SUPPLEMENTARY MATERIAL

Supplemental Table S1. Participant listing of demographic and other measurements

	Demographics			Questionnaires and Exacerbation History								Spirometry			Ventilation Heterogeneity	
	Age	Sex	BMI	Duration	ACQ	AQLQ	Dyspnoea Scores		Exacerbations	ED visits	Hospitalizations	FEV_1	FVC	FEV_1/FVC	LCI	VDP
Subject	(yrs)	(M/F)	(kg/m^2)	(yrs)	Score	Score	mMRC	Borg	(n)*	(n)*	(n)*	Pre/Post (L)	Pre/Post (L)	Pre/Post (%)	Pre/Post	Pre/Post (%)
001	34	F	40	16	-	-	-	-	0/2	0/0	0/0	2.2/2.5	3.0/3.2	74/80	9.5/8.8	12/10
002	67	M	28	7	-	-	-	-	0/0	0/0	0/0	3.1/3.4	4.8/5.0	66/68	12.6/8.8	11/6
003	61	M	33	7	2.1	4.6	0.0	4.0	1/3	0/0	0/0	2.7/3.4	5.0/5.8	54/59	13.4/12.1	30/17
004	60	F	33	39	4.3	3.2	3.0	9.0	2/4	0/2	0/0	1.0/0.9	2.1/2.0	46/46	14.0/14.4	35/20
005	38	F	30	36	1.9	5.9	1.0	1.0	0/1	0/0	0/0	1.4/1.6	1.7/2.0	82/79	11.5/9.3	7/6
006	45	M	25	44	2.7	4.7	1.0	1.0	0/0	0/0	0/0	1.5/1.6	3.3/3.4	44/47	11.5/10.6	14/11
007	55	F	33	20	1.4	5.0	1.0	3.0	0/1	0/0	0/0	2.1/2.3	2.9/3.1	71/76	9.7/9.3	2/3
008	47	F	30	34	2.3	5.3	2.0	2.0	2/5	1/1	0/0	3.0/3.0	3.7/3.6	80/83	6.3/7.1	2/2
009	21	F	20	18	2.7	3.1	2.0	5.0	0/5	0/0	0/0	3.4/3.5	3.8/3.7	88/94	7.0/7.3	1/2
010	45	F	31	41	1.6	4.0	0.0	0.5	4/18	0/0	0/0	3.0/3.3	3.8/3.8	78/86	7.4/6.6	4/1
011	40	F	29	27	2.3	4.8	1.0	1.0	6/12	0/0	0/0	2.1/2.4	3.3/3.4	65/72	10.6/9.8	18/7
012	31	F	37	28	2.0	5.8	2.0	1.0	3/4	0/3	0/1	0.9/1.4	2.3/3.1	42/46	13.4/NA	15/5
013	56	M	25	55	3.1	4.2	-	-	2/3	0/0	0/0	1.5/1.5	4.4/4.2	35/37	17.5/15.5	33/29
014	44	F	27	23	1.0	5.6	1.0	0.5	0/1	0/0	0/0	2.9/3.0	3.8/3.9	74/79	7.7/7.3	3/2
015	42	M	33	28	1.4	4.6	1.0	2.0	0/0	0/0	0/0	2.7/3.1	4.0/4.4	67/71	9.5/10.1	8/4
016	48	M	30	46	2.3	5.5	0.0	3.0	0/1	0/0	0/0	2.9/3.2	4.2/4.4	69/72	8.6/8.2	8/8
017	39	F	22	36	1.7	6.1	1.0	0.5	5/7	0/0	0/0	2.2/2.4	4.0/3.9	56/62	6.7/6.1	3/2
018	59	F	23	57	4.3	1.7	3.0	4.0	4/8	0/1	0/0	1.4/1.6	1.9/2.7	71/58	11.6/11.0	15/16
Mean	46	12F/	29	31	2.3	4.6	1.3	2.5	9(50%)/	1(6%)/	0(0%)/	2.2(0.8)/	3.5(1.0)/	65(15)/	10.5(3.0)/	12(11)/
(±SD)	(12)	6M	(5)	(15)	(0.9)	(1.2)	(1.0)	(2.3)	15(83%)	4(22%)	1(6%)	2.5(0.8)	3.6(1.0)	68(16)	9.5(2.7)	8(8)

