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Environmental Allergies and Respiratory Morbidities in Cystic Fibrosis

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SUMMARY

Background—Cystic fibrosis (CF) is characterized by recurrent respiratory infections and progressive lung disease. Although environmental factors account for 50% of the variation in CF lung function, few specific exposures have been identified. Studies using small study samples focusing on environmental allergies in CF have had inconsistent results. Our objective was to examine the role of environmental allergies in upper and lower respiratory tract morbidities in CF.

Methods—A total of 1321 subjects with CF were recruited through the U.S. CF Twin-Sibling Study. Questionnaires were used to determine the presence/absence of environmental allergies. Questionnaires, chart review, and U.S. CF Foundation Patient Registry data were used to track outcomes.

Results—Within the study sample 14% reported environmental allergies. Environmental allergies were associated with a higher risk of sinus disease (adjusted OR: 2.68; $p < 0.001$) and nasal polyps (adjusted OR: 1.74; $p = 0.003$). Environmental allergies were also associated with a more rapid decline in lung function (additional $-1.1\%/year$; $p = 0.001$). However, allergies were associated with a later median age of acquisition of *Pseudomonas aeruginosa* (6.6 yo vs. 4.4 yo; log rank $p = 0.027$). The reported use of common allergy medications, anti-histamines and leukotriene inhibitors, did not alter the frequency of respiratory morbidities.

Conclusions—Environmental allergies are associated with an increased risk of sinus disease and nasal polyps and a more rapid decline in CF lung function, but may have a protective effect against the acquisition of *P. aeruginosa*. Prospective studies are needed to confirm these associations which have implications for more aggressive management of allergies.

Keywords

Cystic Fibrosis; Lung Function; FEV₁; Allergies; Sinus Disease; Nasal Polyps; *Pseudomonas aeruginosa*

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INTRODUCTION

Cystic fibrosis (CF) is characterized clinically by recurrent respiratory infections and progressive lung disease, which account for the majority of morbidity and mortality associated with this disorder. As half of the variation in CF lung function is due to non-genetic factors,¹ examining the role of environmental factors is essential in ameliorating disease. Environmental factors previously shown to impact lung function in CF include secondhand smoke,² health insurance,³ household income,⁴ air pollution,⁵ and ambient temperature.⁶ The association of warmer temperatures and worse CF lung function replicated in the United States and Australia is only partially explained by the prevalence of a common CF respiratory pathogen, *Pseudomonas aeruginosa*, thus there may be other geographically-based environmental factors playing a role in lung function variation, such as environmental allergens.

The presence of environmental allergens has been associated with worse respiratory outcomes in other obstructive lung diseases, most notably asthma⁷ and COPD.⁸ However, with the exception of allergic bronchopulmonary aspergillosis,⁹ it remains unclear whether an allergic response to specific environmental exposures leads to increased respiratory morbidities in CF.^{10,11} Two studies have demonstrated an association between reduced forced expiratory volume in 1 second (FEV₁) and environmental allergies defined by skin testing (n=25; $p<0.01$; n=48; $p<0.05$).^{12,13} Other studies have found similar associations between FEV₁ and allergies when defined by other methods, such as urinary cysteinyl leukotriene E₄ (n=35; $p<0.01$).¹⁴ However, some studies have shown no association between skin testing response and FEV₁ (n=104; $p>0.05$)¹⁵ or peak expiratory flow rates (n=31; $p>0.05$).¹⁶ No difference has been observed in survival among CF patients with and without allergies as defined by skin testing (n=117; $p>0.05$).¹⁷

Several relationships between CF lung disease and allergic response have been postulated. First, airway epithelium inflamed through infections may retain inhaled allergens more effectively.^{10,11} Second, inflammation secondary to allergies may predispose towards pathogen colonization and infection. Third, *CFTR* mutations may predispose individuals to atopy compared to the general population.¹⁸ In any case, allergic inflammation may exacerbate the baseline inflammation associated with CF lung disease^{15,19} in an additive or multiplicative manner. If environmental allergies are associated with respiratory morbidities, then management of environmental allergies would be an attractive target for intervention as therapies do exist for decreasing allergic inflammation, such as allergen avoidance, antihistamines, leukotriene inhibitors, allergen immunotherapy, and omalizumab.

