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Susceptibility to Exacerbations in Black Adults with Asthma

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ABSTRACT

OBJECTIVE: Exacerbations account for much of the morbidity in asthma. In a large intervention study, we sought to test the hypothesis that a Black adult exacerbation-prone phenotype -- a group of Black people with asthma who are at high risk of repeat exacerbation within one year -- exists in asthma independent of clinical control.

METHODS: We analyzed exacerbation risk factors in 536 self-identified Black Americans with asthma eligible for, or on, Step 3 NAEPP therapy who participated in a randomized 6-18 month trial of tiotropium versus long acting beta agonist as add-on therapy to inhaled corticosteroids. Exacerbations were defined as events treated by oral or systemic corticosteroids. Clinical control was assessed by a validated asthma control questionnaire (ACQ5).

RESULTS: Exacerbations became more likely with loss of clinical control. The mean baseline ACQs for exacerbators and non-exacerbators were 2.41 and 1.91 respectively ($p < 0.001$). The strongest independent factor associated with exacerbations across all ACQ levels was an exacerbation in the preceding year (adjusted OR 3.26; $P < 0.001$). The severity of prior exacerbations did not correlate with the likelihood of a future exacerbation. Lower baseline FEV1/FVC was also associated with increased risk of exacerbations.

CONCLUSIONS: Even though exacerbations increase with loss of clinical control, an exacerbation susceptibility phenotype exists in Black adults with asthma, independent of clinical control. This phenotype requires precision therapeutic targeting.

Introduction

Asthma is a disease punctuated by exacerbations -- acute episodes of worsened symptoms with airway narrowing, reversible airflow obstruction, and significant associated morbidity and mortality. Of the 8% of American adults with asthma, more than half report that they have had an exacerbation in the prior year.^{1,2} These exacerbations, when severe, are associated with an above average decline in lung function in patients not on controller agents.³ They account for 1.8 million emergency room visits, 3,600 deaths, and more than 23 billion dollars in direct cost per year in the United States.^{4,5}

Exacerbation patterns remain unpredictable. While exacerbations become more frequent as asthma control decreases, studies suggest that a history of exacerbations may be a good predictor of subsequent exacerbations.^{6,7, 8, 9, 10,11} Studies also suggest that exacerbations may occur in patients with apparent good control.^{12,13} Thus, there may be an “exacerbation-prone phenotype” – a group of people at high risk of future exacerbation -- that even includes patients with mild asthma.

Whether an asthma exacerbation-prone phenotype exists independent of clinical control is still unclear. While an investigation of an exacerbation-prone phenotype in COPD was made possible by the existence of a large cohort in a single study,¹⁴ the lack of large asthma cohorts with consistent definitions and adequate rates of exacerbations has previously hampered the focused investigation of an exacerbation-prone phenotype in asthma.

We used data from 1,070 self identified Black adults patients with asthma who participated in the Blacks and Exacerbations on LABA v. Tiotropium (BELT) trial¹⁵ to test the hypothesis that an exacerbation-prone phenotype exists in adult asthma patients independent of clinical control.

Methods

Study design and patients

We performed a secondary analysis of data collected as a part of the BELT trial. The trial was approved by the appropriate institutional review boards, and all involved patients provided written informed consent.

The full study design of BELT has been previously published.¹⁵ Briefly, it was a randomized pragmatic, open label trial of Black adults with asthma, conducted at 20 sites within the United States between 2011 and 2012. Inclusion criteria included self identification as Black, age 18-75, physician diagnosed asthma, forced expiratory volume in 1 second (FEV1) of $\geq 40\%$ of predicted, and eligibility for (or on) Step 3 NAEPP therapy. Major exclusion criteria were an exacerbation requiring oral corticosteroids within 3 months of enrollment, current smoking or >10 pack year smoking history, use of a dose equivalent of $>1,000$ mcg inhaled fluticasone daily, or history of life-threatening asthma requiring intubation within 5 years of enrollment.

Eligible BELT subjects completed study questionnaires and provided a medical history, spirometric measurements, and saliva sample for genetic analysis. They were randomized to daily inhaled corticosteroids (ICS) plus either long acting beta agonists (LABA) or tiotropium for 6 to 18 months. Adherence information was obtained by usage of a pharmacy credit card that tracked refills.¹⁶

All subjects with at least one exacerbation or those followed for at least 12 months without an exacerbation were included in this analysis. Patients without an exacerbation who had follow-up of < 1 year were not included since it is not known whether they would have had an exacerbation had they continued in the study.

