing was completed within 3 months for 84% of patients. The initial protocol was amended in 2006 to include postbronchodilator studies after inhalation of albuterol sulfate, as well as prebronchodilator spirometry. Reversibility was defined as a 12% and 200-ml improvement in forced expiratory volume in 1 second (FEV_1) after inhalation of albuterol sulfate.

LRSs were defined as cough, chest tightness, DOE, and daytime wheeze or nocturnal wheeze. "New-onset" respiratory symptoms were defined as symptoms that began after September 11, 2001. "Persistent symptoms" were defined as symptoms that were present at a frequency $\geq$2 times each week in the month preceding entry into WTC EHC. The Asthma Symptom Utility Index was utilized in the questionnaire, and wheezing was assessed by frequency (0, 1–2, or 3–7 days per week) and by severity (none, mild, moderate, or severe) (26).

Predicted values for FVC and FEV_1 were derived from National Health and Nutrition Examination Survey III (NHANES III) (27). Spirometry was categorized by spirometric pattern as normal, obstructed ($FEV_1/FVC < LLN_{FEV1/FVC}$), or low FVC ($FEV_1/FVC > LLN_{FEV1/FVC}$ and $FVC < LLN_{FVC}$), and these patterns were used for further analysis (28).

Blood eosinophil counts (absolute eosinophil blood counts) were performed using an automated clinical system. Eosinophil counts were analyzed, and considered elevated if the blood eosinophil counts were $\geq$4% (high eosinophils), reflecting elevated and normal values in the reference laboratory. A peripheral blood eosinophil count of $>0.5 \times 10^9 L^{-1}$ blood was also considered elevated. Since initial analyses did not demonstrate a difference between these two parameters (data not shown), data are presented after dichotomizing by percent eosinophils.

Data Analysis

We describe the population as a whole and after stratification by eosinophil percentage. Descriptive statistics of counts and proportions were calculated for categorical variables. Means and standard deviations were calculated for continuous variables. We performed univariate analysis using the chi-square test for categorical variables and the *t*-test or Wilcoxon rank-sum test for continuous variables.

Multivariate nominal logistic regression was performed to examine the association between the spirometry patterns and the eosinophil levels controlling for significant variables on univariate analysis (i.e., age and gender). *P*-values less than .05 were considered statistically significant. For each individual analysis, individuals with missing values were excluded from the calculations. All statistical analyses were conducted using Statistical Analysis System (SAS, version 9.2, SAS Institute).

RESULTS

Patient's Characteristics

Two thousand four hundred and sixty-two patients of age >17 years were consecutively enrolled and signed consent between September 2005 and March 2009 (Figure 1). Nine hundred and forty-five patients were excluded for the presence of respiratory symptoms or respiratory diagnosis prior to September 11, 2001 ($n = 414$) and current or >5 pack-year tobacco history ($n = 531$). The baseline demographics of the eligible patients ($n = 1517$) are shown in Table 1. Although nearly equal, there were more women (51%) than men. The mean age was 47.5 years, and the average body mass index (BMI) was 28.2. The group was racially and ethnically diverse. Many patients (42%) reported being in the initial dust cloud created as the buildings collapsed on September 11, 2001.

The population was stratified into those with high eosinophils ($n = 220$) and those with low eosinophils ($n = 1195$). More males were in the high-eosinophils group compared with the low-eosinophils group (59% vs. 41%, respectively; $p = .002$). The high-eosinophils group was slightly younger than the low-eosinophils group (45.6 ± 1.0 years vs. 47.7 ± 0.4 years; $p = .04$), but there was no significant difference in race/ethnicity or BMI. There was no association between exposure and eosinophils, neither initial WTC dust cloud exposure nor potential exposure as resident, local worker, or cleanup worker was associated with high eosinophils. These findings did not differ when data were analyzed using absolute eosinophil counts (data not shown).

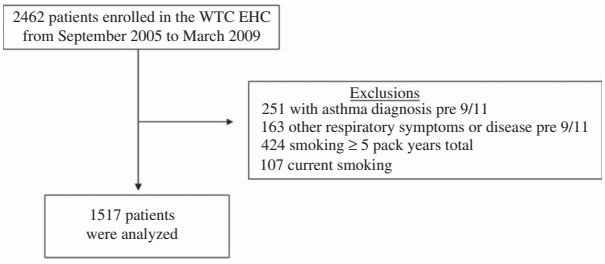

FIGURE 1.—World Trade Center Environmental Health Center (WTC EHC) population were enrolled.

