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Childhood Asthma Clusters and Response to Therapy in Clinical Trials

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Abstract

Background—Childhood asthma clusters, or subclass, have been developed by computational methods without evaluation of clinical utility.

Objective—To replicate and determine if childhood asthma clusters previously identified computationally in the Severe Asthma Research Program (SARP) are associated with treatment responses in Childhood Asthma Research and Education (CARE) network clinical trials.

Methods—A cluster assignment model was determined using SARP participant data. 611 participants 6-18 years old from three CARE trials were assigned to SARP pediatric clusters. Primary and secondary outcomes were analyzed by cluster in each trial.

Results—CARE participants were assigned to SARP clusters with high accuracy. Baseline characteristics were similar between the SARP and CARE children of the same cluster. Treatment response in the CARE trials was generally similar across clusters. However, with the caveat of a smaller sample size, children in the early-onset/severe-lung function cluster had best response with fluticasone/salmeterol (64% versus 23% 2.5x fluticasone and 13% fluticasone/montelukast in the BADGER trial, $p=0.011$) and the early-onset/comorbidity cluster had the least clinical efficacy to treatments (e.g. -0.076% change in FEV₁ in the CLIC trial).

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Conclusions—In this study, we replicated the SARP pediatric asthma clusters using a separate, large clinical trials network. Early-onset/severe-lung function and early-onset/comorbidity clusters were associated with differential and limited response to therapy, respectively. Further prospective study of therapeutic response by cluster could provide new insights into childhood asthma treatment.

Keywords

asthma; clustering; clinical trials; replication; pediatric; therapy response

Introduction

Asthma is likely not a single disease, but rather a syndrome comprised of multiple complex phenotypes¹. Researchers have recognized this and have attempted to sub-classify asthma using expert opinion or computational techniques such as clustering.

Expert panels have also sub-classified asthma. For example, the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR3)³ has classified asthma severity as intermittent, mild-persistent, moderate-persistent and severe-persistent³. Once therapy is initiated, asthma control is defined based on symptoms and lung function. Similar classification has been used in the Global Initiative for Asthma⁴ (GINA). In both EPR3 and GINA, asthma phenotypes, applicable to large patient groups, are defined based on the amount of therapy necessary to achieve adequate control. However, one phenotype may consist of sub-phenotypes, each with a different optimal treatment.

While asthma guidelines have led to improvements in asthma care, it has been argued that they do not reflect the heterogeneous nature of the disease. Miller et al.⁵ identified a lack of classification agreement among guidelines, physician assessment, and health care usage. Wenzel¹ proposed new asthma phenotype definitions based on clinical history, triggers, and inflammatory markers.

There is extensive literature on asthma clustering for phenotype identification using clinical, genetic and imaging data^{6–14}. For example, Moore et al⁷ studied adults from the Severe Asthma Research Program (SARP) and identified five adult asthma clusters. Few studies have focused on clustering in childhood asthma. Fitzpatrick et al¹⁵ studied 161 6–17 year old SARP children, roughly one-half with severe asthma. The authors described four pediatric clusters distinct from the adult clusters: cluster 1 had late-onset (73 month mean age) symptomatic asthma with normal lung function (late-onset/normal-lung); cluster 2 had early-onset (30 month mean age) atopic asthma with mild airflow limitation (early-onset/normal-lung); cluster 3 had earliest-onset (14 month mean age) atopic asthma with mild airflow limitation and greater comorbidity (early-onset/comorbidity); and cluster 4 had early-onset (17 month mean age) atopic asthma with advanced airflow limitation and the greatest medication use (early-onset/severe-lung). The SARP analysis¹⁵ was intended to identify pediatric asthma clusters, but was unable to evaluate the clinical utility of this differentiation.

Although clustering methodology has provided additional perspective in asthma phenotypes, the computationally derived phenotypes have not been evaluated for applicability to other asthma populations or clinical utility. Therefore, we used a large well-characterized population of children who participated in the Childhood Asthma Research and Education (CARE) network clinical trials to determine first, if the SARP pediatric asthma clusters could be replicated in a new population and second, if these clusters were associated with response to therapy.