Study Outcomes

The primary outcome of this analysis was the occurrence of at least one asthma exacerbation by 12 months. Exacerbations were defined as self-reported events of worsening asthma that resulted in prescription of oral or parenteral corticosteroid. The original BELT trial design included an algorithm for practitioners to review possible deteriorations and exacerbations, to guide corticosteroid administration. Asthma control was measured by the Asthma Control Questionnaire – short version (ACQ5).¹⁷ Secondly, we evaluated exacerbation risk by self-reported severity of exacerbations in the year prior to randomization, graded on a spectrum as exacerbations that required oral corticosteroid versus hospitalization. Pre-specified exploratory predictors chosen to investigate the associations between baseline patient variables and exacerbation risk included demographics (age, gender, BMI, smoking history and environment); environmental allergies; years from first asthma diagnosis; baseline lung function [FEV1 (liters and % predicted), FEV1/FVC, FEV1 reversibility]; baseline patient-reported asthma burden assessments (ACQ5, Asthma Quality of Life Questionnaire,¹⁸ Asthma Symptom Utility Index¹⁹); asthma related emergency department visits in the 12 months prior to enrollment; and medication compliance during the study.

Statistical analysis

Univariate logistic regression was used to identify predictors that were independently associated with the primary outcome. Multivariable logistic regression was then performed to determine which factors were independently predictive of one or more asthma exacerbation by 12 months. Variables were chosen for the multivariable logistic regression if they were thought to be clinically important or showed a significant univariate association with the outcome. Starting from a full model including treatment randomization, age, female gender, BMI, smoking history, smoking

environment, years from first asthma diagnosis, FEV1 (% predicted), FEV1/FVC, FEV1 reversibility, ACQ5, average daily puffs of SABA, history of systemic steroids for asthma in the prior 12 months, history of emergency department visits for asthma in the prior 12 months, history of hospitalizations for asthma in the prior 12 months, environmental allergies, and region of the country in which they lived, we used backward elimination and a retention at $P < 0.05$ to select a more parsimonious model.

The predictive performance of this model was determined using threshold independent measures (Receiver Operating Curve analysis). Calibration was tested using Hosmer and Lemeshow chi-square test statistics while discrimination was assessed using the area under the curve (AUC) statistic.

All data analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and p values < 0.05 were considered statistically significant.

Results

Characteristics of the patients

A total of 1,070 patients were randomized to LABA/ICS (538) or tiotropium/ICS (532). 536 subjects had an exacerbation or completed 1 full year -- 264 in the LABA/ICS group and 272 in the tiotropium/ICS group. The median number of study participation days for our population was 358, compared to 335 for the entire BELT population. 352 of 536 (65.7%) evaluable subjects had no exacerbations by 1 year, 23.4% had 1 exacerbation, and 10.8% had ≥ 2 .

Exacerbators versus Non-Exacerbators

Exacerbators were more likely to have had an exacerbation in the prior year (59.2% vs 27.6%, $p<0.001$), an asthma-related ER visit in the prior year (51.6% vs 28.4%, $p<0.001$), and an asthma-related hospitalization in the prior year (20.1% vs 8.2%, $p<0.001$). The mean baseline ACQs for exacerbators and non-exacerbators were 2.41 and 1.91 respectively ($p<0.001$). Those who exacerbated also had lower FEV1 (1.87L vs 2.13L, $p=0.01$) and higher FEV1 reversibility after albuterol (9% vs 6%, $p=0.02$). Additional differences between those who exacerbated and those who did not are reported in Table 1.

Factors associated with exacerbations

Table 2 shows the univariate associations with future exacerbations, expressed as an odds ratio per standard deviation of change for continuous variables. The strongest univariate predictor of an exacerbation was an exacerbation in the year prior to enrollment (OR 3.85; 95% confidence interval [CI] 2.64-5.62; $P<0.001$). History of an exacerbation in the year prior to enrollment was also associated with an increased risk of future exacerbation when the outcomes were time to first exacerbation or number of exacerbations in the follow-up year (HR 3.00; 95% CI, 2.23-4.04; $P<0.001$ and annualized rate ratio 3.21; 95% CI, 2.54-4.07; $P<0.001$ respectively). The severity of a past exacerbation (requiring systemic corticosteroids versus hospitalization) did not affect the likelihood of a future exacerbation. The likelihood of a future exacerbation increased with worse baseline clinical control, worse quality of life, and declining airway function.

