Treatment responsiveness of phenotypes of symptomatic airways obstruction in adults

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Background: Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous disorders encompassing different phenotypes of airflow obstruction, which might differ in their response to treatment.
Objective: The aim of this study was to determine distinct phenotypes comprising the syndromes of asthma and COPD and the treatment responsiveness of these phenotypes to inhaled β-agonist, antimuscarinic, and corticosteroid therapy.
Methods: We undertook a cross-sectional study with 3 phases. In phase 1, 1,264 participants aged 18 to 75 years with self-reported current wheeze and breathlessness were identified from a random population sample of 16,459. In phase 2, 451 participants attended for detailed assessment, including responsiveness to inhaled salbutamol and ipratropium bromide. In phase 3, 168 steroid-naive participants were enrolled in a 12-week trial of inhaled budesonide. Cluster analysis was performed in 389 participants who completed phase 2 with full data. Treatment responsiveness was compared between phenotypes.
Results: Cluster analysis identified 5 phenotypes: moderate-to-severe childhood-onset atopic asthma, asthma-COPD overlap, obese-comorbid, mild childhood-onset atopic asthma, and mild intermittent. Bronchodilation after salbutamol was equal to or greater than that after ipratropium for all phenotypes. The moderate-to-severe childhood-onset atopic asthma, asthma-COPD overlap, and obese-comorbid phenotypes had greater efficacy with inhaled corticosteroid treatment than the mild intermittent group.
Conclusion: Cluster analysis of adults with symptomatic airflow obstruction identifies 5 disease phenotypes, including asthma-COPD overlap and obese-comorbid phenotypes, and provides evidence that patients with the asthma-COPD overlap syndrome might benefit from inhaled corticosteroid therapy. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Phenotype, asthma, chronic obstructive pulmonary disease, inhaled corticosteroid, bronchodilator*

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous disorders encompassing different phenotypes of airflow obstruction with distinct clinical characteristics.[1-4] Traditionally, the specific clinical phenotypes have been defined by their pathogenesis, risk factors, natural history, prognosis, and treatment responsiveness. Identification of clinical features or biomarkers that predict treatment responsiveness to novel therapies has led to the concept of personalized treatment in which therapeutic strategies are targeted to individual subjects based on the presence or absence of these features.[5,6]

An alternative approach is to assess treatment responsiveness in different phenotypes of obstructive airways disease identified by means of multidimensional characterization of subjects, such as by using cluster analysis.[7-9] In a proof-of-concept analysis in patients with refractory asthma, the benefit of titrating inhaled corticosteroid (ICS) therapy according to inflammometry was different depending on the subject's phenotype, as defined by level of agreement between symptoms and eosinophilic airways inflammation.[10]

In this study we determined candidate phenotypes of airways disease through cluster analysis using prospectively collected clinical data from adults with symptoms of airways obstruction selected from a random population sample. We assessed treatment responsiveness of each phenotype to the 3 main classes of medications used in the treatment of asthma and COPD. The objectives were to determine distinct phenotypes comprising the syndromes of asthma and COPD; to determine the treatment responsiveness of these phenotypes to inhaled β-agonist, antimuscarinic, and corticosteroid therapy; and to develop an allocation rule by which future patients could be assigned to the appropriate phenotype.[11]

METHODS

This study was a 3-phase cross-sectional study. Study methods are summarized, with additional details provided in this article's Online Repository at www.jacionline.org. The study was approved by the New Zealand Central Ethics Committee, and all participants provided written informed consent. The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12610000666022).

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Abbreviations used
ACOS: Asthma-COPD overlap syndrome
ACQ: Asthma Control Questionnaire
ATS: American Thoracic Society
COPD: Chronic obstructive pulmonary disease
FENO: Fraction of exhaled nitric oxide
hsCRP: High-sensitivity C-reactive protein
ICS: Inhaled corticosteroid
SGRQ: St George Respiratory Questionnaire

Phase 1

Participants aged 18 to 75 years were recruited from a random sample of the electoral roll in the greater Wellington region of New Zealand. All participants were sent a simple screening questionnaire by post, collecting information on demographics, respiratory symptoms, smoking status, and respiratory diagnoses. Nonrespondents received up to 2 follow-up letters and a telephone call to optimize the response rate.

Phase 2

Respondents with symptoms of wheeze and breathlessness in the last 12 months were invited to attend for further assessment over 2 visits.