Lower Respiratory Symptoms and Eosinophils

Most symptoms reported by the 1517 patients in the study included upper respiratory tract symptoms and LRSs, with more than 75% reporting the presence of a new-onset and persistent LRS. DOE and cough were the most common symptoms (68% and 57%, respectively), although many described chest tightness (46%) and wheeze (33%). The most common non-LRSs included nasal/sinus symptoms (48%), gastroesophageal reflux symptoms (48%), headaches (45%), and rash (23%). The association of LRS, a specific LRS, and non-LRSs with the high- and low-eosinophils groups is shown in Figure 2. There was no association between high and low eosinophils and presence of LRS. When dichotomized by high and low eosinophils, examination of specific LRS symptoms revealed that more patients with wheeze had high eosinophils compared with low eosinophils (56% vs. 43% for daytime wheeze, respectively; $p < .001$ and 37% vs. 27% for nocturnal wheeze, respectively; $p < .002$; panel A). No significant difference in the patients with specific symptoms of DOE, cough, and chest tightness was noted for these eosinophils groups. No difference in specific non-LRS (nasal congestion, gastroesophageal reflux symptoms, headache, and rash) was noted between high- and low-eosinophils groups (Figure 2, Panel B). The association between wheeze and high eosinophils remained

TABLE 1.—Characteristics of the WTC EHC population with new-onset and persistent LRSs as whole and stratified by eosinophil percentage.

	Total* $n = 1517$	High eosinophils $n = 220$	Low eosinophils $n = 1195$	*P*-value**
Gender, *n* (%)				.002
Male	743 (49)	130 (59)	567 (47)	
Female	774 (51)	90 (41)	628 (53)	
Age, mean ± SE	47.5 ± 0.3	45.6 ± 1.0	47.7 ± 0.4	.04
BMI, mean ± SE	28.2 ± 0.2	28.0 ± 0.4	28.2 ± 0.2	NS
Race/ethnicity, *n* (%)				NS
Non-Hispanic white	393 (26)	47 (21)	309 (26)	
Non-Hispanic black	232 (15)	34 (16)	180 (15)	
Hispanic	684 (45)	110 (50)	542 (45)	
Asian	192 (13)	27 (15)	151 (13)	
No answer	16 (1)	2 (1)	13 (2)	
Exposure category, *n* (%)				NS
Cleanup worker	440 (29)	66 (31)	360 (30)	
Rescue and recovery	83 (5)	14 (6)	66 (5)	
Resident	289 (19)	35 (16)	229 (19)	
Local worker	575 (37)	83 (38)	450 (37)	
Other	130 (8)	22 (10)	90 (7)	
Dust cloud exposure, *n* (%)				NS
Yes	630 (42)	97 (45)	498 (43)	
No	854 (58)	118 (55)	672 (57)	

Note: *One hundred and two patients did not have phlebotomy performed; dust cloud data are missing in 33 subjects.
**Univariate analysis using Wilcoxon rank-sum test or chi-square test.

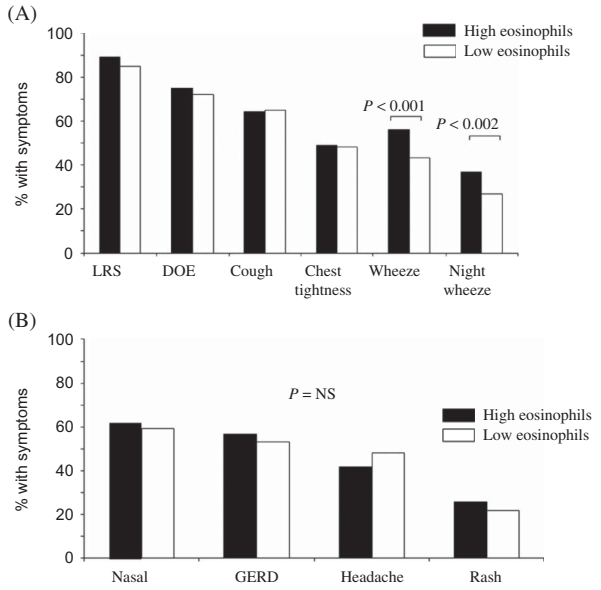

FIGURE 2.—Comparison of symptoms in the high- and low-eosinophil groups.
Percent of individuals in high- and low-eosinophils groups with (A) lower respiratory symptoms and (B) non-lower respiratory symptoms.

significant even when patients were stratified by time of enrollment in the clinic ($p < .04$ for patients enrolled in the first tertile and $p < .001$ for patients enrolled in the last tertile is shown in Appendix Figure 1).

