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Ventilation defects on hyperpolarized helium-3 MRI in asthma are predictive of 2-year exacerbation frequency

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Abstract

Background—There is an unmet need for an objective biomarker to predict asthma exacerbations.

Objective—Here, we assess the ventilation defect percent (VDP) on hyperpolarized (HP) ³He MRI as a predictor of exacerbation frequency following imaging.

Methods—Subjects underwent HP ³He MRI and conventional clinical measurements, including pulmonary function tests, during a period of disease stability, and exacerbations were recorded prospectively over the following two years. We used a Poisson regression tree model to estimate an optimal VDP threshold for classifying subjects into high versus low exacerbation groups, and then used statistical regression to compare this VDP threshold against conventional clinical measures as predictors of exacerbations.

Results—Sixty-seven asthmatics (27M 40F, 28 mild/moderate and 39 severe) had median [1Q–3Q] VDP of 3.75% [1.2%–7.9%]. An optimal VDP threshold of 4.28% was selected based on

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maximum likelihood estimation of the regression tree model. Subjects with VDP > 4.28% (N=32) had a median of 1.5 exacerbations vs. 0.0 for subjects with VDP < 4.28% (N=35). In a stepwise multivariate regression model, VDP > 4.28% was associated with an exacerbation incidence rate ratio of 2.5 (95% CI 1.3–4.7) vs. VDP < 4.28%. However, once individual medical history was included in the model, VDP was no longer significant. Nonetheless, VDP may provide an objective and complementary quantitative marker of individual exacerbation risk useful for monitoring individual change in disease status, selecting patients for therapy, and assessing treatment response.

Conclusion—VDP measured with MRI shows promise as a biomarker of prospective asthma exacerbations.

Graphical Abstract

Ventilation Defects on ³He MRI Are Predictive of 2-Year Asthma Exacerbation

Capsule summary:

The ventilation defect percent (VDP) derived from hyperpolarized gas lung MRI is predictive of 2-year asthma exacerbation. This builds on previous work showing that VDP was associated with history of severe exacerbation.

Keywords

asthma; magnetic resonance imaging; functional; airway obstruction; patient outcomes assessment

I. INTRODUCTION

Prevention and management of exacerbations is of paramount concern in the care of patients with asthma. In addition to the impact on patient quality of life, exacerbations are associated with increased health care costs¹. Multiple risk factors for asthma exacerbation have been proposed, including forced expiratory volume in one second (FEV₁)², bronchodilator reversibility³, and sputum and blood eosinophils^{3,4}. However, there remains a need for a strong individualized predictor of asthma exacerbation in moderate and severe asthma to support personalized therapy decision-making and clinical trials in smaller populations of

asthmatics over shorter time scales. Here, we examine the use of hyperpolarized helium-3 magnetic resonance imaging (HP ^3He MRI) as a biomarker of exacerbation in a subpopulation of asthmatics drawn from the NHLBI Severe Asthma Research Program III (SARP3) study.

The widely accepted metric for measuring ventilation defect extent using HP gas MRI is the ventilation defect percent (VDP), defined as the ratio of ventilation defect volume to total lung volume⁵⁻⁷, and VDP has been shown to predict exacerbations in chronic obstructive pulmonary disease (COPD)⁸. In asthma, VDP has recently been shown to be associated with history of severe clinical outcomes, including asthma-related emergency department visits and hospitalizations⁹. Though prior studies have investigated multiple aspects of VDP in the context of asthma, including response to bronchial thermoplasty⁶, sputum eosinophilia¹⁰, and mucus plugs on CT¹¹, no study to date has examined VDP as a predictor of prospective asthma exacerbation. The purpose of this study was to evaluate VDP as a predictor of asthma exacerbation frequency in a two-year period following imaging in a mixed population of mild/moderate and severe asthmatics. Establishing VDP as a biomarker of asthma exacerbation is of interest in evaluating drug efficacy in clinical trials, selecting patients for targeted therapies, and monitoring treatment response.