Respiratory history and comorbidities. Participants completed a detailed medical questionnaire designed to obtain information on respiratory symptoms, risk factors, medications, previous diagnoses and comorbidities, with questions compiled from a series of validated questionnaires.

Lung function. Lung volume, spirometric, and transfer factor values were measured by means of body plethysmography (Masterscreen Body; Erich-Jaeger, Friedberg, Germany) in accordance with American Thoracic Society (ATS) guidelines.[12] New Zealand–specific reference ranges were used.[13] Peak flow diaries were completed over a week between visits 1 and 2 (Mini-Wright with the ATS scale; Clement Clarke International, Harlow, United Kingdom).

Reversibility testing. Postbronchodilator FEV_1 measurements were performed 30 minutes after inhalation of 80 μg of ipratropium (visit 1) or 400 μg of salbutamol (visit 2) by using a metered-dose inhaler through a spacer (Volumatic; GlaxoSmithKline, Brentford, United Kingdom).

Biomarkers. Blood was drawn for full blood count and differential (Sysmex, Mundelein, Ill). Serum IgE levels, high-sensitivity C-reactive protein (hsCRP) levels (Roche modular, Indianapolis, Ind), and serum Phadiatop (Phadia, Uppsala, Sweden) results were measured by using an ELISA. Serum periostin levels were measured with a proprietary assay (Genentech, South San Francisco, Calif) using the same antibodies previously reported by Jia et al.[14] Fraction of exhaled nitric oxide (FENO) values were measured by means of chemiluminescence with an online nitric oxide monitor (NiOX; Aerocrine AB, Solna, Sweden), according to ATS guidelines.[15]

Disease control and health status. Respiratory health status and disease control were assessed by using the Asthma Control Questionnaire (ACQ-7)[16] and the New Zealand version of the St George Respiratory Questionnaire (SGRQ), which has been validated for use in both asthmatic patients and those with COPD.[17]

Phase 3

Participants were enrolled in an open-label ICS trial if they had received no oral or inhaled steroids in the last 90 days. Participants self-administered 400 μg of budesonide twice daily through a Turbuhaler (AstraZeneca Limited, Auckland, New Zealand) for 12 weeks before repeat testing. Investigators and participants were blind to cluster allocation at the time of testing.

Statistical analysis

Phases 1 and 2. Research participant characteristics and questionnaire response rates are described by using simple data summaries. The main analysis for phase 2 was phenotype description by means of cluster analysis. Hierarchical cluster analysis was performed on all participants with complete data for the selected cluster analysis variables by using the Agnes and Diana algorithms and Gower distance metric (R package "cluster"), as previously described.[18] The Ward minimum variance method was applied to the Agnes algorithm because this is less affected by random variation, or noise, in the data set.[19] The cluster analysis used 13 variables (Table I) chosen to represent multiple dimensions of airways disease, including airflow obstruction, variability, parenchymal damage, symptoms, risk factors, and inflammatory biomarkers. The number of potential clusters was determined by establishing cut points for the dendrograms, with a preference for at least 30 participants in the smallest cluster to provide explanatory power for the ICS responsiveness analysis. Consistency of cluster descriptions was explored by repeating the cluster analysis with an alternate distance metric, the Euclidean distance. If cluster solutions differed, priority was given to the solution that met the preferred size criterion and appeared to describe clinically coherent disease patterns. Data summaries were calculated by cluster group for the 13 variables used in the cluster analysis and for a wider panel of additional descriptor variables. Bronchodilator reversibility to salbutamol and ipratropium for each cluster group, measured as the percentage change in FEV_1 from baseline and absolute change in liters, was analyzed by means of ANOVA.

A classification tree was developed to allow prediction of cluster group membership, with cluster analysis variables as potential predictors.[11] This used the R package rpart and tree-pruning with 10-fold cross-validation with the 1 − SE approach.

Phase 3. The ACQ-7 score after 12 weeks of ICS treatment was used as the main response variable in mixed linear models to compare mean ACQ-7 scores between clusters adjusted for baseline. The models used a main effect for visit and cluster and a visit-cluster interaction term. Participants were treated as random effects to take account of repeated measures. Other response variables were total SGRQ score, peak flow variability, FENO value, FEV_1 (percent predicted), and difference in severe adverse events between clusters. The cluster with the least severe airways obstruction (based on FEV_1 percent predicted) was selected as the reference for this analysis.