Methods

The study population consisted of 611 children 6-18 years old with asthma enrolled in three CARE Network clinical trials¹⁶⁻¹⁸. The trials are summarized in Table 1. Briefly, the Pediatric Asthma Controller Trial (PACT)¹⁷ was a three-arm (1x fluticasone, 0.5x fluticasone plus salmeterol, or montelukast) double-blind study of children with mild-moderate asthma and used percentage of asthma control days as the primary outcome. The Characterizing Response to Leukotriene Receptor Antagonist and Inhaled Corticosteroid (CLIC)¹⁶ trial was a crossover study comparing fluticasone 100 [proportional]g one inhalation twice daily and montelukast in children with mild-moderate asthma and utilized percent change in forced expiratory volume in 1 second (FEV₁) as its primary outcome. The Best ADD-on Therapy Giving Effective Responses (BADGER)¹⁸ trial was a triple crossover study evaluating step-up therapy for children with mild-moderate asthma uncontrolled on low doses of inhaled corticosteroids (100 µg of fluticasone twice daily = 1x). Treatments included 2.5x fluticasone, 1x fluticasone plus salmeterol, and 1x fluticasone plus montelukast. The primary outcome was the best treatment based on a composite evaluation considering prednisone usage for exacerbations, asthma control days, and percent change in FEV₁. The present post-hoc analysis was submitted to the University of Wisconsin Institutional Review Board and determined exempt from review.

Cluster Assignment Procedure

Linear discriminant analysis (LDA) was the model used by Fitzpatrick et al¹⁵ to classify participants into the SARP clusters with percent-predicted FEV₁, asthma duration, and number of controller medications as variables. The CARE dataset, which the model would later be applied to, did not contain number of controller medications. Therefore, leave-one-out cross validation^{19,20} was used to evaluate LDA and quadratic discriminant analysis (QDA) using SARP data FEV₁ and asthma duration variables. The LDA models with two and three variables were compared with the Wilks' lambda F-test. (See Detailed Methods-LDA and QDA in the Online Repository at www.jacionline.org for assumptions and risks of LDA and QDA).

Compared with LDA, the QDA classification model had better performance and was used to assign CARE participants to SARP pediatric clusters. Missing data was replaced using multiple imputation²¹. Three participants in BADGER were missing FEV₁ percent-predicted measurements. (See Detailed Methods-Multiple Imputation in the Online Repository at www.jacionline.org for imputation parameters).

Demographics and run-in clinical characteristics were summarized with complete non-missing data using descriptive statistics and compared across clusters using ANOVA for continuous measures and Fisher's exact test for categorical measures.

Association of Clusters with Clinical Trials Outcome

We analyzed the association of clusters and treatment outcomes for PACT, CLIC, and BADGER. Possible interactions between treatment and cluster were evaluated for the primary outcome and secondary outcomes (percent asthma control days, percent change in FEV₁, and time to first exacerbation) for each trial. Percent asthma control days in PACT was analyzed using a quasi-binomial generalized linear model with a logit link; percent asthma control days in CLIC and BADGER was analyzed using a quasi-binomial generalized estimating equations model with an independent working correlation matrix²⁴. Linear regression models were used to analyze percent change in FEV₁ for PACT; mixed effect linear models were used to analyze repeated measurements of percent change in FEV₁ for CLIC and BADGER. Time to first exacerbation was analyzed using a Cox proportional

hazards model for all three studies; frailty models²⁵ accounted for repeated measurements on the same participant in CLIC and BADGER. Differences in best treatment by cluster in BADGER were assessed using a Monte Carlo test based on Pearson's χ^2 statistic for independence in a 2×2 table.