Because wheeze was the cardinal symptom associated with blood eosinophils, we evaluated whether there was an association of peripheral eosinophils with severity of wheeze using frequency of symptoms or severity of symptoms described as mild, moderate, or severe (Figure 3). Patients with high eosinophils were more likely to have an increase in wheezing frequency and wheeze severity, with the percentage of high-eosinophils patients increasing from 16.7% in the mild group to 22.3% in the severe group (Figure 3, panel B; p for trend < .001).

Spirometry and LRSs

Spirometry results were available for 1159 patients (Table 2). Mean values for FVC, FEV_1, and FEV_1/FVC were within the normal limits for the total population (data not shown). As a whole, the majority of the population (75%) demonstrated a normal spirometry pattern with an obstructive pattern in 9% of the population. The presence of wheeze was noted in 36% of the study population, and

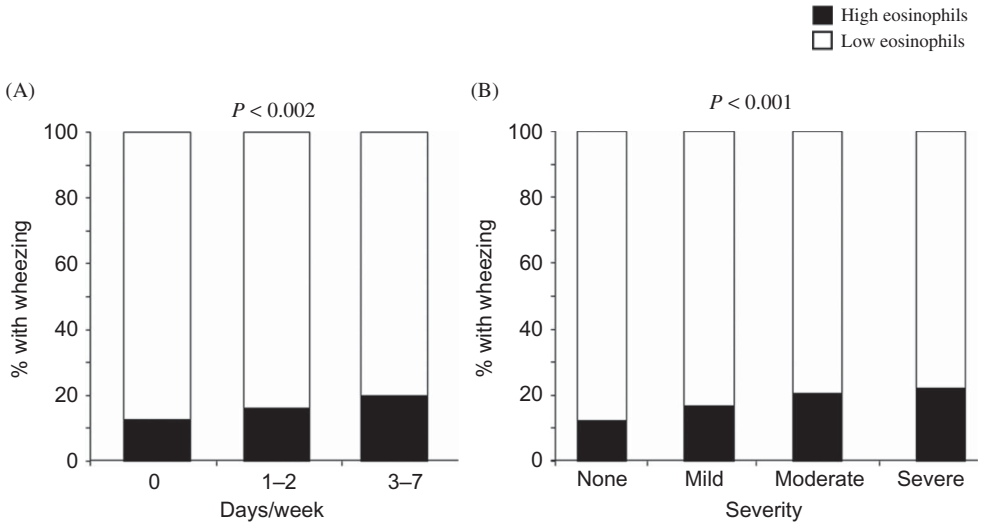

FIGURE 3.—Wheezing severity and eosinophil group. Percent of population with wheezing severity categorized as (A) number of days/week with wheezing and (B) description of severity. *P*-values <.05 are significant.

TABLE 2.—Presence of wheezing and spirometry category.

Category	Total* $n = 1159$	Wheeze yes $n = 412$	Wheeze no $n = 747$	OR†	*P*-value**
Spirometry pattern, *n* (%)					.002‡
Normal	865 (75)	285 (69)	580 (78)	1	
Obstructed[a]	99 (9)	49 (12)	50 (7)	1.99	.001¶
Low FVC[b]	195 (17)	78 (19)	117 (16)	1.36	NS¶

Note: [a]FEV_1/FVC<LLN FEV_1/FVC.
[b]FVC<LLN FVC and FEV_1/FVC>LLN FEV_1/FVC.
[c]Unadjusted OR.
*Three hundred and ten patients from the total population did not have spirometry adequate for evaluation and 63 patients had missing values for wheeze.
**Univariate analysis using chi-square test.
‡*P*-value represents comparison of all three categorical subgroups.
¶*P*-values represent comparison of specific subgroup with the baseline subgroup with the OR of 1.

TABLE 3.—Presence of eosinophils within each spirometry category.

Category	Total* $n = 1140$	High eosinophils $n = 176$	Low eosinophils $n = 964$	OR†	*P*-value
Spirometry pattern, *n* (%)					.001
Normal	852 (75)	117 (66)	735 (76)	1	
Obstructed[a]	97 (9)	27 (16)	70 (7)	2.42	.0002
Low FVC[b]	191 (17)	32 (18)	159 (17)	1.27	NS

Note: [a]$FEV_1/FVC<LLN\ FEV_1/FVC$.
[b]$FVC<LLN\ FVC$ and $FEV_1/FVC>LLN\ FEV_1/FVC$.
†Unadjusted OR.
*PFT category is missing in 310 subjects. Eosinophil counts are missing in 102 subjects.

was associated with an obstructive spirometry pattern [odds ratio (OR) 1.99, $p < .001$]. New-onset and persistent DOE were noted in 68% of the population and were associated with a low-FVC spirometry pattern (OR 1.54, $p < .02$). Neither cough nor chest tightness discriminated between any lung function patterns, and thus was not included in subsequent analyses.