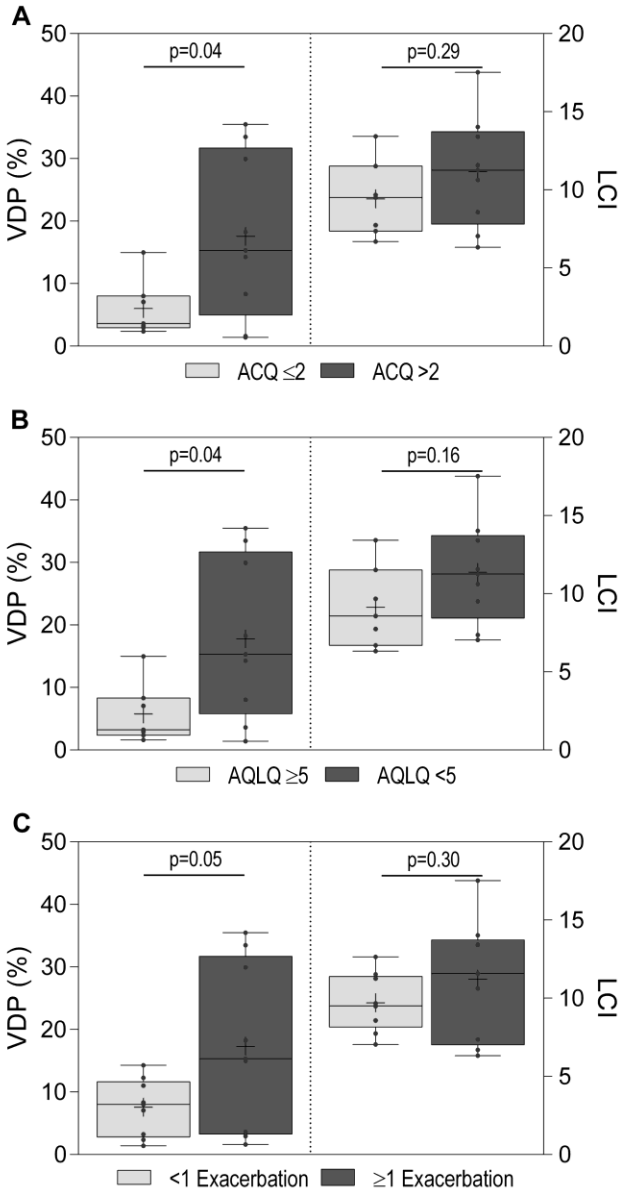
SD=standard deviation; M=Male; F=Female; BMI=body mass index; ACQ=asthma control questionnaire; AQLQ=asthma quality of life questionnaire; mMRC=modified Medical Research Council; ED=emergency department; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; LCI=lung clearance index; VDP=ventilation defect percent.

*in previous 6 months/in previous year.

Supplemental Table S2. Participant listing of asthma medications

	SABA	LABA		LAAC		ICS		OCS		LTRA		Anti-IgE	
Subject			Dose(μg/d)		Dose(μg/d)		Dose(μg/d)		Dose(mg/d)		Dose(mg/d)		Dose(mg)
001	Salbutamol	Formoterol	12	--	--	Budesonide	400	Prednisone	4	--	--	--	--
002	Salbutamol	Formoterol	24	--	--	Budesonide	800	Prednisone	12.5	--	--	--	--
003	Salbutamol	Formoterol	24	Tiotropium	18	Budesonide	800	Prednisone	20	Montelukast	10	--	--
004	Salbutamol	Salmeterol	100	Tiotropium	18	Fluticasone	2500	Prednisone	50	Montelukast	10	--	--
005	Salbutamol	Formoterol	36	--	--	Budesonide/Beclometasone	1200/800	Prednisone	2.5	--	--	--	--
006	Salbutamol	Formoterol	20	Tiotropium	18	Mometasone furoate/Fluticasone	800/1000	--	--	Montelukast	10	--	--
007	Salbutamol	Formoterol	24	Tiotropium	18	Budesonide	1600	Prednisone	7.5	--	--	--	--
008	Salbutamol	Salmeterol	100	--	--	Fluticasone	1000	--	--	Montelukast	10	--	--
009	Terbutaline	Formoterol	24	--	--	Budesonide	800	--	--	Montelukast	10	--	--
010	Salbutamol	Salmeterol	100	--	--	Fluticasone	1500	--	--	Montelukast	10	--	--
011	Salbutamol	Formoterol	24	--	--	Budesonide/Ciclesonide	800/800	Prednisone	7.5	Montelukast	10	--	--
012	Salbutamol	Salmeterol	100	Tiotropium	18	Fluticasone/Ciclesonide	1000/400	Prednisone	3	Montelukast	10	--	--
013	Salbutamol	Salmeterol	100	Tiotropium	18	Fluticasone	1000	--	--	--	--	--	--
014	Salbutamol	Formoterol	24	--	--	Budesonide	800	--	--	--	--	--	--
015	Salbutamol	Formoterol	24	--	--	Budesonide	1200	--	--	--	--	--	--
016	Salbutamol	Formoterol	24	--	--	Budesonide/Ciclesonide	800/800	--	--	--	--	Omalizumab	150
017	Salbutamol	Formoterol	24	--	--	Budesonide	800	--	--	Montelukast	10	--	--
018	Salbutamol	Formoterol	20	Aclidinium bromide	800	Mometasone furoate/Ciclesonide	800/800	--	--	--	--	--	--

SABA=Short-acting β-agonist; LABA=Long-acting β-agonist; LAAC=Long-acting anticholinergics; ICS=Inhaled corticosteroids; OCS=Oral corticosteroids; LTRA=Leukotriene receptor antagonists; Anti-IgE=Anti-immunoglobulin E.