II. METHODS

Study Population

Non-smoking subjects with asthma age 6 and older were recruited as part of the SARP3 multisite study^{12,13} (NIH [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01606826) identifier NCT01606826), with a particular emphasis on subjects who had used high-dose inhaled corticosteroids (ICS) and a second controller therapy for the last 3 months at recruitment. Asthma diagnosis was confirmed by demonstration of relative change in post-albuterol FEV₁ of at least 12%, or a methacholine provocative concentration less than or equal to 16 mg/ml associated with a 20% decline in FEV₁. The imaging-based study population was drawn from the larger SARP3 population recruited at the University of Wisconsin-Madison (UW-Madison), and this study was approved by the UW-Madison Health Sciences IRB (HS-2012-0571). The use of HP ^3He gas as an inhaled contrast agent was regulated by the FDA (IND# 064867). Informed consent was obtained for all subjects. SARP3-wide inclusion and exclusion criteria together with specific UW-Madison exclusion steps are shown in the Online Repository for this article (_____). Note that eight subjects were excluded from the analysis due to images that were not of diagnostic quality (i.e. coil/gas delivery issue, incomplete coverage of thoracic cavity, or SNR < 5.0).

Exacerbations were determined from self-reported number of asthma-related oral corticosteroid (OCS) courses lasting three or more days within the previous year. This information was collected at the baseline imaging visit and at visits occurring one year and two years following baseline, with phone call interviews at 6 months in between the longitudinal visits.

Imaging Methods

Image data for this analysis were collected after withholding bronchodilators for 4 hours for short acting agonists and 6-24 hours for long-acting products. Specific MRI acquisition parameters and techniques are described in detail in the Online Repository. Proton MRI was registered to HP ^3He MRI using a 3D rigid registration algorithm implemented using ANTs (<http://picsl.upenn.edu/software/ants/>). The lung boundary on HP ^3He MRI was segmented with reference to the proton MRI and regions of ventilation defect were classified on HP ^3He MRI using a semi-automated adaptive k-means algorithm.⁷

Subject Characterization

Characterization procedures were adapted from the SARP I and II studies¹³⁻¹⁷ and included spirometry, maximum reversibility following bronchodilator, measurements of blood serum and sputum eosinophils, fractional exhaled nitric oxide (FeNO), GERD and sinusitis assessment, and administration of the asthma control test (ACT) and asthma control questionnaire (ACQ) surveys. Percent predicted (%P) values for FEV₁ and FVC were generated using the Global Lung Function Initiative reference values¹⁸. Blood, sputum, and FeNO assessments were all administered on the same day as imaging. Spirometry was also performed on the same day as imaging unless the subject had already undergone spirometry within the previous six weeks as part of their consent visit, in which case those values were used.

Inhaled corticosteroid (ICS) dosing level at baseline was assessed in our data set on an ordinal scale of 0-3, corresponding to “none”, “low”, “medium”, and “high”. High dose was determined by site coordinators with reference to treatment history codes. Medium and low dose was determined from dosing information provided from two ICS inhalers, with threshold for medium dose defined as at least half the high-dose definition and low dose being half of medium dose. The reported dose was assumed to be that prescribed, and determination of category was made without regard to reports of less-than-daily use.

Statistical Methods

Specific predictors under consideration included VDP, age, sex, BMI, FEV₁ %P, FVC %P, FEV₁/FVC, ACT, ACQ, GERD and sinusitis status, serum and sputum eosinophils, FeNO, and maximum reversibility following bronchodilator.

We assessed associations between these predictors and two-year exacerbation frequency in two stages. First, we used Poisson model-based recursive partitioning¹⁹ to examine the association between VDP and cumulative exacerbations, and selected an optimal VDP threshold for dividing the population into high- and low-exacerbators used maximum likelihood estimation. We then used three types of negative binomial regression models of exacerbation frequency to assess the performance of the VDP threshold with respect to other demographic and clinical metrics gathered at baseline as predictors of cumulative two-year exacerbations. These models included (1) individual univariate models for each predictor, (2) a multivariate model with all predictors included, and (3) a parsimonious multivariate model with a subset of predictors chosen using stepwise model selection based on the Akaike Information Criterion (AIC). The relationships between baseline predictor variables

and subsequent exacerbation counts are summarized as exacerbation incidence rate ratios (IRR) with 95% confidence intervals, obtained by exponentiating the regression coefficient estimates. Predictor variables were scaled or log-transformed as needed to facilitate easier interpretation of results as follows: IRRs are estimated with respect to 10-unit changes in age, BMI, FVC %P, or FEV₁ reversibility and two-fold changes in FeNO or EOS. Variables were termed significant if the 95% confidence interval for the estimated exacerbation IRR did not include 1.