Spirometry and Eosinophil Levels

Spirometry results and eosinophil counts were available for 1140 patients. There was no significant association between high eosinophils and a reduction in specific spirometry measurements, including FVC, FEV_1, and FEV_1/FVC (data not shown). In contrast, as shown in Table 3, the presence of high eosinophils was associated with an obstructed spirometry pattern (OR 2.42, $p < .0002$). A significant bronchodilator response (200 mL increase in FEV_1 and 12% improvement in FEV_1) was also associated with high-eosinophils group compared with low-eosinophils group (34% vs. 24%; $p = .01$). The presence of high eosinophils was not associated with a low-FVC spirometry pattern.

DISCUSSION

Many local residents, local workers, and individuals involved in the cleanup activities after the destruction of the WTC towers on September 11, 2001 were exposed to WTC dust, gases, and fumes. An association between WTC exposures and LRS has been described (14, 17). As has been described for firefighters and responders, community members commonly presented with diverse LRSs and heterogeneous lung function patterns (15, 16, 29). We now report the association of elevated blood eosinophils with new-onset and persistent wheeze and an obstructive lung function pattern suggesting a role of eosinophils in the underlying inflammatory process.

The finding of an increase in peripheral eosinophils in symptomatic WTC-exposed patients is in accordance with the few descriptions of inflammatory responses in WTC-exposed residents. A case report of a firefighter, and a study of WTC-firefighters compared with Israeli firefighters both demonstrated eosinophils in the bronchoalveolar lavage and in induced sputum (21, 22). Our study, using a peripheral biomarker, is consistent with these studies and suggests that in some patients with WTC dust and fume exposure that occurred as a result of exposure as a local worker, resident, or cleanup worker, an eosinophilic process may be present. The presence of eosinophils is consistent with the finding of elevated levels of GM-CSF in serum from the firefighter population (23). The persistence of elevated eosinophils and symptoms identified in this population 4–7 years after September 11 suggests an ongoing process.

The presence of increased peripheral eosinophils was associated with specific symptoms of wheeze, but not DOE. LRSs of wheeze have been suggested to have high sensitivity for asthma in epidemiologic studies, although they are not diagnostic of asthma (30). The finding of the association of elevated eosinophils with this symptom, but not with overall LRS or symptoms of cough or chest tightness, suggests, but does not prove, that eosinophils were associated with a more "asthma-like" syndrome in these patients.

Asthma is a heterogeneous disease with different phenotypes. Elevated eosinophils, identified in induced sputum, bronchoalveolar lavage, or bronchial biopsy, have been associated with many, but not with all adults and children with asthma (24, 31). Blood eosinophils have been suggested as a biomarker to monitor asthma (24). A "low-T_h2" lymphocyte/eosinophil and "high-T_h2" lymphocyte/eosinophil asthmatic populations have also been suggested based on the microarray studies of brushed bronchial epithelial cells (32). A recent multidimensional cluster analysis of common clinical factors and measurements distinguished seven clinical subphenotypes, three of which demonstrated an eosinophil predominance (33). Eosinophilic inflammation has been associated with airway basement membrane remodeling, bronchial hyperreactivity, spirometric parameters of airflow obstruction, physiological and clinical improvements, and fewer exacerbations after treatment with inhaled corticosteroids (34–40). Subgroup analysis of patients enrolled in the WTC EHC with a diagnosis of asthma prior to September 11, 2001 ($n = 251$) also showed an association between the presence of wheeze and high eosinophils ($p < .0003$). These studies highlight the presence of eosinophilic inflammation in subgroups of individuals with asthma. We now suggest the presence of elevated eosinophils in a subgroup of individuals with wheezing after an environmental exposure.