Using data from the CF Twin and Sibling Study, we sought to determine whether environmental allergies were associated with CF morbidities, including lower lung function, a higher risk of sinus disease and/or nasal polyps, and a higher prevalence of common respiratory pathogens in CF. Secondary analyses included determining (i) whether environmental allergies were associated with a higher risk of surgery for sinus disease and/or nasal polyps and (ii) whether commonly used medications for allergies improved CF-related respiratory morbidities in individuals with allergies.

METHODS

Study Sample

All subjects were part of the CF Twin-Sibling Study (n=1765 individuals in 866 families) and recruited on the basis of having a twin or sibling with CF. Written consent was obtained from all subjects and the study was approved by the Johns Hopkins University Institutional Review Board (Protocol #NA_00035659). Baseline questionnaires were obtained on

enrollment and included questions on the presence and source of allergies. The questionnaire used is not validated and not age-specific; caregivers routinely completed questionnaires for children less than 18 years of age, which may underestimate the prevalence of allergies as suggested from the asthma literature.^{20–22} Subjects were excluded from analyses if complete questionnaire data were not available, which yielded a study sample of 1321 individuals. Excluded subjects were more likely to be non-white (12.4%) than subjects in the study sample (8.6%; $p=0.02$), but did not differ in other key characteristics (E-Table 1 in the online data supplement).

Demographics

Age for each subject was defined by the date the questionnaire was completed. Race/Ethnicity was self-defined with subjects with any reported non-white ancestry defined as non-white. Pancreatic sufficiency was defined as having one or more “pancreatic sufficient” mutations, and by clinical data where genotype data was indeterminate or not available.

Definition of Allergies

The presence of environmental allergies was defined from the questionnaire as any report of allergies to pets, pollen, grasses, trees, dust mites, and/or mold as well as the presence of “seasonal allergies” between the time of diagnosis of CF to the time of questionnaire completion. The questionnaires do not distinguish between resolved and current allergies, merely the history of any allergies.

Outcome Ascertainment

Clinical outcome data was collected through chart review with data supplementation from the U.S. Cystic Fibrosis Foundation Patient Registry and questionnaires. Two measures of cross-sectional lung function were derived using the best FEV₁ in the 12 months preceding or after the questionnaire date. The first was a CF-specific percentile of FEV₁,²³ and the second was FEV₁ percent predicted as defined by the U.S. CF Foundation.^{24,25} Lung function decline was calculated from linear regression of all FEV₁ percent predicted measurements in the 5 years following questionnaire completion for subjects with a minimum of 2 years of lung function data and a minimum of 4 FEV₁ values. Missing lung function data were not imputed. Allergic bronchopulmonary aspergillosis, sinus disease, nasal polyps, and surgery for these conditions were defined from the questionnaire, and were defined as occurring between the time of diagnosis of CF to the time of questionnaire completion; sinus disease included a minimum of 1 episode of sinus disease longer than 3 months in duration or > 3 episodes of at least 10 days duration per year. Infection with specific organisms, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Aspergillus fumigatus*, were defined as ever having a positive culture for that organism. Age of acquisition was defined by the date of the first positive culture for an organism with documentation at least one negative prior culture.

Definition of Medication Use

Leukotriene inhibitor and/or antihistamine use was defined as any use of these agents within the 3 months prior to questionnaire completion. Questionnaires did not assess for the use of intranasal corticosteroids.

Statistical Analysis

Differences in baseline characteristics and clinical outcomes were compared using *T*-tests for continuous variables and Pearson’s chi-square for categorical variables. The magnitude of effect of the presence of environmental allergies on outcomes was assessed using generalized estimating equations (GEE) methodology clustered by family to account for

possible family correlation. These clustered regressions were also adjusted for baseline characteristics that differed in those with allergies compared to those without, specifically, age, age at diagnosis, race/ethnicity, and pancreatic function. Time to event analysis was conducted using the age of acquisition of specific organisms with log rank tests. The likelihood of sinus or polyp surgery was only assessed in subjects with the disease condition requiring surgery. The associations of medication use with clinical outcomes were only assessed in subjects who reported environmental allergies. *P* values of less than 0.05 were considered statistically significant. All analyses were performed using Stata IC 11.0 (StataCorp LP, College Station, TX).