Results

Classification Model and Assignment

For early-onset/normal-lung, late-onset/normal-lung, early-onset/comorbidity, and early-onset/severe-lung clusters, cross-validated QDA recall using SARP data with FEV₁ and asthma duration was 96%, 94%, 97%, and 90%, while precision was 96%, 94%, 94%, and 93%, respectively (See Table E1 in the Online Repository at www.jacionline.org). Using SARP data with the same two variables, cross-validation LDA recall was 90%, 96%, 94%, and 90%, and precision was 98%, 89%, 94%, and 90%. These results were similar to the original SARP LDA model using percent-predicted FEV₁, asthma duration, and number of controller medications, which had recall between 86% and 100% and precision between 86% and 96%. It is possible for stepwise LDA to identify three instead of two significant variables ($p=4.54 \times 10^{-5}$) while cross validation shows little difference between LDA with two or three variable because the former is based on the *F* test and the latter is based on precision and recall cross validation.

CARE trial participants were assigned to SARP pediatric asthma clusters using the two variable QDA model as precision and recall were slightly improved compared to LDA. The number of PACT, CLIC, and BADGER participants assigned to SARP pediatric clusters is shown in Table 2. The majority of participants were assigned to the early-onset/normal-lung cluster (41%) or late-onset/normal-lung cluster (40%). The early-onset/comorbidity cluster had the fewest participants (7%) and the early-onset/severe-lung cluster had slightly more (12%).

Demographics and Clinical Characteristics of Clusters

Table 3 summarizes baseline demographic and clinical characteristics of all participants. As expected, FEV₁ percent-predicted ($p<0.001$) and asthma duration ($p<0.001$), the two variables utilized for cluster assignment, were significantly different among clusters. The early-onset/normal-lung cluster had the shortest mean asthma duration and highest FEV₁ percent-predicted while the early-onset/severe-lung cluster had the longest mean asthma duration and lowest FEV₁ percent-predicted. Body mass index (BMI) was highest in the early-onset/comorbidity cluster at 23 kg/m². There was no difference in race among clusters. Although FEV₁ percent-predicted in the early-onset/comorbidity cluster was slightly higher compared to the late-onset/normal-lung cluster, the FEV₁/FVC was slightly lower in the early-onset/comorbidity cluster. The early-onset/comorbidity cluster had the highest percentage of positive skin tests, total immunoglobulin E, and fractional exhaled nitric oxide.

Baseline demographic and clinical characteristics of the SARP children in the clusters described by Fitzpatrick et al.¹⁵ were similar in the CARE children assigned to SARP clusters. Asthma duration and FEV₁ had similar trends across clusters. Late-onset/normal-lung and early-onset/normal-lung clusters were similar in gender and lung function. CARE and SARP participants in the early-onset/comorbidity cluster had the highest BMI, but had contrasting methacholine responsiveness. The early-onset/severe-lung cluster had lower lung function. There were fewer black participants in the CARE trials for this cluster.

Clusters and Clinical Trial Outcomes

The association of clusters and treatment response for Step 2 therapy was examined in PACT and CLIC. For PACT, the cluster and treatment interaction was not significant for primary outcome, percent asthma control days (Table 4). However, treatment responses were significantly different in the late-onset/normal-lung cluster ($p=0.008$) with montelukast being the least beneficial for these children. Across all treatment arms, percent asthma control days was lowest in the early-onset/comorbidity cluster (36%), with all other clusters having 55% asthma control days, although this difference was not statistically significant ($p=0.10$).

Considering secondary outcomes in PACT (Table 4), 1x fluticasone was significantly beneficial for percent change in FEV₁ in the late-onset/normal-lung cluster (8.0%, $p=0.004$) and early-onset/normal-lung cluster (6.8%, $p=0.005$). The early-onset/comorbidity cluster had the smallest overall percent change in FEV₁ (-0.25%) and the highest rate of exacerbations (54%) (See Table E2 in the Online Repository at www.jacionline.org), though not significantly different from the other clusters.

In CLIC, while no significant cluster and treatment interaction was found for the primary outcome of percent FEV₁ improvement from baseline, fluticasone was significantly superior to montelukast for the late-onset/normal-lung, early-onset/normal-lung, and early-onset/severe-lung clusters with a 3.6%, 5.3%, and 8.0% improvement (Table 5). Similar to the primary percent asthma control days outcome in PACT, CLIC children in the early-onset/comorbidity cluster demonstrated no improvement in FEV₁ from baseline with an average percent FEV₁ change of -0.076% across treatments. Secondary outcomes in CLIC identified consistent significant benefit of fluticasone in the early-onset/normal-lung cluster for percent asthma control days (81%, $p=0.003$) (Table 5) and time to first exacerbation ($p=0.008$) (See Table E2 in the Online Repository at www.jacionline.org).