Sample size. The sample size was calculated to detect a difference of 0.5 units on the ACQ-7 (ie, the minimal clinically important difference with an SD of 0.5 based on a published study of eosinophilic versus noneosinophilic asthma[20]) with 80% power and an α value of 5%. Our assumptions were that enrollment of 450 participants in phase 2 would ensure that 16 steroid-naive participants from each cluster would be enrolled in the ICS trial.

RESULTS

Screening and enrollment

Participant flow through the study is shown in Fig 1. Of 16,459 subjects, 11,397 (69.2%) responded to the questionnaire, and 1,264 (14.8%) of 8,563 respondents with completed questionnaires had wheeze and breathlessness in the last 12 months and were invited to attend for detailed evaluation. Four hundred fifty-one participants were enrolled in phase 2, and 389 (86.3%) had complete data. A description of the 389 participants included in the cluster analysis is shown in Table I.

Cluster analysis

Cluster analysis with the Agnes-Gower-Ward method described 5 groups, which showed different patterns when characterized by using the 13 cluster variables (Table I) and other phenotypic descriptors (Table II). Comparison with alternative 5-cluster solutions generated by using the Diana algorithm or the Euclidean distance metric showed similar overall clinical phenotypes, with differences in cluster size and the magnitude of separation for specific variables (see this article's Online Repository). Not all groups within the alternative solutions met

TABLE I. Baseline characteristics and cluster analysis variables by cluster allocation

Variable	All participants* (n = 389)	Cluster A: Moderate-to-severe atopic asthma (n = 59)	B: Asthma-COPD overlap (n = 34)	C: Obese/comorbid (n = 61)	D: Mild atopic asthma (n = 155)	E: Mild-intermittent (n = 80)
FEV_1 (% predicted)†	81.7 (19.0)	59.9 (15.0)	62.0 (24.8)	80.9 (13.4)	89.4 (12.2)	92.0 (13.0)
FEV_1/FVC ratio (%)†	70.3 (12.5)	56.0 (9.3)	51.5 (15.2)	74.0 (6.5)	76.6 (7.8)	73.6 (7.1)
FRC (% predicted)†	93.5 (26.2)	113.9 (25.2)	133.5 (35.9)	75.9 (14.5)	86.0 (16.2)	89.5 (18.0)
Reversibility (% change)	10.0 (11.8)	24.1 (18.7)	16.4 (12.4)	5.7 (5.3)	6.9 (5.8)	6.2 (8.1)
PEF variability§	20.7 (12.6)	33.3 (15.3)	34.1 (15.2)	18.8 (8.1)	15.9 (7.5)	16.7 (9.6)
KCO (% predicted)‡	99.1 (17.4)	99.4 (18.7)	73.5 (21.3)	106.8 (13.9)	102.0 (13.3)	98.4 (14.5)
FENO (ppb)‖	33.7 (35.2)	42.1 (41.2)	12.3 (8.3)	21.2 (20.4)	42.7 (41.3)	28.9 (24.6)
Log FENO	3.15 (0.84)	3.4 (0.8)	2.3 (0.6)	2.8 (0.7)	3.4 (0.8)	3.1 (0.7)
IgE (IU/L)‖	343 (1162)	452 (1103)	397 (872)	203 (663)	428 (1543)	181 (617)
Log IgE	4.32 (1.77)	5.0 (1.7)	4.5 (1.8)	3.6 (1.8)	4.6 (1.7)	3.8 (1.6)
hsCRP (mg/L)‖	2.88 (4.43)	3.3 (6.4)	2.7 (2.7)	4.0 (2.9)	2.9 (5.2)	1.7 (1.2)
Log hsCRP	0.59 (0.89)	0.5 (1.0)	0.7 (0.7)	1.1 (0.8)	0.5 (0.9)	0.3 (0.7)
Age of onset (y)	23.8 (19.1)	11.5 (10.5)	35.5 (19.8)	32.6 (15.9)	11.1 (9.8)	42.8 (11.7)
BMI (kg/m^2)	28.6 (6.6)	26.5 (5.4)	26.2 (4.3)	36.3 (6.0)	27.3 (6.4)	27.6 (4.5)
SGRQ score	23.7 (16.8)	26.2 (15.0)	43.6 (16.8)	35.3 (15.1)	15.3 (10.6)	20.8 (16.8)
Smoking (pack years)	8.20 (15.1)	4.4 (5.9)	35.5 (17.8)	14.7 (18.8)	1.3 (3.8)	7.9 (12.9)