109 of 206 subjects who had at least one exacerbation in the year prior to enrollment went on to have at least one exacerbation in the follow-up year (positive predictive value 52.9%), and 49 of 91 subjects with 2 exacerbations in the year prior to enrollment went on to have one or more

exacerbations in the follow-up year (PPV 53.8%). 250 of 323 subjects who did not have an exacerbation in the year prior to enrollment did not have an exacerbation in the year following randomization (negative predictive value 77.4%). History of exacerbation in the prior year was 59.9% sensitive and 72.0% specific for predicting a future exacerbation by 1 year.

In a multivariable regression model, 3 factors were significantly independently associated with exacerbations: History of an exacerbation in the preceding year was the most significant predictor of exacerbations (aOR 3.26; 95% CI, 2.17-4.92; $P < 0.001$). ACQ scores had a less significant association (aOR 1.56; 95% CI, 1.27-1.93; $P < 0.001$). Lower baseline FEV1/FVC was also associated with the exacerbation phenotype (aOR 1.42; 95% CI 1.18-1.71; $P < 0.001$).

Subgroup analysis within each ACQ group revealed that a history of exacerbation was the strongest predictor of future exacerbations across all levels of clinical control (Table 3). Across all ACQ subgroups, the percent of subjects with a future exacerbation rose dramatically as the number of asthma related steroid courses in the prior year increased (Figure 1).

Discussion

Using data from a large group of Black adults with asthma, we found that a history of exacerbation in the prior year identified a group at high risk of exacerbation, irrespective of clinical control. Our observation supports the notion that there is a cluster of adults with asthma that has an intrinsic susceptibility to repeated exacerbations separate from their apparent level of asthma control. Individuals in this cluster can be identified simply through a history of exacerbations within the past year.

Many variables are known to be associated with an increased risk of exacerbations. The independent associations between future exacerbations and exacerbation history, poor disease control (ACQ) and poor lung function (lower FEV1/FVC) have been previously described.²⁰ While prior studies have shown that individuals with asthma and a history of exacerbations or poor baseline control both have an increased likelihood of experiencing future exacerbations, they did not focus on separating exacerbation susceptibility from clinical control.^{21,22,23,24,25,26,27,28,29,30,31,32,33,34} Until now, it has been unclear whether these 2 characteristics merely reflect each other. Namely, it has been unknown whether patients with poor clinical control are more likely to recall exacerbations or whether those who exacerbate frequently are more likely to report poor clinical control. Our finding that the best predictor of a future exacerbation is a prior exacerbation, irrespective of baseline clinical control, supports the idea that there is a distinct population of adults with asthma that, regardless of baseline clinical control, is particularly susceptible to exacerbations. This observation has broad implications, as mild and moderate asthma together are more prevalent than severe disease.

By defining exacerbations as episodes requiring steroids, we built our models to predict a subset of severe exacerbations – those that are most burdensome to patients and society at large. The association between prior steroid-requiring exacerbations and future steroid-requiring exacerbations was even stronger than the association between prior asthma-related hospitalizations and future exacerbations, suggesting that the severity of prior exacerbations actually may not influence exacerbation risk. Rather, the strength of the association between prior exacerbations and future ones is likely attributable to the sum of many steady influences on prior exacerbations – asthma control, severity, biomarkers, genetics, environment, exposure, medication compliance, and healthcare literacy, to name a few.

A limitation of this study is that the BELT population is comprised of Black American adults only. We chose to study exacerbation predictors in individuals who experience frequent exacerbations. It is

believed that Black Americans have a higher exacerbation risk per year than Caucasians.³⁵ By including all exacerbators regardless of their study duration and only non-exacerbators who were studied for at least 12 months, we intended to avoid diluting our sample with subjects who had minimal inclusion time and would not be expected to exacerbate during their limited time in the study. In doing so, we acknowledge that we selected for a group of subjects that had a longer study enrollment and was more exacerbation-prone than the overall BELT population. Additionally, given that the non-exacerbators had to have lasted at least 12 months in the study, they may be inherently more compliant than the exacerbators. Importantly, subjects were excluded from BELT if they had taken oral corticosteroids for asthma in the 3 months prior to enrollment. As such, the data may under-represent the relationship between baseline corticosteroid use and future exacerbations. Nevertheless, subjects with corticosteroid use in the 12 months before enrollment had an odds of future exacerbation that was still 3.3 times higher than those who did not. Another major limitation is that we do not have biologic biomarker predictors of exacerbations at baseline; for example, we did not collect blood or sputum eosinophils as predictors of exacerbations for the study. A main strength of our study is that the cohort was large and had diverse clinical control.