Association among clusters and Step 3 treatment response was examined in BADGER. In this trial, a significant cluster and best treatment response interaction was not observed ($p=0.55$). Table 6 shows the percentage of participants within each cluster that had a specific treatment as their best treatment determined by the composite outcome. Fluticasone/salmeterol was most likely to provide the best response (64%) for the early-onset/severe-lung cluster ($p=0.01$). Similar to the primary BADGER analysis, fluticasone/salmeterol tended to have the greatest chance of best response (~40%) in the other three clusters.

Significant treatment benefits were observed in the late-onset/normal-lung and early-onset/severe-lung clusters secondary outcomes (Table 6). Fluticasone/salmeterol was the best treatment for the late-onset/normal-lung cluster according to percent asthma control days (80%, $p<0.001$). The early-onset/severe-lung cluster had the greatest benefit with fluticasone/salmeterol (7.7%) and 2.5x fluticasone (7.6%) with percent change FEV₁ as the outcome ($p=0.008$).

Discussion

In this study, we replicated the SARP pediatric asthma clusters by demonstrating CARE Network participants assigned to SARP clusters had similar characteristics. Furthermore, overall patterns of treatment response in PACT, CLIC, and BADGER were similar across clusters when compared to the responses in the entire study populations. Interestingly, however, the early-onset/severe-lung cluster had a clearly best Step 3 response with fluticasone/salmeterol in BADGER, while the early-onset/comorbidity cluster had a poor overall step 2 treatment response in PACT and CLIC.

Using readily available clinical information (asthma duration and FEV₁ percent-predicted), we were able to assign the CARE children to the original SARP pediatric clusters with very high recall and precision. We also found that the baseline demographic and clinical characteristics of the SARP children in the clusters described by Fitzpatrick et al.¹⁵ were quite similar in the CARE children assigned to SARP clusters, with a few exceptions. Asthma duration trended in the same fashion. The late-onset/normal-lung cluster had the highest FEV₁ percent-predicted and the early-onset/severe-lung cluster had the lowest. However, the FEV₁ percent-predicted values were globally higher in the CARE children as would be expected since many SARP participants had severe asthma and CARE participants included in this study had mild-moderate asthma.

Similar to the SARP children, CARE children in the late-onset/normal-lung cluster had the youngest age, greatest percentage of white race, highest percentage of females, lowest total IgE, and lowest FeNO. The CARE participant early-onset/normal-lung cluster was similar to the original SARP early-onset/normal-lung cluster, but had lower total IgE levels. The small number of participants in the early-onset/comorbidity and early-onset/severe-lung clusters limited the power to detect differences between clusters, but trends were noted. Similar to the original SARP early-onset/comorbidity cluster, CARE children in this cluster had the highest BMI. For CARE participants, this cluster had the least methacholine responsiveness, in contrast to the SARP cluster participants who had the greatest methacholine responsiveness. This reduced methacholine responsiveness may be related to the higher FEV₁ percent-predicted of 98% in CARE participants versus 90% in SARP participants. The CARE participant early-onset/severe-lung cluster did not contain the highest percentage of black participants as described in the original SARP early-onset/severe-lung cluster, but did have the worst baseline asthma control as reflected by asthma control days. Male gender, more predominant in this cluster, was associated with lower lung function as reported in other studies including previous SARP analyses²⁶ and the Dunedin study²⁷.

We next evaluated the ability of pediatric asthma cluster assignment to predict treatment responses. For many outcomes, the treatment responses were similar across clusters. However, there were some differences in treatment response by clusters, which are of interest. For example, in the BADGER study investigating Step 3 therapy, fluticasone/salmeterol combination therapy provided the greatest likelihood of best response in comparison to 2.5x fluticasone and fluticasone/montelukast for the early-onset/severe-lung cluster.