Differences in measurements between subjects with and without exacerbations, between the groups above and below the VDP threshold, and in other subgroup comparisons were assessed using the Wilcoxon rank-sum test, or the chi-square test for categorical variables when appropriate. Correlations between VDP and other predictors of exacerbation were assessed using the Spearman correlation. Analyses were conducted using R version 3.6.0²⁰.

III. Results

Study Population

The study population consisted of 67 subjects, with 28 classified as mild/moderate asthmatics and 39 as severe per the SARP3 criteria¹⁵. These subjects in aggregate experienced a total of 78 exacerbations in the two years following imaging, with 46 (59.0%) of exacerbations occurring in the first year and 32 (41.0%) in the second year. A total of 36 subjects (53.7%) experienced one or more exacerbations, with the remaining 31 subjects (46.3%) experiencing zero exacerbations. Subjects with one or more exacerbations experienced a median of 2 exacerbations (1Q = 1, 3Q = 3). Four subjects (6.0%) received biologic therapy within three months prior to baseline. Over the course of the study, 31 subjects (46.3%) were on the same ICS dose at baseline and two-year follow-up, 6 subjects (9.0%) had an increased ICS dose at follow-up, 19 subjects (28.4%) had a decreased ICS dose, and 11 subjects (16.4%) were not on ICS at either time point.

A summary of population characteristics stratified by presence or absence of one or more prospective exacerbations is presented in Table I. All measurements were acquired for all subjects except FeNO (N=64, 95.5%) and sputum eosinophils (N=50, 74.6%). Of all the predictors under consideration, only sex, FVC %P and VDP were significantly different between the two groups at the $p = .05$ level, although GERD status was on the cusp of significance. VDP was greater in the subjects with one or more two-year exacerbations, with a median [1Q – 3Q] value of 5.5 [3.0 – 9.8] vs. 2.2 [0.9 – 4.9] in subjects with no exacerbations ($p = .010$). Subjects with one or more exacerbations were more likely to be female ($p = .024$) and have decreased FVC %P ($p < .01$). The number of exacerbations in the year prior to imaging was also significantly increased in the exacerbation group ($p < .001$). Subjects who underwent an exacerbation in the 2nd year only (N = 10) had a median [1Q – 3Q] VDP of 4.4% [1.3% – 6.4%] vs. 6.1% [3.6% – 13.5%] for subjects with an exacerbation in the 1st year (N = 26). Although the median and quartile VDP values were reduced in subjects who exacerbated later relative to the time of imaging, the difference in distributions was not significant ($p = .16$). Example images from three individual subjects demonstrating different patterns and incidence of 2-year exacerbations are shown in Figure 1.

Correlations between VDP and Clinical Measures

Figure 2 shows a box and whisker plot comparing VDP in subject groups without and with one or more exacerbations. Median [1Q – 3Q] VDP is 5.5% [3.0% – 9.8%] in subjects with one or more exacerbations vs. 2.2% [0.9% – 4.9%] in subjects with no exacerbations ($p = .010$).

Correlations between VDP and selected clinical measurements are shown in Table II. VDP was negatively and moderately correlated to FVC %P, maximum reversibility following bronchodilator, sputum eosinophils, and the ACQ and ACT scores. VDP was not correlated with FeNO or serum eosinophils. For categorical variables, specifically GERD and sinusitis status, VDP was not significantly different across the two categories ($p = .12$ and $p = .73$ respectively). VDP was also correlated with FEV₁ %P ($p < .001$, $p = -0.47$) and FEV₁/FVC ($p < .001$, $p = -0.60$), but both of these measurements are also correlated with FVC %P ($p < .001$, $p = 0.90$ and $p < .001$, $p = 0.56$ respectively) and are omitted from the table for clarity.

Determining a Maximum Likelihood VDP Threshold

Using maximum likelihood estimation on the Poisson regression tree model fit, a VDP of 4.28% was selected as the threshold that most accurately classified subjects based on cumulative exacerbation history (Figure 3).

Subjects with VDP exceeding the 4.28% threshold ($N = 32$) had a median [first quartile – third quartile] of 1.5 [0.75 – 3.0] exacerbations, vs. 0.0 [0.0 – 1.0] for subjects below the threshold ($N = 35$), as shown in Figure 4. Study population descriptive statistics stratified by VDP threshold are shown in Online Repository Table E2.