In conclusion, our results support the hypothesis that an exacerbation-prone phenotype of Black adults with asthma who are at increased risk of future exacerbation exists independent of clinical control. Exacerbation-prone asthmatics can be identified simply by asking poor and well controlled subjects to recall recent steroid treatments. These findings call for further investigation of the exacerbation-prone phenotype in order to lessen the burden of exacerbation-specific morbidity, mortality, and cost.

Declaration of interest statement:

Dr. Grossman has nothing to disclose. Dr. Doros has nothing to disclose. Nicolas Fandino has nothing to disclose. Dr. Fuhlbrigge has received grant support from the NHBLI, AHRQ and PCORI related to asthma and COPD studies. She also has received personal fees from GSK, AstraZeneca and Icon Medical Imaging for consulting on investigations in asthma and COPD. Dr. Pace reports grants from Agency for Healthcare Research and Quality, during the conduct of the study. Dr. Wechsler reports personal fees from AstraZeneca, personal fees from BSCI, personal fees from Novartis, grants and personal fees from Sanofi, personal fees from Vectura, personal fees from Sunovion, personal fees from Regeneron, personal fees from Ambit BioScience, personal fees from Meda, personal fees from Mylan, personal fees from Gilacure, personal fees from Tunitas, personal fees from Genentech, personal fees from Theravance, personal fees from Neurotronic, personal fees from Sentien, personal fees from Teva, personal fees from Boehringer Ingelheim, grants and personal fees from GlaxoSmithKline, outside the submitted work. Dr. Yawn reports grants from AHRQ, during the conduct of the study; personal fees from Astra Zeneca, personal fees from GSK, personal fees from BI, other from TEVA, outside the submitted work. Dr. Israel reports personal fees from AstraZeneca, personal fees and other from Novartis, personal fees from Philips Respironics, personal fees from Regeneron Pharmaceuticals, other from Research in Real Life (RiRL), personal fees and other from TEVA Specialty Pharmaceuticals, grants from Genentech, non-financial support from Boehringer Ingelheim, non-financial support from GlaxoSmithKline, non-financial support from Merck, non-financial support from Sunovion, non-financial support from TEVA, grants from Sanofi, personal fees from Bird Rock Bio, personal fees from Nuvelution Pharmaceuticals, personal fees from Vitaeris, Inc, grants from Boehringer Ingelheim, non-financial support from TEVA Specialty Pharmaceuticals, outside the submitted work

Conclusions:

Our data suggest that there is a cluster of Black adults with asthma that has intrinsic susceptibility to repeated exacerbations. Individuals with increased risk of future asthma exacerbations distribute across all levels of clinical control and can be identified simply by asking those with asthma about their exacerbation history in the prior year.