Children in the early-onset/comorbidity cluster tended to have the least clinical efficacy in PACT and CLIC investigating Step 2 therapy. However, this group was the smallest, decreasing our power to detect differences. Further study of the early-onset/comorbidity cluster is warranted based upon these study results and their unique characteristics from the pediatric SARP analysis including high co-morbidities (gastroesophageal reflux and chronic sinusitis), high daily oral corticosteroid usage, lower total lung capacity, and increased airway resistance.

Derivation of clusters is dependent on the population, as was evident in the different clusters identified from SARP clustering in adults and children. This study attempted to generalize previous childhood clustering results by determining if the same clusters exist in a new, more prevalent mild to moderate childhood asthma population as a form of validation. The second component of this study, associating cluster assignment with treatment outcome, is hypothesis generating and necessitates validation in future prospective studies in children.

A strength of our analysis is the large and well characterized patient population that participated in rigorously performed CARE Network clinical trials. Compared to SARP,

CARE had adherence monitoring, broad recruitment from both pediatricians and asthma specialists to reduce selection bias, and a racial/ethnic distribution more consistent with US census data allowing better generalization. Additionally, rather than creating new clusters, we have taken the “next step” by assessing if pediatric asthma phenotype clusters could be considered endotypes based on clinical treatment response²⁸. The full clinical utility of asthma clusters has yet to be determined.

A limitation of this study is the smaller number of participants assigned to the early-onset/comorbidity and early-onset/severe-lung clusters. The larger number of participants assigned to the late-onset/normal-lung and early-onset/normal-lung clusters suggest sub-clustering these more mild-moderate children may be warranted. Additionally, the retrospective nature of the study limited the analyzable characteristics.

Overall, we replicated previously developed pediatric asthma clusters in a large, well-defined population. While this study cannot be used to make treatment recommendations, our findings suggest that clusters can provide insight into which patients will have the most beneficial treatment response or potentially no preference, particularly in Step 2 or 3 asthma care. Further investigation of these childhood asthma clusters is warranted and could aid clinicians in personalizing treatment regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CARE	Childhood Asthma Research and Education
SARP	Severe Asthma Research Program
PACT	Pediatric Asthma Controller Trial
CLIC	Characterizing Response to Leukotriene Receptor Antagonist and Inhaled Corticosteroid
BADGER	Best ADd-on Therapy Giving Effective Responses

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Clinical Implication

Therapeutic responses across pediatric asthma clusters, or subclasses, were similar. One cluster/subclass showed most benefit with fluticasone/salmeterol, and another cluster/subclass showed limited treatment response warranting investigation to facilitate individualizing therapy.

Capsule Summary

We evaluated the clinical utility of pediatric asthma clusters, or subclasses. While treatment responses across clusters were generally similar, further study is warranted to identify the most efficacious and individualized therapy for specific clusters.

Table 1

Summary of the three CARE network clinical trials

Trial	Participants	N	Treatment	Primary Outcome	Results
Pediatric Asthma Controller Trial (PACT)	mild-moderate persistent asthma, 6-14 Years	285	1 of 3 double blind: 1x ICS (fluticasone), 0.5x ICS + LABA (salmeterol), or LTRA (montelukast)	percent asthma control days	1x Fluticasone and 0.5x Fluticasone + Salmeterol
Characterizing Response to Leukotriene Receptor Antagonist and Inhaled Corticosteroid (CLIC)	mild-moderate persistent asthma, 6-17 Years	144	Crossover: ICS (fluticasone), LTRA (montelukast)	percent change FEV1	Fluticasone
Best ADd-on Therapy Giving Effective Response (BADGER)	mild-moderate asthma not controlled by low dose ICS (fluticasone), 6-17 Years	182	Triple crossover: 2x ICS (fluticasone), 1x ICS + LABA (salmeterol), 1x ICS + LTRA (montelukast)	differential period response for prednisone usage, asthma control days, and percent change FEV1	1x Fluticasone + Salmeterol

ICS = inhaled corticosteroid, LABA=long acting beta-agonist, LTRA=leukotriene receptor antagonist, FEV1 = forced expiratory volume in 1 second

Table 2

Numbers of Participants in Each Cluster

Trial	Late-onset/normal-lung (1)	Early-onset/normal-lung (2)	Early-onset/comorbidity (3)	Early-onset/severe-lung (4)
PACT	109	133	9	34
CLIC	61	48	15	20
BADGER	78	62	20	22

CLIC and BADGER were double and triple cross-over trials, respectively. The effective number of participants given each treatment is roughly double and triple.