RESULTS

Study Sample

Fourteen percent of subjects (184/1321) reported an environmental allergy (Table 1), a rate that is similar to unrelated CF patients in previous studies,^{16,19,26,27} but lower than in the general population as almost 40% in the 2005–2006 NHANES cohort reported hay fever, rhinitis, or allergies.²⁸ Subjects who reported environmental allergies were almost 3 years older on average than those who did not ($p<0.001$), which corresponds to previous studies where the prevalence of allergies was noted to increase with age in CF (Figure 1).^{11,16,19,29} Subjects reporting allergies were more likely to be white (9.4 vs. 3.8%; $p=0.01$). Subjects reporting environmental allergies were over a year older at the age of diagnosis ($p=0.01$) and more likely to be pancreatic sufficient (22.3% vs. 16.4%; $p=0.049$), but there was no difference in the frequency of subjects homozygous for *F508del*, the most common mutation of *CFTR* that causes CF ($p=0.71$).

Environmental Allergies and Respiratory Morbidities

Although cross-sectional measures of lung function did not differ among subjects who reported an environmental allergy vs. those that did not (CF-specific FEV₁ $p=0.49$; FEV₁ percent predicted $p=0.47$), the decline in lung function was more rapid in those reporting an environmental allergy ($-2.3\%/yr$ vs. $-1.4\%/yr$; $p=0.01$) (Table 2). Subjects reporting environmental allergies were also more likely to report a history of sinus disease (60% vs. 37%; $p<0.001$) and nasal polyps (44% vs. 30%; $p<0.001$). To exclude the possibility of *CFTR* genotype effects, we reexamined the data in *F508del* homozygous subjects only, and continued to observe a more rapid lung function decline and a greater likelihood of sinus disease and nasal polyps in those reporting environmental allergies (Table 2). To reduce the likelihood of confounding, particularly by age, as older subjects are more likely to have a more rapid decline in lung function as well as sinus disease and nasal polyps, we performed linear regression adjusted for demographic factors that differed between those who reported environmental allergies vs. those who did not, specifically race/ethnicity, age, age at diagnosis, and exocrine pancreatic function (Table 3). After adjustment, those with environmental allergies had a 1.1% more rapid decline in FEV₁ percent predicted ($p=0.005$) than those without allergies. Also after adjustment, those with allergies were 2.68 times more likely to have sinus disease ($p<0.001$) and 1.74 times more likely to have nasal polyps ($p<0.001$) than those without allergies.

Environmental Allergies and Infectious Organisms

We observed a greater prevalence of ever having *P. aeruginosa* among individuals reporting allergies (91.9%) vs. those who did not report allergies (85.8%; $p=0.024$) (Table 2); this finding remained significant when adjusted for age and other demographic factors (Adjusted OR: 2.25; $p=0.031$) (Table 3). Again, to exclude the possibility of *CFTR* genotype effects, we re-examined the data in *F508del* homozygous subjects only, and found that this difference was not statistically significant (chi square $p=0.07$; adjusted OR: 1.97; $p=0.28$).

The reduced significance with the *F508del* mutation may reflect an interaction with the *CFTR* genotype as mutations with residual *CFTR* function are associated with lower rates of infection.³⁰ In order to determine whether allergies were protective or a risk factor for acquiring respiratory pathogens, we used time-to-event analysis to examine the age of acquisition of *P. aeruginosa*, MRSA, and *Aspergillus* as defined by the age of the first positive culture in *F508del* homozygotes. *F508del* homozygous subjects reporting environmental allergies had a later median age of acquisition (6.6 years) of *P. aeruginosa* compared to subjects not reporting allergies (4.4 years; log rank $p=0.027$) (Figure 2). It should be noted that subjects reporting allergies had a similar mean of 3.3 ± 1.7 respiratory cultures obtained per year compared to 3.5 ± 1.8 cultures for those who did not report allergies ($p=0.23$). There were no differences in the age of acquisition for MRSA or *Aspergillus* by environmental allergy status.

Environmental Allergies and Surgery

For only those subjects with sinus disease or nasal polyps we examined the frequency of associated surgeries to ascertain whether environmental allergies were associated with more severe disease (E-Table 1 in the online data supplement). We found no difference in the likelihood of requiring surgery for sinus disease ($p=0.76$) or nasal polyps ($p=1.00$) by the presence or absence of environmental allergies after adjustment for relevant demographic factors.