Regression Models

Table III shows exacerbation IRR values with 95% CIs from negative binomial regression models of cumulative exacerbations gathered for each study participant. These include estimates from (1) individual univariate models for each predictor, (2) a multivariate model with all predictors included, and (3) a parsimonious multivariate model with a subset of predictors chosen using stepwise model selection based on the AIC. Note that since FEV₁ %P and FEV₁/FVC were both correlated with FVC %P as noted earlier, we chose to include only FVC %P in the model-based analyses, since initial analysis (see Table I) showed that it was significantly reduced in the exacerbation vs. no exacerbation groups, whereas neither FEV₁ %P nor FEV₁/FVC were significantly different across the two groups.

In all three sets of models, VDP was a strong predictor of subsequent exacerbations, with subjects over the threshold having over twice the exacerbation IRR as subjects below the threshold, as illustrated in Figure 5. In the univariate models, age, GERD, and FVC %P were significant predictors in addition to VDP. In the full multivariate model, only VDP was a significant predictor. In the stepwise multivariate model, BMI, GERD, and FVC %P were selected in addition to VDP, with GERD and FVC %P significant and BMI not significant.

Incorporation of Baseline ICS Dose and Exacerbation History

To test the predictive power of VDP when medical history was known, we reran two additional sets of models, each with one added predictor: first, categorical ICS dose at baseline, and second, number of exacerbations in the year prior to baseline.

When categorical ICS dose at baseline was included in the multivariate model, VDP was no longer significant (IRR 1.57, 95% CI 0.74 – 3.39), although it was selected in the multivariate stepwise model. Subjects on medium- and high-dose ICS were significantly more likely to exacerbate (IRR 10.7, 95% CI 1.7 – 208.6 and IRR 9.5, 95% CI 1.7 – 180.0, respectively) than subjects with no ICS use. Complete results from these models are shown in Table E3 in the Online Repository.

When exacerbation history was incorporated in the multivariate model (IRR 1.36, 95% CI 1.20–1.6, per prior exacerbation), the VDP threshold no longer provided significant additional predictive power (IRR 1.15, 95% CI 0.53–2.53). Complete results for these models are shown in Online Repository Table E4.

IV. DISCUSSION

We found that the VDP on hyperpolarized gas MRI is predictive of asthma exacerbation rate in the two years following imaging. VDP was a significant predictor of exacerbation rate in both univariate and multivariate regression models incorporating a suite of conventional demographic and clinical measures assessed at baseline. In each of these models, a VDP measurement over the threshold of 4.28% was associated with more than double the exacerbation rate vs. subjects with VDP below the threshold. This finding adds to previously published results which showed that VDP was associated with a history of one or more severe exacerbations prior to imaging⁹. However, this work differs from and extends that result in several key aspects. First and foremost, the prospective rather than retrospective study design enables an assessment of predictive value, rather than a retrospective association. Second, the definition of exacerbation in this work was broadened: rather than tracking severe clinical outcomes (ED visits and hospitalizations), exacerbations were defined as any event requiring three consecutive days of oral corticosteroid (OCS) use, thus allowing the assessment of the ability of VDP to predict less severe outcomes. Finally, we tracked *cumulative* exacerbations (i.e. exacerbation frequency) over a set time period of two years prospective to imaging instead of a binary indicator of exacerbation at any time prior to imaging.

We also found that FVC %P was significantly lower in subjects who went on to have one or more exacerbations (Table I), a risk factor related to air trapping identified in previous studies²¹, whereas FEV₁ %P, FEV₁/FVC, and FEV₁ reversibility following bronchodilator showed no significant difference. FVC %P was also a significant predictor in our stepwise multivariate model of two-year exacerbations (Table III), even when that model was expanded to include exacerbation history (Online Repository Table E2), highlighting the role of air trapping as a driver of instability in this population. Given that VDP is individually correlated with FVC across the population as a whole, it is plausible that the increase in VDP in the exacerbation group is driven to a large extent by peripheral air trapping.