Occupational asthma, one asthma phenotype, has been categorized into reactive-airways dysfunction syndrome (RADS) and irritant-induced asthma. Whereas, RADS involves the sudden onset of asthma symptoms after a single brief, high-level exposure (41–43), irritant-induced asthma typically requires a longer exposure period and often has a delayed onset of symptoms. Irritant-induced asthma has been suggested to result from direct

airway epithelial damage with a subsequent release of proinflammatory mediators (44). A few case reports or retrospective cohort studies of irritant-induced asthma resulting from a variety of exposures suggest the presence of eosinophils, although these findings have been inconsistent (44–50). The pattern of exposure and the presence of LRS have suggested the possible diagnosis of irritant-induced asthma in many of the WTC-exposed community members and cleanup workers (4, 15, 51). In addition, the presence of airway hyperreactivity in very limited studies also supports the diagnosis of asthma (1, 2, 4, 23, 52). Our data, using blood eosinophils as a biologic marker, suggest an eosinophilic process in some patients with WTC exposure and asthma-like symptoms. Eosinophils were most strongly associated with the symptom of wheeze and an obstructive pattern on spirometry. These data suggest that symptoms consistent with WTC-related irritant-induced asthma may be associated with an eosinophilic process.

We were only able to detect an association between elevated eosinophils and asthma-like symptom of wheeze, and an obstructed spirometry pattern. We did not detect an association between eosinophils and other respiratory symptoms. Moreover, DOE was associated with a reduced FVC rather than an obstructive pattern. These findings suggest that there may be differences in the underlying mechanisms resulting in LRS and may have implications for diagnosis and treatment.

There are several potential limitations to our study. Most patients had normal spirometry, and we did not routinely perform methacholine testing. Thus, we can only suggest a diagnosis of asthma. This was a study of a population affected by a disaster. As such, we do not have preexisting lung function data and use self-report of symptoms. Thus, we cannot confirm the attribution of symptoms to WTC exposures, but use the combination of reported exposure, temporal association, and pattern of symptoms, shown in previous epidemiological studies, to suggest a likely cause and effect (14, 17). The quantification of eosinophils performed in sputum and bronchoalveolar lavage has been suggested as a preferred biomarker in asthma. As a large clinical program it was not feasible to obtain sputum on a routine basis and thus evaluated only peripheral eosinophils. Despite this, we detected an association of peripheral eosinophils and specific symptoms. The quantification of eosinophil counts and percentages were performed with automated systems, which may be less accurate than manual count but all patients were examined in the same manner, thus providing a technical bias that would have affected all patients. Atopic status is an important phenotype in asthma and the presence of allergen-specific IgE can serve as a biomarker for atopic asthma. Our program was a treatment program, and our clinical protocol, as per Expert Panel Report III (EPR III) recommendations, did not routinely include allergy testing or total or allergen-specific IgE measurements. The possibility exists that atopy could influence the presence of symptoms in our population. Although the presence of allergic sensitization to multiple allergens is well documented as a risk for asthma, airway hyperresponsiveness, and wheeze (53), a recent study of atopy and upper and lower airway disease in WTC workers and volunteers did not show a relationship between atopy and lower airway symptoms (54). This finding may not be directly comparable to our community population with WTC dust and fume exposure.

In summary, these data suggest a potential inflammatory mechanism for WTC-related lung disease in a subpopulation of patients who present with symptoms consistent with asthma and an obstructive lung pattern. The possibility exists that a different pathophysiologic mechanism may be invoked for those with other symptoms. Further exploration of underlying cellular process in these populations will help characterize the underlying lung injury in this considerable population of symptomatic individuals with a unique environmental and occupational exposure.

Conclusion

Peripheral eosinophils were associated with wheeze and obstructive lung function in a diverse WTC-exposed population. These data suggest that eosinophils may participate in lung inflammation in this population with symptoms consistent with WTC-related asthma.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article. Grant sponsor: this study received grants from The Centers for Disease Control National Institute for Occupational Safety and Health, New York, NY, USA, with the grant number 1E11OH009630 and also received grants from The National Institutes of Health with the grant number T32 ES007267.

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APPENDIX

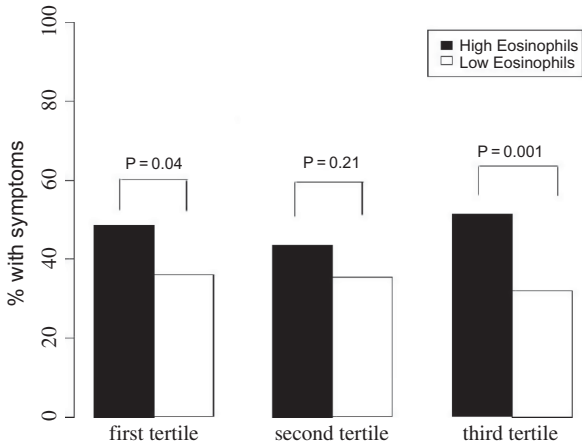

FIGURE A1.—Comparison of wheezing symptoms in the high- and low-eosinophil groups for each tertile follow-up time group.