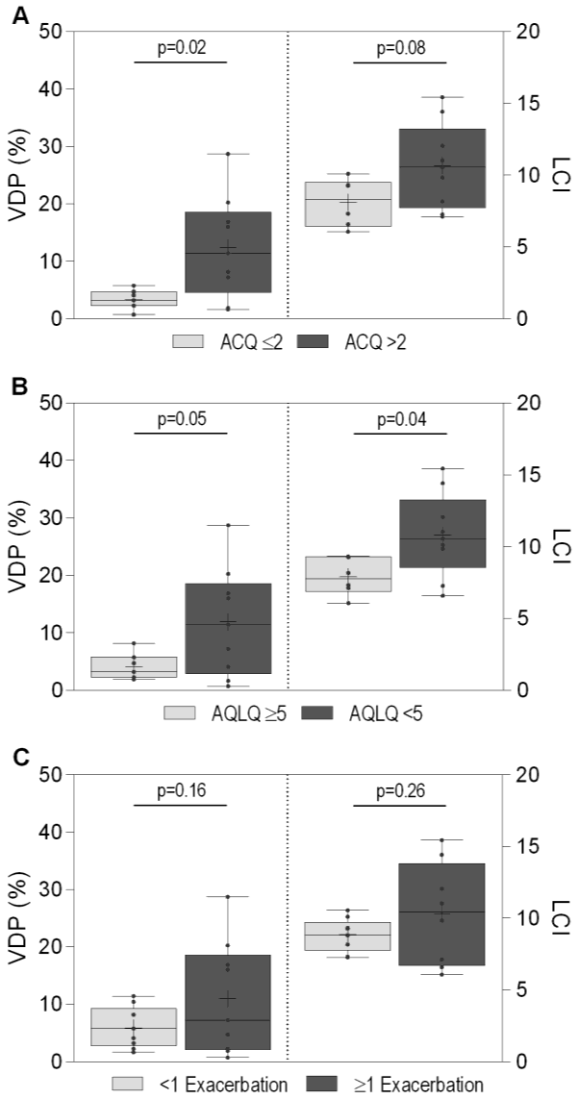
Supplemental Figure S1. Ventilation heterogeneity stratified by ACQ and AQLQ scores and self-reported exacerbations

A) Significantly worse VDP (>2 ACQ, VDP=18±13%; ≤2 ACQ, VDP=6±5, p=0.04), but not LCI (>2 ACQ, LCI=11.2±3.6; ACQ≤2, LCI=9.4±2.4, p=0.29) for subjects with ACQ >2.

B) Significantly worse VDP (AQLQ<5, VDP=18±13; AQLQ≥5, VDP=6±5, p=0.04), but not LCI (AQLQ<5, LCI=11.4±3.3; AQLQ≥5, LCI= 9.1±2.6, p=0.16), for subjects with AQLQ total scores <5.

C) There was a trend towards greater VDP (exacerbations ≥1, VDP=17±13%; exacerbations<1, VDP=8±5%; p=0.053), but not LCI (exacerbations ≥1, LCI=11.2±3.8 exacerbations<1, LCI= 9.7±1.8; p=0.3), for subjects with ≥1 exacerbation in past 6-months.

Box-and-whiskers plots show minimum, 25th percentile, median, 75th percentile, and maximum with each individual value superimposed on the graph. += mean. ACQ=asthma control questionnaire; AQLQ=asthma quality of life questionnaire; LCI=lung clearance index; VDP=ventilation defect percent.



Supplemental Figure S2. Post-bronchodilator ventilation heterogeneity stratified by ACQ and AQLQ scores and self-reported exacerbations