	Moderate-to-severe atopic asthma	Asthma-COPD overlap	Obese-comorbid	Mild atopic asthma	Mild intermittent
FEV_1 (% predicted)†	− −	− −	•	•	+
FEV_1/FVC ratio (%)†	− −	− −	•	•	•
FRC (% predicted)†	+ +	+ +	−	•	•
Reversibility (% change)	+ +	+ +	− −	− −	− −
PEF variability§	+ +	+ +	•	− −	− −
KCO (% predicted)‡	•	− −	•	•	•
Log FENO	•	− −	−	•	•
Log IgE	+	•	−	•	−
Log hsCRP	−	+	+ +	−	− −
Age of onset (y)	− −	+ +	+ +	− −	+ +
BMI (kg/m^2)	•	•	+ +	•	•
SGRQ score	+	+ +	+ +	− −	−
Smoking (pack years)	− −	+ +	+ +	− −	•

Compared with overall mean value of all participants as reference: + +, Greater than 20% above the overall mean value; +, greater than 10% and less than 20% above the overall mean value; •, within 10% of the overall mean value; −, greater than 10% and less than 20% below the overall mean value; − −, greater than 20% below the overall mean value. *Age of onset*, Age at onset of respiratory symptoms; *BMI*, body mass index; *FRC*, functional residual capacity; *FVC*, forced vital capacity; *KCO*, transfer factor adjusted for lung volume and corrected for hemoglobin; *PEF*, peak expiratory flow.

*Denotes all participants included in the cluster analysis. Values are reported as means (SDs).

†Prebronchodilator.

‡Postbronchodilator.

§Peak expiratory flow variability: peak flow variability expressed as a percentage of the mean.

‖IgE, FENO, and hsCRP values were log-transformed for the cluster analysis, but nontransformed values are presented here for ease of interpretation.

the size criteria, and therefore the Agnes-Gower-Ward clusters were used for phenotype description and ICS responsiveness analyses.

Clusters A and D were characterized by early-onset disease with evidence of atopy, increased FENO values, and high rates of eczema and rhinitis separated by severity of obstruction, magnitude of bronchodilator responsiveness, and peak flow variability and might represent moderate-to-severe (A) and mild (D) atopic asthma, respectively.

Cluster B was characterized by late-onset disease with moderate-to-severe obstruction, hyperinflation, marked bronchodilator reversibility and peak flow variability, reduced transfer factor, and increased IgE levels but low FENO values in smokers. This group had the worst symptom control and health status and might represent an asthma-COPD overlap group.

Cluster C was characterized by obesity and late-onset disease, with preserved lung function but poor health status, multiple comorbidities, and an increased hsCRP level, representing an obese comorbid phenotype.

Cluster E is a group with mild adult-onset disease and normal lung function who might have intermittent disease. This mild intermittent disease cluster was used as a reference group for the ICS responsiveness analyses.

Mean serum IgE levels were increased in all cluster groups compared with the local reference range (<100 IU/L). The 2 childhood-onset asthma phenotypes had the highest serum IgE levels, FENO values, and proportion with positive Phadiatop results. Periostin levels and blood eosinophil numbers were highest in the severe atopic asthma phenotype. The overlap and obese-comorbid phenotypes had the highest neutrophil counts and hsCRP levels, respectively, which is consistent with systemic inflammation.

Medication responsiveness

Short-acting β-agonist and antimuscarinic responsiveness. For further information on short-acting β-agonist and antimuscarinic responsiveness, see Tables I-III. Bronchodilation