Table 3**Demographics and Run-in Clinical Characteristics Among Clusters**

Variable	Late-onset/normal-lung (1)	Early-onset/normal-lung (2)	Early-onset/comorbidity (3)	Early-onset/severe-lung (4)	P value
Participants (n)	248	243	44	76	<0.001
<u>Demographics</u>					
Age at Study Entry (yr)	9.4(2.6)	9.9(2.2)	15(1.7)	13(1.7)	<0.001
Age Asthma Onset (yr)	5.9(3)	2.2(2)	1.4(1)	1.8(1.6)	<0.001
Duration (yr)	3.5(1.6)	7.7(1.2)	14(1.4)	11(0.83)	<0.001
Height (cm)	137(15)	140(14)	165(10)	157(13)	<0.001
Weight (kg)	38(16)	40(16)	64(16)	56(19)	<0.001
BMI (kg/m ²)	19(4.5)	20(4.8)	23(5)	22(5.2)	<0.001
BMI >90 th percentile (%)	76(31)	84(35)	13(30)	29(38)	0.56
Gender (% female)	113(46)	86(35)	14(32)	19(25)	0.004
Ethnicity (% non-hispanic)	187(75)	184(76)	32(73)	56(74)	0.95
White (%)	183(74)	161(66)	27(61)	52(68)	0.18
Black (%)	46(19)	63(26)	12(27)	18(24)	0.20
American Indian (%)	14(5.6)	13(5.3)	4(9.1)	4(5.3)	0.76
Asian (%)	5(2)	5(2.1)	0(0)	1(1.3)	1.0
Pacific Islander (%)	0(0)	1(0.41)	1(2.3)	1(1.3)	0.08
<u>Family History</u>					
Father asthma (%)	63(29)	57(27)	14(36)	24(35)	0.47
Father atopic (%)	82(39)	74(36)	14(39)	25(37)	0.93
Mother asthma (%)	73(30)	77(33)	9(21)	22(30)	0.45
Mother atopic (%)	99(41)	96(42)	16(36)	33(45)	0.85
<u>Lung Function</u>					
FEV ₁ (L)	1.9(0.62)	1.9(0.63)	3.1(0.61)	2.5(0.78)	<0.001
FEV ₁ % predicted	99(13)	97(12)	98(18)	90(11)	<0.001
FVC (L)	2.4(0.77)	2.4(0.79)	4(0.79)	3.4(1.1)	<0.001
FVC % predicted	107(12.3)	106(12.2)	109(13.9)	105(11.8)	0.23
FEV ₁ /FVC %	82(7.4)	81(7)	78(7.4)	75(8.5)	<0.001
Max BD % change FEV ₁	12(8.2)	11(9)	15(11)	15(11)	<0.001
Average ACD (per week)	2.1(1.7)	2.1(1.8)	2.3(2)	2.1(1.9)	0.87
# Prednisone (per yr)	0.49(0.92)	0.51(0.9)	0.59(0.9)	0.43(0.77)	0.82
PC ₂₀ (mg/dl), median (range) *	0.97(0-12)	1.4(0-37)	1.8(0-37)	0.44(0-37)	0.36
<u>Allergic Biomarkers</u>					
Eczema (%)	83(33)	100(41)	15(34)	30(39)	0.33
Positive skin test (%)	190(77)	187(77)	37(84)	65(88)	0.16
IgE (kU/L), median (range) *	170(1-2713)	190(1-4929)	310(5-2871)	250(1-3026)	0.041
ECP (ng/ml), median (range) *	15(1-136)	15(1-175)	17(7-64)	19(1-316)	0.03