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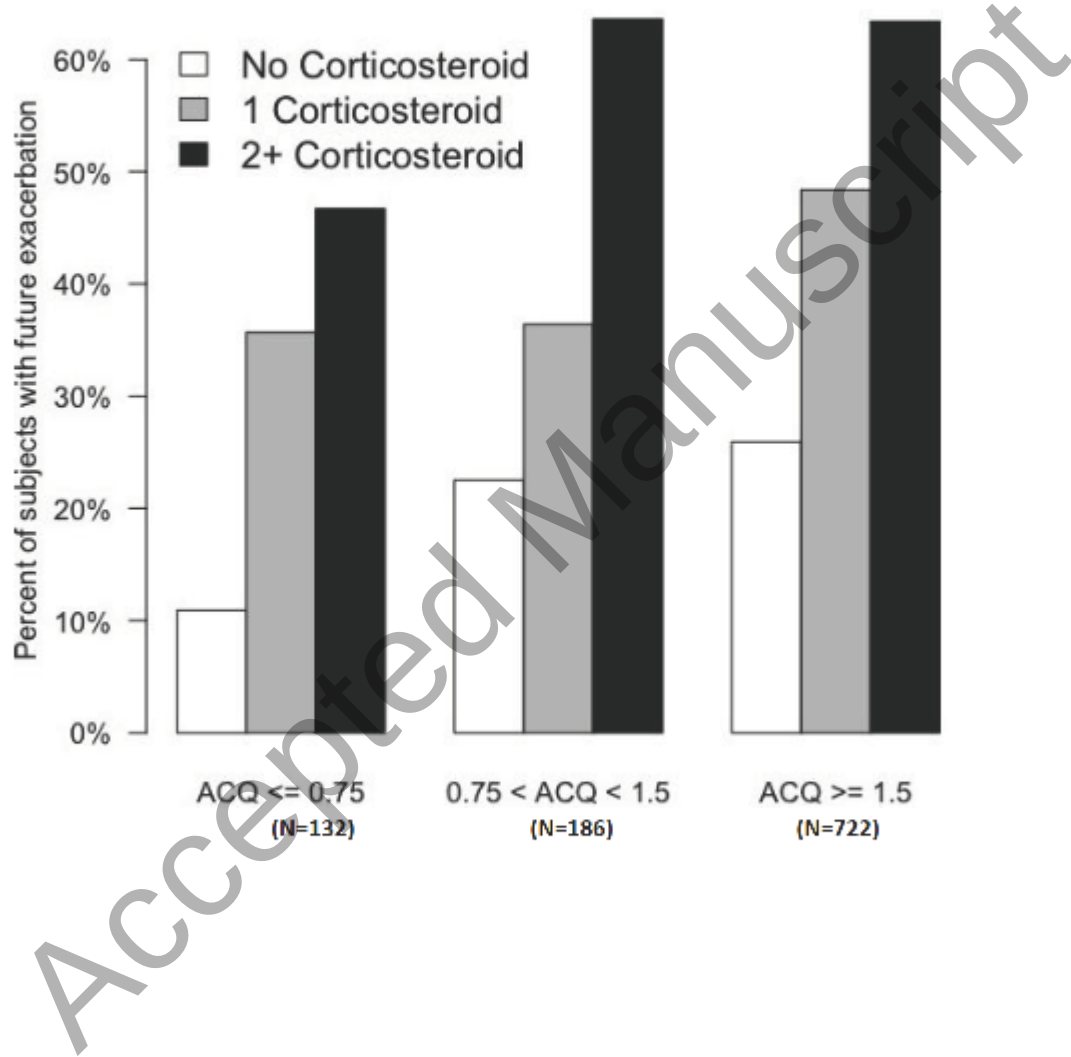


Table 1: Characteristics of Patients According to Exacerbation Status

	No Exacerbation (N = 352 Patients)	Exacerbation (N = 184 Patients)	p-value
Age (years)	45.68±13.17 (352)	45.70±11.98 (184)	0.992
Female sex	77.8%	78.8%	0.83
BMI	35.31±9.33	35.74±10.25 (184)	0.63
Environmental allergies to hay, animals, mold, or pollen	81.5%	80.4%	0.82
Never smoker (%)	70.7%	63.6%	0.097
Smoking Environment	13.4%	13.7%	1.00
Years from first asthma diagnosis	24.88±15.90	25.57±15.92	0.65
Spirometry			
FEV1 in liters	2.13±0.60	1.97±0.64	0.01
FEV1,% predicted	79.75±17.43	75.88±19.51	0.03
FEV1/FVC	0.75±0.09	0.72±0.12	<0.001
FEV1Reversibility at 30days	0.06±0.10	0.09±0.18	0.02
Patient reported outcomes			
ACQ5	1.91±1.19	2.41±1.26	<0.001
AQLQ	4.35±1.41	3.81±1.38	<0.001
ASUI	0.72±0.23	0.64±0.24	<0.001
Average daily puffs of SABA	3.0±3.3	3.7±3.5	0.05
Exacerbations			
Asthma-related CS in the prior 12 mo	27.6%	59.2%	<0.001
Asthma-related ER visit in the preceding 12mo	28.4%	51.6%	<0.001
Asthma-related hospitalization in the preceding 12mo	8.2%	20.1%	<0.001
Adherence compliance >= 50%	63.9%	67.4%	0.45

Analysis includes patients who had an exacerbation by 12 months or who were followed for at least 12months. It excludes patients who had an exacerbation before 1 month.

Values are mean +/- standard deviation for exacerbators and non-exacerbators, unless otherwise stated.