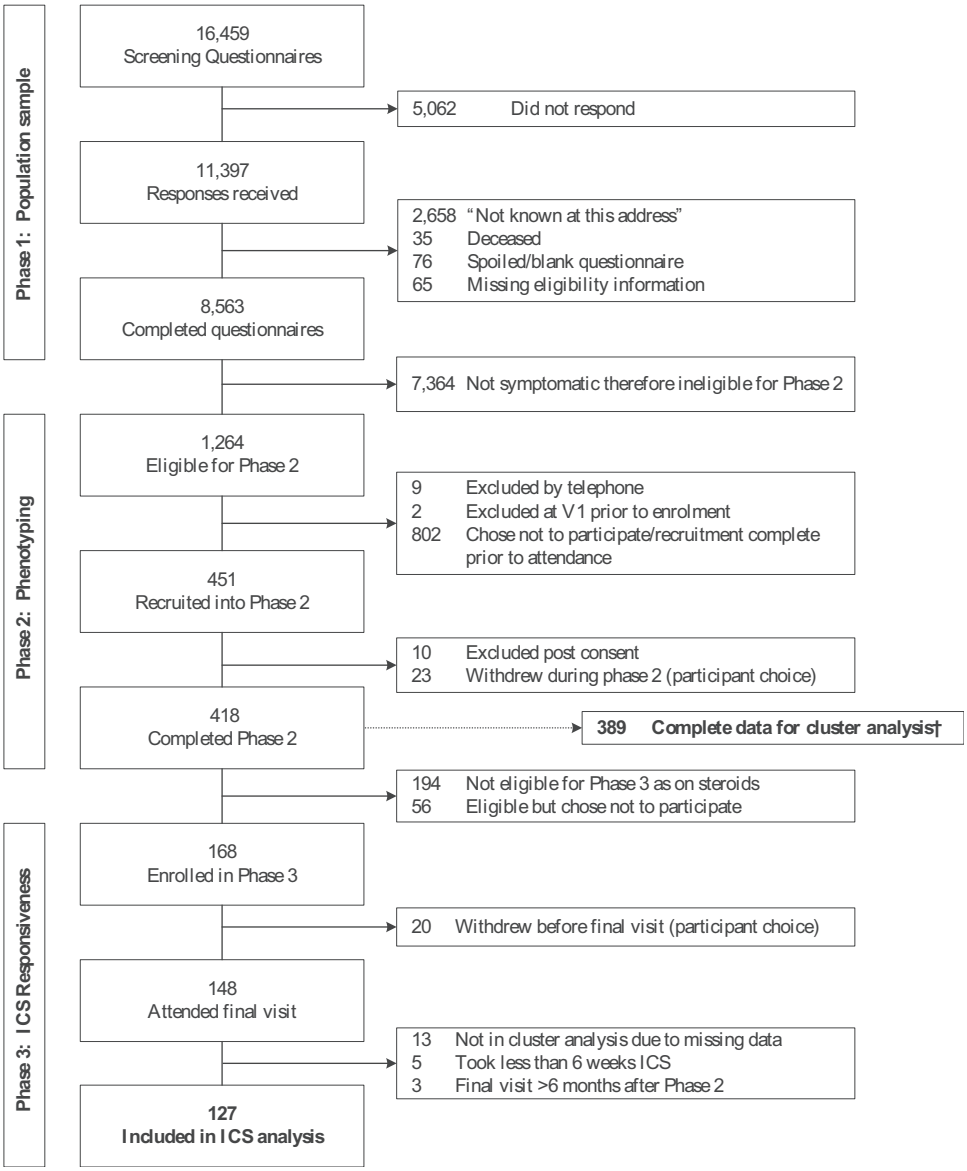

FIG 1. Study flow diagram. Twenty-nine of the 418 participants who completed phase 2 were missing data for 1 or more of the 13 cluster analysis variables and therefore could not be included in the cluster analysis.

after salbutamol was equal to or greater than that after ipratropium for all phenotypes, so that no phenotype showed a greater mean response to ipratropium than salbutamol. The moderate-to-severe atopic asthma and overlap phenotypes showed greater bronchodilator reversibility, expressed as FEV_1 percent predicted values, although the differences were less marked when expressed as absolute change from baseline.

ICS responsiveness. The characteristics of the 168 participants who undertook the ICS responsiveness trial are shown in this article's Online Repository (Table E6). Data from 127 participants were analyzed (see Fig 1). There was no evidence of a significant difference in change in ACQ-7 scores between the clusters (Table III). There was evidence of a significant difference between clusters for change in SGRQ score ($P = .005$) and peak flow variability ($P < .001$). Relative to the reference cluster (mild intermittent), the mean improvement in SGRQ score was significantly greater in the overlap, (8.2; 95% CI, 2.2-14.2; $P = .008$) and obese-comorbid (9.5; 95% CI, 4.2-14.8; $P < .001$) phenotypes, with point estimates consistent with greater improvement for the mild and moderate-to-severe asthma phenotypes (4.2 [95% CI, −0.1 to 8.4; $P = .054$] and 7.2 [95% CI, −0.2 to 14.6; $P = .057$], respectively). Reduction in peak flow variability was significantly greater relative to the reference group in the overlap (6.8; 95% CI, 0.7-12.9; $P = .028$) and moderate-to-severe atopic asthma (17.9; 95% CI, 10.6-25.2; $P < .001$) phenotypes and less for the obese-comorbid phenotype (−5.4; 95% CI, −10.6 to −0.1; $P = .044$). Change with ICS therapy was not significantly different between the groups for FEV_1, FENO values, or severe adverse events.