Variable	Late-onset/normal-lung (1)	Early-onset/normal-lung (2)	Early-onset/comorbidity (3)	Early-onset/severe-lung (4)	P value
Urinary LTE4 (pg/mg), median (range) *	98(27-525)	110(25-438)	81(45-354)	92(23-363)	0.56
FeNO (ppb), median (range) *	15(2-198)	19(2-207)	34(7-216)	29(4-218)	<0.001
Peripheral Eosinophils (%) median (range),	4.3(0-30)	4.8(0-18)	5(0-17)	4.7(1-25)	0.50

BMI = body mass index, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, BD = bronchodilator, # Prednisone = number of prednisone courses in the year before enrollment, ACD = asthma control days, ECP = eosinophil cationic protein, LTE4 = leukotriene E4, FeNO = fractional exhaled nitric oxide. Data represents mean (SD) or frequency (%) unless otherwise specified.

* Data was log transformed before analysis

Table 4

PACT Outcomes across Treatments and Clusters

Treatment	% ACD ($p=0.54$)				
	Late-onset/normal-lung 1* ($p=0.008$)	Early-onset/normal-lung 2 ($p=0.23$)	Early-onset/comorbidity 3 ($p=0.78$)	Early-onset/severe-lung 4 ($p=0.44$)	All Clusters
0.5x Fluticasone + Salmeterol	76 (62,86)	52 (40,64)	50 (9,4,91)	66 (45,82)	63 (55,70)
1x Fluticasone	69 (56,80)	63 (51,73)	21 (2,7,72)	65 (29,89)	64 (56,72)
Montelukast	50 (37,62)	49 (36,61)	40 (11,77)	46 (26,67)	48 (40,57)
All Treatments ($p=0.10$)	64 (57,71)	55 (48,62)	36 (16,63)	58 (44,71)	

Treatment	% change FEV ₁ ($p=0.46$)			
	1* ($p=0.004$)	2* ($p=0.005$)	3 ($p=0.22$)	4 ($p=0.81$)
0.5x Fluticasone + Salmeterol	2.2 (-1.0,5.5)	3.5 (-0.030,7.0)	4.4 (1.8,7.0)	3.4 (-3.3,10)
1x Fluticasone	8.0 (4.6,11)	6.8 (4.0,9.5)	-0.61 (-7.6,6.4)	3.4 (-3.3,10)
Montelukast	-0.026 (-3.5,3.4)	-0.61 (-3.5,2.3)	-2.3 (-4.3,-0.25)	7.3 (-4.9,20)
All Treatments ($p=.69$)	3.4 (1.4,5.5)	3.5 (1.7,5.4)	-0.25 (-3.1,2.6)	4.9 (-0.73,11)

ACD = asthma control days, FEV₁ = forced expiratory volume in 1 second. Bold numbers indicate treatments beneficial for asthma. Italic numbers indicate treatments not beneficial for asthma. 95% confidence intervals are shown in parentheses. p -values in primary outcome header test cluster and treatment interaction. p -values in cluster number column headers test treatment effect within that cluster. p -values in the row header "All Treatments" test cluster effect for all participants.

* Clusters where significant differences ($p<0.05$) were identified among treatments

Table 5

CLIC Outcomes across Treatments and Clusters

Treatment	% change FEV ₁ (p=0.18)				
	Late-onset/normal-lung 1 [*] (p=0.006)	Early-onset/normal-lung 2 [*] (p<0.001)	Early-onset/comorbidity 3 (p=0.31)	Early-onset/severe-lung 4 [*] (p<0.001)	All Clusters
Fluticasone	3.6 (0.61,6.6)	5.3 (1.7,9.0)	0.73 (-4.6,6.1)	8.0 (3.5,13)	4.5 (2.6,6.5)
Montelukast	-0.23 (-3.1,2.7)	-0.21 (-2.9,2.5)	-0.88 (-5.1,3.3)	-0.55 (-3.2,2.1)	-0.34 (-2.0,1.3)
All Treatments (p=0.58)	1.7 (-0.41,3.8)	2.7 (0.35,5.0)	-0.076 (-3.4,3.3)	3.7 (0.83,6.6)	