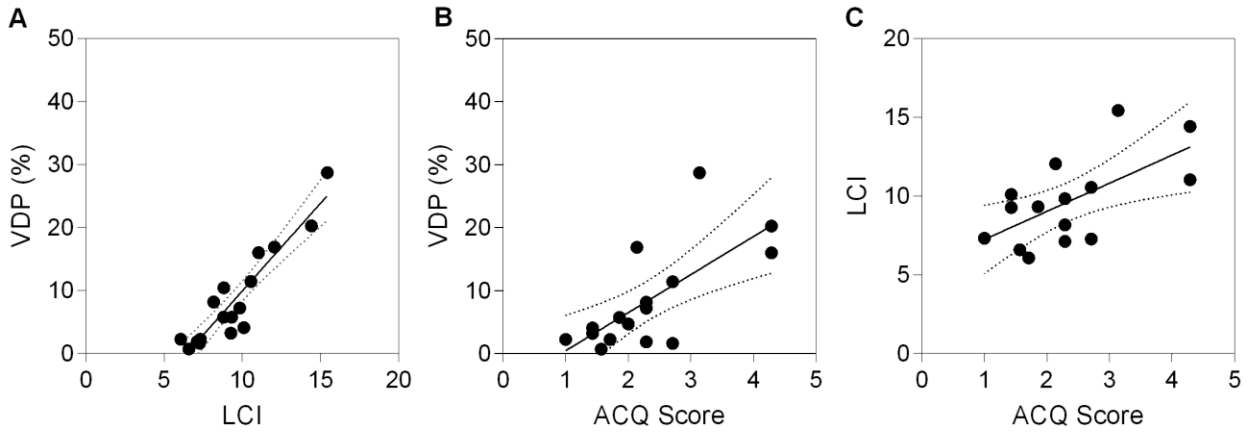
A) Significantly worse post-bronchodilator VDP (>2 ACQ, VDP=12±9%; ≤2 ACQ, VDP=3±2, p=0.02), but not post-bronchodilator LCI (>2 ACQ, LCI=10.7±3.0; ACQ≤2, LCI=8.1±1.7, p=0.08) for subjects with ACQ >2.

B) There was a trend towards worse post-bronchodilator VDP (AQLQ<5, VDP=12±9; AQLQ≥5, VDP=4±2, p=0.05) and post-bronchodilator LCI was significantly worse (AQLQ<5, LCI=10.8±2.9; AQLQ≥5, LCI= 7.9±1.3, p=0.04) for subjects with AQLQ total scores <5.

C) Post-bronchodilator VDP (exacerbations ≥1, VDP=11±10%; exacerbations<1, VDP=6±4%; p=0.16) and post-bronchodilator LCI (exacerbations ≥1, LCI=10.3±3.6 exacerbations<1, LCI= 8.9±1.3; p=0.26), were not different for subjects with ≥1 exacerbation in past 6-months.

Box-and-whiskers plots show minimum, 25th percentile, median, 75th percentile, and maximum with each individual value superimposed on the graph. += mean. ACQ=asthma control

questionnaire; AQLQ=asthma quality of life questionnaire; LCI=lung clearance index; VDP=ventilation defect percent.



Supplemental Figure S3. Relationship for post-bronchodilator ventilation heterogeneity and asthma control

A) Post-bronchodilator VDP was significantly correlated with post-bronchodilator LCI ($r=0.89$, $r^2=0.86$, $p<0.0001$, $y=2.8x-18.0$).

B) Post-bronchodilator VDP was significantly correlated with ACQ ($r=0.59$, $r^2=0.50$, $p=0.02$, $y=6.0x-5.6$).

C) Post-bronchodilator LCI was significantly correlated with ACQ ($r=0.63$, $r^2=0.39$, $p=0.01$, $y=1.8x+5.5$).

Dotted lines=95% confidence intervals; ACQ=asthma control questionnaire; LCI=lung clearance index; VDP=ventilation defect percent.

Supplemental Text

We note that we have previously observed but not reported, that patients with severe asthma and eosinophilic bronchitis often do not exhibit bronchodilator reversibility but it reappears when the eosinophilic bronchitis is controlled. We did not investigate the mechanisms underlying this but there are a number of potential reasons that may be explained by our current results. One of these could be that when the airway lumen is filled with cells, bronchodilators cannot improve airway calibre any further. Another reason is that eosinophil granular cationic products could potentially induce a beta-receptor dysfunction that improves when the eosinophilia is controlled. A third explanation, recently supported by Wenzel and colleagues [1] is that IL-13 (that may induce eosinophilia and airway hyper-responsiveness) may contribute to beta-receptor dysfunction.

Therefore, assuming that the dose of prednisone was optimally used in the current study, it might be expected that a greater bronchodilator response (and change in VDP) would be observed in patients who were not treated with prednisone (and who presumably had ongoing inflammation). This bronchodilator response, could very well be mediated by airway hyper-responsiveness that is mediated through a less-steroid sensitive pathway (for example smooth muscle dysfunction, residual IL-13 effects, etc).

Reference List

1. Albano GD, Zhao J, Etling EB, Park SY, Hu H, Trudeau JB, Profita M, Wenzel SE. IL-13 desensitizes beta2-adrenergic receptors in human airway epithelial cells through a 15-lipoxygenase/G protein receptor kinase 2 mechanism. *J Allergy Clin Immunol* 2015; 135: 1144-1153 e1141-1149.