Allocation rule

A classification tree based on age of onset, body mass index, and FEV_1 percent predicted allocated participants to their

TABLE II. Phenotype description using additional analysis variables

Characteristic	Cluster				
	A: Moderate-to-severe atopic asthma	B: Asthma-COPD overlap	C: Obese-comorbid	D: Mild atopic asthma	E: Mild intermittent
Demographics					
Age (y)	53.4 (13.5)	56.1 (8.5)	53.8 (11.3)	40.1 (12.6)	55.8 (11.3)
Height (cm)	169.0 (9.5)	169.4 (9.0)	168.7 (9.3)	170.4 (8.8)	170.4 (8.0)
Sex (male)	24/59 (40.7)	22/34 (64.7)	27/61 (44.3)	67/155 (43.2)	40/80 (50.0)
Risk factors					
Smoking status					
Current smoker	6/59 (10.2)	22/34 (64.7)	11/61 (18.0)	11/155 (7.1)	8/80 (10.0)
Exsmoker	22/59 (37.3)	12/34 (35.3)	26/61 (42.6)	39/155 (25.2)	33/80 (41.3)
Never smoker	31/59 (52.5)	0/34 (0)	24/61 (39.3)	105/155 (67.7)	39/80 (48.8)
Biomass exposure	14/59 (23.7)	2/34 (5.9)	10/61 (16.4)	35/155 (22.6)	11/80 (13.8)
Occupational exposure	27/59 (45.8)	23/34 (67.6)	35/61 (57.4)	73/155 (47.1)	43/80 (53.8)
Previous respiratory diagnoses					
Asthma	55/59 (93.2)	20/34 (58.8)	42/61 (68.9)	135/155 (87.1)	35/80 (43.8)
Chronic bronchitis	9/59 (15.3)	12/34 (35.3)	7/61 (11.5)	21/155 (13.5)	6/80 (7.5)
COPD	6/59 (10.2)	7/34 (20.6)	2/61 (3.3)	0/155 (0)	2/80 (2.5)
Emphysema	4/59 (6.8)	5/34 (14.7)	3/61 (4.9)	0/155 (0)	1/80 (1.3)
No prior diagnosis	3/59 (5.0)	8/34 (23.5)	17/61 (27.9)	17/155 (11.0)	43/80 (53.8)
Symptoms					
Cough	34/59 (57.6)	24/34 (70.6)	43/61 (70.5)	62/155 (40.0)	41/80 (51.3)
Sputum	22/59 (37.3)	23/34 (67.7)	24/61 (39.3)	29/155 (18.7)	23/80 (28.8)
Rhinitis	43/59 (72.9)	19/34 (55.9)	39/61 (63.9)	137/155 (88.4)	50/80 (62.5)
GERD	24/59 (40.7)	17/34 (50.0)	35/61 (57.4)	56/155 (36.1)	46/80 (57.5)
ACQ-7 score	1.5 (0.8)	1.9 (1.0)	1.0 (0.7)	0.6 (0.5)	0.5 (0.5)
Atopy					
Phadiatop (positive result)	50/59 (84.7)	15/34 (44.1)	24/61 (39.3)	121/155 (78.1)	33/80 (41.3)
Eczema diagnosis	36/59 (61.0)	13/34 (38.2)	28/61 (45.9)	97/155 (62.6)	39/80 (48.8)