Interventions for Environmental Allergies

As some respiratory morbidities were associated with the presence of environmental allergies, this implies that interventions may be possible to ameliorate the morbidities. Both prescription and over-the-counter medications are frequently utilized to treat allergy symptoms. Among the 181 subjects with allergies for whom medication use was ascertained, 18% reported using a leukotriene inhibitor in the 3 months prior to questionnaire reporting and 54% reported using an antihistamine. Those using a leukotriene inhibitor were more likely to be pancreatic sufficient (43% vs. 18%; $p<0.002$) than those who did not, and those using an antihistamine were younger (14.1 yrs vs. 18.0 yrs; $p=0.01$) than those who did not (E-Table 2 in the online data supplement). There were no other significant differences between those who used medications vs. those who did not. Among those with reported environmental allergies, we assessed whether symptomatic treatment improved outcomes (Table 4). A higher FEV₁ percent predicted was observed in subjects using an antihistamine compared to those who did not ($p=0.01$), but after adjustment for relevant demographic factors (i.e., age), no difference in lung function with antihistamine use was observed ($p=0.15$). Of interest, for subjects who did not report allergies, 10.0% ($n=1118$) reported using a leukotriene inhibitor and 22.2% ($n=1117$) used an antihistamine.

DISCUSSION

Using a multicenter sample of individuals with CF, we have demonstrated that a history of environmental allergies is associated with 2.7-fold increased risk of sinus disease and 1.7-fold risk of nasal polyps. The magnitude of the association for sinusitis is similar to that observed in the general population,³¹ suggesting that some common mechanisms exist between individuals with CF and the general population. These mechanisms which may promote the development of sinus disease include increased upper airway inflammation, increased nasal drainage, and increased obstruction of nasal drainage.³² This pathophysiology is compounded by the impaired ciliary clearance that is a hallmark of CF. In contrast, the link between allergic disease and nasal polyps is less evident in the general population,³³ and other studies in CF have presented mixed results concerning this relationship.^{34,35} It may be that previous CF studies were underpowered to detect this

association, or that our means of ascertaining allergy status (i.e., by questionnaire) identifies a different population compared to blood or skin testing. Although a higher prevalence of sinus disease and nasal polyps was observed in those with environmental allergies in our study, this did not correspond to more severe upper airway disease as measured by the need for surgical procedures.

We hypothesized that individuals with environmental allergies would have lower lung function than those without allergies because obstructive lung disease and environmental allergies are highly associated in the general population. We observed that the presence of environmental allergies was associated with a more rapid decline in lung function. We speculate that post-nasal drip associated with allergic rhinitis may be contributing to additional lower airway inflammation. An alternate explanation is that an allergic inflammatory milieu including more activated eosinophils may lead to greater lung injury.³⁶ In addition, it is possible that respiratory symptoms due to lower airway infection could be undertreated in those with environmental allergies as their symptoms may be mistakenly attributed to allergies. Furthermore, modifier genes could play a role in the association between allergies and lung function decline. For example, polymorphisms in the transforming growth factor $\beta 1$ gene (*TGFB1*) are likely associated with lung function in CF,³⁷ and limited data in healthy infants/children demonstrates associations between *TGFB1* genotypes and allergic rhinitis.^{38,39} Lastly, selection bias may exist as patients with allergies may be more likely to have pulmonary function tests, thus lung function decline may be more easily ascertained.

Unexpectedly, we found that *F508del*/homozygous subjects reporting environmental allergies had a later median age of acquisition of *P. aeruginosa* (6.6 years) compared to subjects not reporting allergies (4.4 years), which had also been reported on a previous study of 47 CF patients.⁴⁰ Assuming that patients with environmental allergies have a different lower airway inflammatory milieu, this milieu may provide some protection against certain pathogens. Conversely, this inflammatory milieu may promote the acquisition of other organisms that we did not study. However, we found the overall prevalence of *P. aeruginosa* was no different in examining all available culture data in *F508del*/homozygous subjects, thus allergies likely do not confer long-term benefit for infection prevention. We also found that allergy prevalence differed by reported race/ethnicity with subjects reporting allergies more likely to be white (9.4 vs. 3.8%; $p=0.01$). In the general population, minorities may have differing documented allergies based on exposures and not genetic differences.⁴¹ Our data does not allow us to determine if cultural reporting biases/perceptions or access-to-care issues play a role as well.