Consistent with this hypothesis is the fact that bronchodilator reversibility was not associated with exacerbation risk in this study. While some previous literature has shown that increased bronchodilator response is associated with asthma exacerbation^{3,22} this effect was not observed by Koga et al., who found that asthma subjects with multiple exacerbations had persistent airflow limitation and reduced reversibility²³. Notably, three-quarters of subjects in our study who experienced at least one exacerbation were already on high-dose ICS at the time of imaging as part of their clinical care. This treatment may be partially suppressing central airway hyper-responsiveness and thereby accentuating the relative roles of persistent airway limitation and peripheral air trapping (as reflected in decreased FVC %P) in driving exacerbation.

Interestingly, there were 8 subjects in our population who had VDP greater than the threshold of 4.28% and yet did not go on to experience an exacerbation; 7 of these subjects were classified as “severe” under the SARP criteria. We did not see significant differences in spirometry or inflammatory markers in these subjects vs. the 24 subjects who were also over the threshold and *did* go on to experience one or more exacerbations. However, only 2 of these 8 non-exacerbators (25%) had a record of an exacerbation in the year prior to imaging, vs. 19 out of 24 (79%) of the subjects who went on to exacerbate. This finding, together with the “severe” asthma status indicating past history of exacerbation and/or step-up in treatment, suggests that these subjects may have disease that has become more stabilized and controlled despite the presence of ventilation defects. In addition, mucus plugs scored on CT in asthma²⁴ were shown by Svenningsen et al. to be associated with VDP¹¹, and thus we further speculate that some of these subjects may have persistent, long-term mucus plugging that is not associated with acute exacerbations. Research to test the associations of mucus plugs and air trapping on CT with regional defects is ongoing.

A previously published SARP3-wide analysis of 709 subjects³ found that in a multivariate model (the basis for the models in this work), bronchodilator reversibility, blood eosinophils, BMI, sinusitis, and GERD were associated with exacerbation frequency in the prior year. Here, we also found an association between prospective exacerbations and both GERD and sinusitis in univariate models, and with GERD in a stepwise multivariate model. Several of the predictors that we compared against VDP in this population have also been found to be associated with exacerbation risk in other asthma studies, including ACQ score²⁵, blood eosinophils²⁶, and FeNO²⁷. However, we did not observe these associations in our population, possibly due to the relatively small study population compared to large-scale cohort studies. That a significant effect was observed for VDP despite our relatively modest study population suggests that there is a potential for VDP to be a useful biomarker to support clinical research studies in smaller more targeted populations, or even on an individual basis to guide therapy in difficult cases.

VDP was no longer a significant predictor of exacerbation in models that included either ICS dose category at baseline, or prior exacerbation history. Specifically, subjects on medium- and high-dose ICS were significantly more likely to exacerbate than those not on ICS, and similarly, the number of exacerbations in the year prior to imaging was a stronger predictor of exacerbation than VDP when included in the comprehensive multivariate models. However, ICS dose decision-making is clearly based in part on medical history, and

exacerbation history can be a subjective measure when applied on an individual basis. Thus, VDP may provide a useful quantitative means of assessing individual exacerbation tendency when disease status has changed over a short time period, or when medical history is not currently reliable, such as when biologic therapy has recently been initiated or can no longer be administered. Since reducing exacerbations is an essential component of improving quality of life in asthma, longitudinal monitoring of VDP in a study population could provide a quantitative marker of individual exacerbation tendency and therapy response, and as a potential surrogate endpoint in clinical trials. VDP could also provide a means of screening to enrich for less stable disease and as a secondary endpoint for monitoring therapy response, thus enabling a potential reduction in both study size and duration. Thus, a VDP-based approach could provide a valuable means of assessing and monitoring response to therapy on a practical time scale for drug development or clinical decision-making.

Further work is needed to evaluate temporal variability, bias and precision to confirm VDP as a surrogate biomarker of exacerbations. Understanding the time course of VDP with respect to the build-up to an exacerbation event, repeatability during stability, and potential bias when disseminated across a network of sites participating in a trial are all necessary goals for future research. Developing a surrogate biomarker of asthma exacerbations would be of clear benefit due to the pressing need for a more reliable means in severe asthma for assessing suitability for costly targeted therapies (e.g. biologics such as mepolizumab or benralizumab) and for monitoring individual treatment response in order to guide dosing and new therapy regimens for tapering other controllers such as OCS.