Comorbidities					
CVD	8/59 (13.6)	8/34 (23.5)	15/61 (24.6)	13/155 (8.4)	14/80 (17.5)
GERD	16/59 (27.1)	17/33 (51.5)	27/61 (44.3)	35/155 (22.6)	23/80 (28.8)
Diabetes	6/59 (10.2)	3/33 (9.1)	8/61 (13.1)	5/155 (3.2)	5/80 (6.3)
Depression or anxiety	7/59 (11.9)	8/33 (24.2)	22/61 (36.1)	49/154 (31.8)	22/80 (27.5)
Hypertension	14/58 (24.1)	9/33 (27.3)	32/61 (52.5)	25/130 (16.1)	22/80 (27.5)
Medication use in last 12 mo					
Any inhaler	57/59 (96.6)	24/34 (70.6)	38/61 (62.3)	118/155 (76.1)	43/80 (53.8)
ICS	31/59 (52.5)	11/34 (32.4)	18/61 (29.5)	56/155 (36.1)	25/80 (31.3)
SABA use in 12 mo	52/59 (88.1)	20/34 (58.8)	37/61 (60.7)	114/155 (73.5)	38/80 (47.5)
Combination ICS/LABA	15/58 (25.9)	7/33 (21.2)	8/61 (13.1)	21/155 (13.5)	8/80 (10.0)
LABA use in 12 mo	10/58 (17.2)	5/34 (14.7)	5/61 (8.2)	9/155 (5.8)	5/80 (6.3)
LAMA use in 12 mo	5/58 (8.6)	2/34 (5.9)	0/61 (0)	0/155 (0)	0/80 (0)
GERD treatment	13/59 (22.0)	10/34 (29.4)	25/61 (41.0)	32/155 (20.6)	28/80 (35.0)
Health care use in last 12 mo					
Oral steroid	11/58 (19.0)	5/34 (14.7)	9/61 (14.8)	15/154 (9.7)	9/80 (11.3)
Urgent ED/hospital visit	1/59 (1.7)	2/34 (5.9)	3/61 (4.9)	2/155 (1.3)	2/80 (2.5)
Courses of antibiotic	0.6 (0.8)	0.4 (0.7)	0.8 (1.3)	0.5 (0.8)	0.7 (1.0)
Chest infections	0.9 (1.0)	0.6 (0.7)	1.1 (1.5)	0.8 (1.0)	0.8 (1.1)
Lung function					
$MMEF_{25-75\%}$ (L/min)	32.2 (13.8)	31.6 (20.1)	74.1 (28.5)	81.5 (24.9)	84.8 (28.7)
TLC/RV	2.5 (0.6)	2.4 (0.7)	2.9 (0.6)	3.6 (0.8)	3.1 (0.7)
Conductance (1/[kPa·s])*	41.8 (19.1)	56.5 (51.6)	66.3 (19.9)	86.9 (43.7)	87.0 (51.3)
Biomarkers					
Blood eosinophils ($\times 10^9$/L)	0.33 (0.31)	0.20 (0.12)	0.22 (0.18)	0.23 (0.15)	0.21 (0.14)
Blood neutrophils ($\times 10^9$/L)	4.0 (2.0)	4.6 (1.3)	4.1 (1.3)	3.8 (1.3)	3.8 (1.3)
Blood white cell count ($\times 10^9$/L)	7.4 (4.0)	7.8 (2.0)	7.4 (1.7)	6.9 (1.7)	6.9 (1.8)
Serum periostin (ng/mL)	63.8 (25.2)	56.1 (15.7)	51.7 (11.5)	57.6 (17.7)	56.9 (18.8)