Strengths of our study include longitudinal data on a large, well characterized, population of patients with CF. As subjects have been recruited from across the United States, with additional subjects from Australia and Scotland, regional biases in allergen exposure are minimized. The most significant limitation of our study is the use of questionnaires to determine allergy status, without diagnostic testing or physician diagnosis data for validation, which may lead to misclassification. Other limitations of our study include retrospective collection of allergy data, which may lead to recall biases. We only had the ability to assess allergies at a single point in time, whereas the changing prevalence by age in our data suggests that allergies may change over time. This single point in time also prevents the use of temporal analysis of allergy assessment and clinical outcomes, thus preventing us from ascribing causality. We did not see any improvements in respiratory morbidities with the use of leukotriene inhibitors or antihistamines. However, our data does not include duration of use, severity of allergies, or other factors which may play a role in the pathophysiology of therapeutic response. Since cross-sectional measures of response to allergy medications may be weak predictors of outcomes, particularly as we could not

account for seasonal effects, our study may be underpowered to detect a therapeutic response. In addition, we did not assess for another commonly used allergy therapy, specifically intranasal corticosteroids.

In conclusion, a history of environmental allergies is associated with sinusitis and nasal polyps in CF. The increased decline in lung function that was also associated with environmental allergies suggests that allergic rhinitis may be more problematic than many clinicians realize. However, in contrast to other epidemiology studies in the general CF population,^{42–44} we did observe an incongruity in subjects with allergies between a later acquisition of *Pseudomonas aeruginosa*, but a more rapid decline in lung function. It is unclear why this may be the case, but we would speculate that different lower airway milieus in patients with CF may shape outcomes and contribute to observed variation in lung function. Prospective longitudinal studies in a large cohort with formal atopy testing are needed to confirm the relationships between allergies, infection, and lung function, and also to determine if more effective treatments than antihistamines and/or leukotriene inhibitors exist for individuals with CF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Table 1

Patient Demographics

	Entire Study Sample (n = 1321)	Environmental Allergy (n = 184)	No Environmental Allergy (n = 1137)	<i>p</i> Value
Sex (% male)	52.4	55.4	51.9	0.37
Age (years, mean $\pm$ SD [range])	13.4 $\pm$ 9.6 [0.1 – 62.7]	15.9 $\pm$ 10.4 [0.8 – 62.7]	13.0 $\pm$ 9.4 [0.1 – 57.5]	<0.001
Race/Ethnicity (% Non-white)	8.6	3.8	9.4	0.012
Age at Diagnosis (years, mean $\pm$ SD [range])	2.2 $\pm$ 5.5 [0.0, 52.9] (n = 1213)	3.3 $\pm$ 6.8 [0.0, 47.2] (n = 162)	2.1 $\pm$ 5.2 [0.0, 52.9] (n = 1051)	0.010
CFTR Genotype (% F508del homozygotes)	50.2 (n = 1317)	48.9	50.4 (n = 1133)	0.71
Pancreatic Function (% Sufficient)	17.2 (n = 1319)	22.3	16.4 (n = 1135)	0.049
Allergic Bronchopulmonary Aspergillosis (% Yes)	6.5 (n = 1275)	9.5 (n = 169)	6.1 (n = 1106)	0.09

Table 2

Environmental Allergies and Clinical Outcomes

		Environmental Allergy (n = 184; <i>F508del</i> homozygote n = 90)	No Environmental Allergy (n = 1137; <i>F508del</i> homozygote n = 571)	<i>p</i> Value
All Subjects	CF-specific FEV ₁ (% mean ± SD)	72.7 ± 26.4 (n = 164)	71.2 ± 25.2 (n = 865)	0.49
	FEV ₁ (% mean ± SD)	92.4 ± 27.7 (n = 164)	90.8 ± 25.2 (n = 865)	0.47
	FEV ₁ Decline (%/year, mean ± SD)	-2.33 ± 3.87 (n = 153)	-1.44 ± 4.04 (n = 738)	0.012
	Sinus Disease (% Yes)	60.2 (n = 181)	37.3 (n = 1111)	<0.001
	Nasal Polyps (% Yes)	44.1 (n = 177)	30.4 (n = 1095)	<0.001
	<i>P. aeruginosa</i> Ever (% Yes)	91.9%	85.8%	0.024
	MRSA Ever (% Yes)	48.4%	41.4%	0.08
	<i>Aspergillus</i> Ever (% Yes)	50.5%	43.3%	0.07
Homozygotes Only <i>F508del</i>	CF-specific FEV ₁ (% mean ± SD)	71.0 ± 27.9 (n = 81)	71.2 ± 24.3 (n = 415)	0.95
	FEV ₁ (% mean ± SD)	90.0 ± 29.5 (n = 81)	90.4 ± 24.5 (n = 415)	0.90
	FEV ₁ Decline (%/year, mean ± SD)	-2.73 ± 4.18 (n = 73)	-1.51 ± 4.16 (n = 368)	0.022
	Sinus Disease (% Yes)	52.3 (n = 88)	34.1 (n = 557)	0.001
	Nasal Polyps (% Yes)	44.8 (n = 87)	30.9 (n = 556)	0.010
	<i>P. aeruginosa</i> Ever (% Yes)	96.7%	91.1%	0.07
	MRSA Ever (% Yes)	43.3%	41.7%	0.77
	<i>Aspergillus</i> Ever (% Yes)	51.1%	46.2%	0.39