Treatment	% ACD (p=0.36)				
	1 (p=0.08)	2 [*] (p=0.003)	3 (p=0.21)	4 (p=0.13)	All Clusters
Fluticasone	65 (55,74)	81 (70,88)	70 (48,85)	62 (45,77)	70 (64,76)
Montelukast	60 (50,69)	66 (55,76)	60 (40,77)	52 (36,69)	61 (54,67)
All Treatments (p=0.25)	63 (56,69)	74 (66,80)	64 (50,77)	57 (45,68)	

FEV₁ = forced expiratory volume in 1 second, ACD = asthma control days. Bold numbers indicate treatments beneficial for asthma. 95% confidence intervals are shown in parentheses. *p*-values in primary outcome header test cluster and treatment interaction, *p*-values in cluster number column headers test treatment effect within that cluster. *p*-values in the row header "All Treatments" test cluster effect for all participants.

* Clusters where significant differences (p<0.05) were identified among treatments

BADGER Outcomes across Treatments and Clusters

Table 6

Treatment	Best Treatment % (p=0.55)				All Clusters
	Late-onset/normal-lung 1 (p=0.17)	Early-onset/normal-lung 2 (p=0.76)	Early-onset/comorbidity 3 (p=0.78)	Early-onset/severe-lung 4* (p=0.01)	
Fluticasone + Salmeterol	44 (32,56)	39 (26,51)	41 (21,64)	64 (41,84)	44 (37,52)
2.5x Fluticasone	26 (16,37)	30 (19,42)	32 (13,54)	23 (7,145)	28 (21,35)
Fluticasone + Montelukast	30 (20,42)	32 (20,44)	27 (9,48)	13 (1,8,312)	28 (21, 35)

Treatment	% change FEV ₁ (p=0.32)				All Clusters
	1 (p=0.77)	2 (p=0.11)	3 (p=0.94)	4* (p=0.008)	
Fluticasone + Salmeterol	1.7 (-0.94,4.3)	1.6 (-0.86,4.1)	1.5 (-2.2,5.2)	7.7 (4.6,11)	2.3 (0.80,3.8)
2.5x Fluticasone	1.9 (-1.0,4.8)	-0.86 (-3.5,1.8)	1.0 (-2.4,4.5)	7.6 (1.8,13)	1.6 (-0.18,3.3)
Fluticasone + Montelukast	0.64 (-1.7,3.0)	-0.91 (-4.0,2.2)	1.3 (-4.0,6.6)	4.3 (-1.4,10)	1.0 (-1.1,2.3)
All Treatments* (p=0.045)	1.4 (-0.11,2.9)	-0.0068 (-1.6,1.6)	1.3 (-1.1,3.7)	6.6 (3.7,9.5)	

Treatment	% ACD (p=0.62)				All Clusters
	1* (p<0.001)	2 (p=0.35)	3 (p=0.33)	4 (p=0.12)	
Fluticasone + Salmeterol	80 (74,85)	77 (70,83)	81 (69,89)	81 (69,89)	79 (75,82)
2.5x Fluticasone	69 (63,75)	74 (67,80)	78 (66,87)	70 (58,80)	72 (68,76)
Fluticasone + Montelukast	74 (68,80)	74 (67,80)	76 (64,85)	70 (58,80)	74 (70,78)
All Treatments (p=0.82)	74 (71,78)	75 (71,79)	78 (72,84)	74 (67,79)	

FEV₁ = forced expiratory volume in 1 second, ACD = asthma control days. Bold numbers indicate treatments beneficial for asthma. Italic numbers indicate treatments not beneficial for asthma. 95% confidence intervals are shown in parentheses. *p*-values in primary outcome header test cluster and treatment interaction. *p*-values in cluster number column headers test treatment effect within that cluster. *p*-values in the row header "All Treatments" test cluster effect for all participants.

* Clusters where significant differences (p<0.05) were identified among treatments