FEV1 denotes forced expiratory volume in 1 second; FVC forced vital capacity; FEV1 reversibility [(Post-bronchodilator -FEV1) - (Pre-bronchodilator-FEV1)] / (Pre-bronchodilator-FEV1); The Asthma Control Questionnaire – 5 item version (ACQ5) is comprised of 5 questions that reflect patients' symptoms over the past week (frequency of nocturnal arousals, severity of morning symptoms, degree of asthma-related activity limitations, degree of dyspnea, frequency of wheeze). Scores range from 0 (totally controlled) to 6 (severely uncontrolled); The Asthma Quality of Life Questionnaire (AQLQ) ranges from 1-7, with higher scores indicating better quality of life; The Asthma Symptom Utility Index (ASUI) ranges

from 0 (worst possible symptoms) to 1 (no symptoms); SABA short acting beta-agonist; CS oral corticosteroid

Table 2: Univariate Predictors of Future Exacerbations (per SD change)

Univariate	Odds Ratio, (95% CI), P-value
Exacerbations	
Asthma-related CS in the prior 12mo	3.85 (2.64, 5.62), <0.001
Asthma-related hospitalization in the preceding 12 months	2.80, (1.66, 4.73), <0.001
Asthma-related ER visit in the preceding 12 months	2.67, (1.84, 3.87), <0.001
Patient reported outcomes	
ACQ (per 1.24 unit increase)	1.51, (1.23, 1.82), <0.001
AQLQ (per 1.43 unit decrease)	1.49, (1.24, 1.80), <0.001
ASUI (per 0.23 unit decrease)	1.37, (1.15, 1.65), <0.001
Spirometry	
FEV1 in liters (per 0.62L decrease)	1.31, (1.08, 1.59), 0.01
FEV1, % predicted (per 18.24% decrease)	1.24, (1.03, 1.50), 0.03
FEV1/FVC (per 0.10 unit decrease)	1.43, (1.19, 1.71), <0.001
FEV1 Reversibility (per 0.13 increase)	1.31, (1.08, 1.59), 0.01
Daily SABA use (per 3.42 puff increase)	1.19, (0.998, 1.42), 0.05
Age (years; per 12.76 year increase)	1.001, (0.84, 1.20), 1.00
Female sex	1.01, (0.92, 1.12), 0.80
BMI (per 9.65 unit increase)	1.05, (0.88, 1.25), 0.63
Environmental allergies to hay, animals, mold, or pollen	0.93, (0.60, 1.47), 0.76
Smoke in the past	1.38, (0.95, 2.02), 0.09
Smoking Environment	1.02, (0.61, 1.72), 0.94
Years from first asthma diagnosis (per 15.9 year increase)	1.05, (0.87, 1.26), 0.65
Adherence compliance $\geq 50\%$ vs $< 50\%$	1.17, (0.80, 1.70), 0.42

FEV1 denotes forced expiratory volume in 1 second; FVC forced vital capacity; FEV1 reversibility [(Post-bronchodilator -FEV1) - (Pre-bronchodilator-FEV1)] / (Pre-bronchodilator-FEV1); The Asthma Control Questionnaire – 5 item version (ACQ5) is comprised of 5 questions that reflect patients' symptoms over the past week (frequency of nocturnal arousals, severity of morning symptoms, degree of asthma-related activity limitations, degree of dyspnea, frequency of wheeze). Scores range from 0 (totally controlled) to 6 (severely uncontrolled); The Asthma Quality of Life Questionnaire (AQLQ) ranges from 1-7, with higher scores indicating better quality of life; The Asthma Symptom Utility Index (ASUI) ranges from 0 (worst possible symptoms) to 1 (no symptoms); SABA short acting beta-agonist; CS oral corticosteroid

**Table 3. Multivariable Associations with the Occurrence of
Exacerbations (per SD change), by ACQ subgroup**

	All subjects aOR, (95% CI), p-value	ACQ≤0.75 aOR, (95% CI), p-value	0.75<ACQ<1.5 aOR, (95% CI), p-value	ACQ≥1.5 aOR, (95% CI), p-value
Asthma-related CS in the prior 12mo	3.26 (2.17, 4.92), p<0.001	6.93 (2.02, 23.78), p=0.002	3.60 (1.20, 10.82), p=0.02	3.13 (1.94, 5.05), p<0.001
FEV1/FVC (per 0.10 unit decrease)	1.42; (1.18, 1.71), p<0.001	1.602 (0.916, 2.803), p=0.099	1.40 (0.96, 2.04), p=0.08	1.43 (1.14, 1.81), p=0.002
ACQ	1.56; (1.27, 1.93), p<0.001	n/a	n/a	n/a

Variables included in multivariable subgroup analyses: treatment randomization, age, female, BMI, smoke in the past, smoking environment, years from asthma diagnosis, FEV1 in liters, FEV1/FVC, FEV1 reversibility, average daily puffs of SABA, asthma related steroid use in the prior 12 mo, asthma related ED visit in the prior 12 mo, asthma related hospitalization in the prior 12 mo, environmental allergies, distance from home to nearest major road (A1, A2, or A3), region of residence

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