The two primary limitations in this work are (1) the relatively small sample size and (2) a study design that did not enable a more refined assessment of the timing of prospective exacerbation frequency and severity with respect to imaging beyond simply counting the number of self-reported exacerbations (regardless of degree and time since imaging) over a two-year period. Although the self-reporting survey was designed to minimize misclassification, this method is still subject to potential recall bias. In addition, a more refined time scale for measuring exacerbations could permit a more accurate assessment of the relationship between VDP magnitude and exacerbation severity/frequency via a statistical approach such as a Cox proportional hazards model. Incorporating specific records of ED visits and/or hospitalizations (indicators of severe exacerbation and significant cost drivers) was not possible since the frequency of those events was too low in a two-year period to allow for a meaningful model; a larger cohort and/or longitudinal monitoring over a longer time scale would enable an analysis of these relatively rare events. However, the definition of exacerbation used here is inclusive of both these severe events and also less severe exacerbations that nonetheless required a treatment escalation (i.e. OCS). That the association between VDP and exacerbation nevertheless persists suggests that VDP is sensitive to ventilation deficits associated with milder outcomes as well as those that require immediate emergency care, as examined previously⁹.

We found that the VDP on hyperpolarized gas MRI is predictive of exacerbation frequency in the two years following imaging, corroborating previously published results showing that VDP was associated with a history of severe exacerbation. VDP was no longer significant once individual medical history was added to the models. Nonetheless, these results suggest

that VDP may provide a quantitative approach for patient selection and to monitor individual treatment response in clinical trials, especially in subjects with uncertain or unknown medical history, or when disease has recently progressed, requiring consideration of a step-up in therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

%P	Percent predicted
AIC	Aikake information criterion
BD	Bronchodilator
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
FeNO	Fractional exhaled nitric oxide
FEV₁	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
HP ³He MRI	Hyperpolarized helium-3 magnetic resonance imaging
ICS	Inhaled corticosteroid
IRR	Incidence rate ratio
VDP	Ventilation defect percent

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Clinical implications: Lung ventilation measurements using hyperpolarized gas MRI are predictive of asthma exacerbation, and may be useful for risk assessment, monitoring therapy response, and as a secondary endpoint in clinical trials.

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Figure 1.
Example ³He MRI images from subjects with a range of clinical patterns, VDP, and exacerbations in the two years following baseline.

Figure 2.

VDP in subjects with zero (left) and one or more (right) two-year exacerbations. Median and quartile [1Q– 3Q] range of VDP is 5.5% [3.0% – 9.8%] in severe subjects vs. 2.2% [0.9% – 4.9%] in mild/moderate ($p = 0.010$). Five outlier points not shown.

Figure 3.

Number of exacerbations predicted by regression tree model of VDP vs. exacerbations (solid line) and 95% confidence interval (shaded area). The maximum likelihood estimate for a VDP threshold (4.28%) stratifying low ($N = 35$) vs. high ($N = 32$) exacerbators is indicated by the solid vertical line.

Figure 4:

Box and whisker plot of 2-year exacerbation frequency for subjects above and below the VDP threshold. Subjects above the threshold experienced a median of 1.5 exacerbations vs. zero exacerbations for subjects below the threshold ($p < 0.001$).

Figure 5.

Exacerbation incidence rate ratio (IRR) and 95% confidence intervals for model predictors. Within each predictor, the top line indicates the IRR in the univariate (individual) models, the second line the inclusive multivariate model, and the third line (if present) the parsimonious multivariate model.

Table I.
Summary of population characteristics.