Table 3

Unadjusted and Adjusted Associations of Environmental Allergies and Clinical Outcomes

Clinical Outcome*		Increased FEV ₁ Decline (%/year) with Environmental Allergies [95% CI]	Odds Ratio of Sinus Disease or Polyps with Environmental Allergies [95% CI]	p Value
FEV₁ Decline (n = 741)	Unadjusted	-1.06 [-1.76, -0.35]	-	0.003
	Adjusted Model	-1.18 [-1.84, -0.52]	-	0.001
	Adjusted Model adjusted for sinus disease/nasal polyps/FEV ₁ **	-1.13 [-1.81, -0.45]	-	0.001
Sinus Disease (n = 1190)	Unadjusted	-	2.85 [1.97, 4.12]	<0.001
	Adjusted Model	-	2.68 [1.84, 3.90]	<0.001
Nasal Polyps (n = 1179)	Unadjusted	-	1.85 [1.32, 2.61]	<0.001
	Adjusted Model	-	1.74 [1.21, 2.49]	0.003
Prevalence of <i>P. aeruginosa</i> (n = 1212)	Adjusted Model	-	2.25 [1.08, 4.70]	0.031
Prevalence of <i>P. aeruginosa</i> in <i>F508del</i> homozygotes (n = 606)	Adjusted Model	-	1.97 [0.58, 6.70]	0.28

* Linear regressions performed for lung function decline; logistic regressions performed for other outcomes. All regressions clustered by family to account for familial relationships. All adjusted regressions include adjustments for race/ethnicity, age, age at diagnosis, and exocrine pancreatic function.

** An age-allergy interaction term was not significant ($p=0.11$), and thus not included in the final adjusted model.

Table 4Allergy Medications and Clinical Outcomes^{*}

		Medication Use	No Medication Use	<i>p</i> Value
Leukotriene Inhibitor	CF-specific FEV₁ (% , mean $\pm$ SD)	75.7 $\pm$ 25.5 (n = 28)	72.2 $\pm$ 26.3 (n = 133)	0.52
	FEV₁ (% , mean $\pm$ SD)	97.9 $\pm$ 29.5 (n = 28)	91.5 $\pm$ 27.1 (n = 133)	0.26
	FEV₁ Decline (%/year, mean $\pm$ SD)	-2.41 $\pm$ 4.72 (n = 25)	-2.31 $\pm$ 3.73 (n = 126)	0.90
	Sinus Disease (% Yes)	68.8 (n = 32)	58.2 (n = 146)	0.27
	Nasal Polyps (% Yes)	35.5 (n = 31)	45.5 (n = 143)	0.31
Antihistamine	CF-specific FEV₁ (% , mean $\pm$ SD)	75.4 $\pm$ 26.1 (n = 86)	69.9 $\pm$ 26.0 (n = 75)	0.19
	FEV₁ (% , mean $\pm$ SD)	98.1 $\pm$ 27.7 (n = 86)	86.3 $\pm$ 26.0 (n = 75)	0.006 ^{**}
	FEV₁ Decline (%/year, mean $\pm$ SD)	-2.49 $\pm$ 3.85 (n = 79)	-2.14 $\pm$ 3.96 (n = 72)	0.58
	Sinus Disease (% Yes)	58.8 (n = 97)	61.7 (n = 81)	0.69
	Nasal Polyps (% Yes)	41.1 (n = 95)	46.8 (n = 79)	0.44

^{*} Only in subjects with environmental allergies.

^{**} The difference in FEV₁ between subjects taking an antihistamine versus those who do not is not significant when adjusted for age using regression clustered by family (n = 161; *p* = 0.15).