Baseline Status	Number of Prospective Exacerbations		Difference
	Zero	One or more	
N	31 (46.3%)	36 (53.7%)	-
Severe asthma	13 (41.9%)	26 (72.2%)	p = 0.012
Sex (F)	14 (45.2%)	26 (72.2%)	p = 0.024
Age (yrs)	30.7 [19.9, 49.0]	46.5 [19.9, 58.8]	p = 0.18
BMI	25.9 [23.6, 29.1]	27.6 [22.8, 32.3]	p = 0.35
Pre-BD FEV1 %P	86.2 [80.0, 99.0]	78.7 [57.9, 96.0]	p = 0.11
Pre-BD FVC %P	95.0 [88.2, 104.5]	89.8 [71.6, 102.7]	p < 0.01
Pre-BD FEV1/FVC	0.76 [0.72, 0.78]	0.71 [0.63, 0.80]	p = 0.32
Pre-BD FEV1/FVC z-score	(1.22) [-1.73, -0.87]	-1.59 [-2.47, -0.55]	p = 0.41
ACQ	0.71 [0.57, 1.22]	1.15 [0.71, 1.86]	p = 0.07
ACT	20.0 [19.0, 21.5]	20.0 [15.0, 22.3]	p = 0.40
FeNO *	19.5 [11.3, 36.0]	22.5 [12.3, 32.3]	p = 0.97
Blood eosinophils (counts/ μ L)	201.0 [126.5, 278.0]	327.0 [147.8, 510.2]	p = 0.09
Sputum eosinophils (%) **	0.70 [0.20, 1.88]	0.75 [0.00, 3.05]	p = 0.86
GERD	10 (32.3%)	20 (55.6%)	p = 0.056
Sinusitis	7 (22.6%)	14 (38.9%)	p = 0.15
Max. Reversibility following BD (%)	10.6 [6.1, 15.2]	10.8 [4.3, 17.4]	p = 0.99
VDP (%)	2.15 [0.91, 4.89]	5.51 [2.95, 9.82]	p = 0.010
On LABA	16 (51.6%)	31 (86.1%)	p < 0.01
On high-dose ICS	15 (48.4%)	28 (77.8%)	p = 0.012
On LABA + high-dose ICS	13 (41.9%)	27 (75.0%)	p < 0.01
# Exacerbations in prior year	0 [0, 0]	2 [0, 3]	p < 0.0001

Results given as median [1st quartile, 3rd quartile] or percent of total. All measurements acquired prior to bronchodilator (BD) administration, except maximum reversibility.

* N=64

** N=50.

Table II.
Spearman's correlation between ventilation defect percent (VDP) and clinical measures of lung function, inflammatory response, and asthma control status.

Clinical Measure	Correlation with VDP
FVC %P	$\rho = -0.45, p < 0.001$
ACQ	$\rho = 0.38, p < 0.01$
Sputum Eos	$\rho = 0.31, p = 0.029$
Max. Reversibility	$\rho = 0.29, p = 0.018$
ACT	$\rho = -0.25, p = 0.038$
Blood Eos	$\rho = 0.16, p = 0.20$
FeNO	$\rho = -0.01, p = 0.95$

FVC %P – forced vital capacity percent predicted; ACQ – asthma control questionnaire; ACT – asthma control test; FeNO – fractional exhaled nitric oxide.

Table III.
Exacerbation Incidence Rate Ratios (IRRs) with 95% CIs from negative binomial regression models of exacerbation counts for each participant (n = 67).

Predictor	Univariate Models			Multivariate Model			Stepwise Multivariate Model		
	IRR	Lower	Upper	IRR	Lower	Upper	IRR	Lower	Upper
VDP > 4.28	2.97	1.68	5.40	2.29	1.08	4.97	2.46	1.32	4.70
Age (per 10 yrs)	1.20	1.04	1.39	1.04	0.86	1.26	NA	NA	NA
Female Sex	1.35	0.72	2.56	1.44	0.77	2.72	NA	NA	NA
BMI (per 10 pts)	1.12	0.70	1.80	0.64	0.38	1.05	0.69	0.44	1.06
ACT	0.98	0.90	1.05	1.05	0.95	1.16	NA	NA	NA
ACQ	1.41	0.98	2.04	1.29	0.71	2.32	NA	NA	NA
GERD	1.87	1.04	3.41	1.39	0.77	2.53	1.76	1.05	2.98
Sinusitis	1.52	0.81	2.87	1.52	0.85	2.68	NA	NA	NA
Serum Eos (log ₂)	1.17	0.89	1.55	1.13	0.87	1.47	NA	NA	NA
FeNO (log ₂)	0.97	0.72	1.31	0.94	0.69	1.30	NA	NA	NA
FVC (per 10%)	0.78	0.66	0.91	0.87	0.68	1.11	0.83	0.7	0.98
Max. Rev (per 10%)	1.11	0.91	1.38	1.05	0.81	1.37	NA	NA	NA

ACT – asthma control test; ACQ – asthma control questionnaire; GERD – gastroesophageal reflux disease; FeNO – fractional inhaled nitric oxide; FVC – forced vital capacity. NA – predictor not chosen in by stepwise model. Transformations or multipliers to each variable are listed inline where applicable.