Categorical variables are expressed as n/N (percentage). Continuous variables are expressed as mean (SDs).
CVD, Cardiovascular disease; *ED*, emergency department; *GERD*, gastroesophageal reflux disease; *LABA*, long-acting β-agonist; *LAMA*, long-acting antimuscarinic agonist; $MMEF_{25-75\%}$, maximum midexpiratory flow; *SABA*, short-acting β-agonist; *TLC/RV*, total lung capacity/residual volume.
*Percent predicted.

assigned cluster with 75% accuracy (see Fig E5 in this article's Online Repository at www.jacionline.org). Additional variables did not significantly improve classification accuracy. Cluster separation was modest, reflecting the heterogeneity of obstructive airways disease. Examination of clusters in a 3-dimensional model (Fig 2) shows cluster groups based on allocation variables.

TABLE III. Medication responsiveness by phenotype*

Outcome	Cluster					*P* value†
	A: Moderate-to-severe atopic asthma	B: Asthma-COPD overlap	C: Obese-comorbid	D: Mild atopic asthma	E: Mild-intermittent	
Bronchodilator reversibility to salbutamol	n = 59	n = 34	n = 61	n = 155	n = 80	
FEV_1 change (% of baseline)	24.1 (18.7)	16.4 (12.4)	5.7 (5.3)	6.9 (5.8)	6.2 (8.1)	<.001
FEV_1 change (L)	0.48 (0.36)	0.30 (0.20)	0.15 (0.14)	0.23 (0.19)	0.17 (0.22)	<.001
Bronchodilator reversibility to ipratropium	n = 59	n = 34	n = 61	n = 155	n = 80	
FEV_1 change (% of baseline)	18.4 (15.3)	13.6 (10.5)	5.3 (6.2)	6.1 (5.4)	5.8 (6.2)	<.001
FEV_1 change (L)	0.35 (0.27)	0.26 (0.18)	0.15 (0.15)	0.20 (0.17)	0.16 (0.80)	<.001
ICS responsiveness	n = 8	n = 14	n = 21	n = 54	n = 30	
Change in ACQ-7 score	−0.36 (0.69)	−0.21 (0.50)	−0.28 (0.65)	−0.16 (0.34)	−0.01 (0.75)	.38
Change in SGRQ score	−8.1 (11.0)	−9.1 (12.6)	−10.4 (12.4)	−5.1 (5.1)	−0.9 (11.0)	.005
Change in PEF variability	−22.2 (14.7)	−9.7 (16.3)	1.1 (7.4)	−4.1 (7.0)	−4.4 (7.6)	<.001
Change in log FENO	−0.22 (0.33)	−0.16 (0.35)	−0.26 (0.65)	−0.41 (0.56)	−0.13 (0.46)	.18
Change in FEV_1 (% predicted)	1.8 (5.0)	1.4 (4.0)	0.6 (3.7)	0.5 (3.4)	0.5 (4.7)	.88
Severe adverse events‡	0/8 (0)	0/14 (0)	1/21 (4.8)	0/54 (0)	1/30 (3.3)	.38

PEF, Peak expiratory flow.
*Values are reported as means (SDs), unless otherwise stated.
†*P* values were calculated by using ANOVA, with cluster groups as the explanatory variables and FEV_1 change as the response variable.
‡Values are reported as n/N (percentage), and *P* values were calculated by using the exact χ^2 test for association.

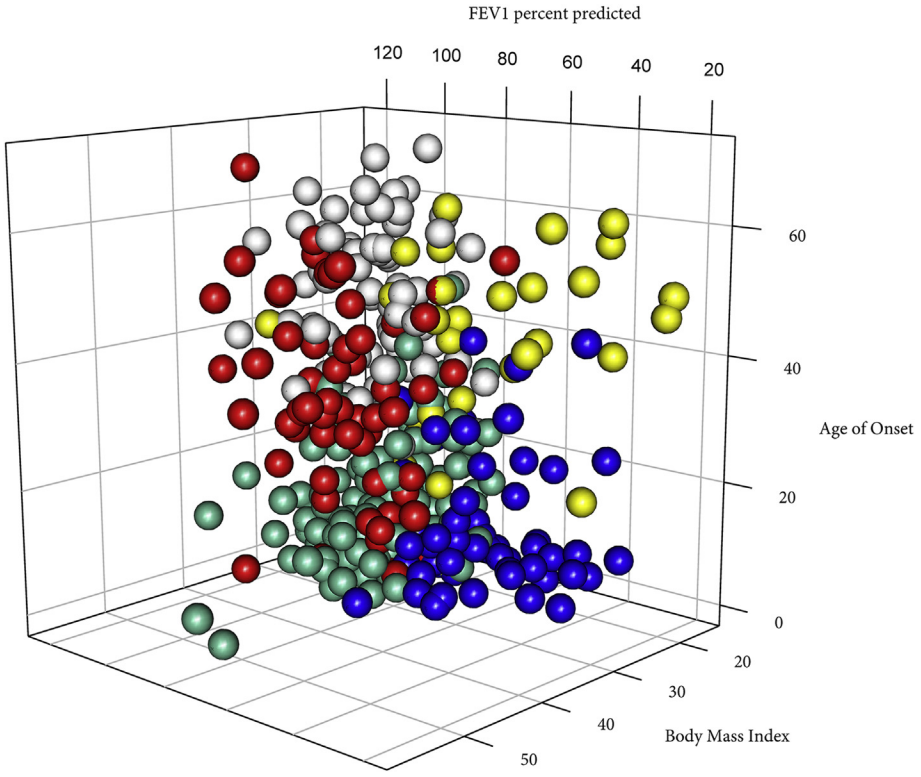

FIG 2. Three-dimensional scatter plot of clusters: *yellow*, asthma-COPD overlap group; *blue*, moderate-to-severe, childhood-onset atopic asthma; *green*, mild, childhood-onset, atopic asthma; *red*, obese with comorbidities; *white*, mild, reference group. The figure shows a 3-dimensional model in which each of the 389 subjects in the cluster analysis is represented by a sphere. The color of the sphere indicates the assigned phenotype. The axes are those used in the allocation rule: FEV_1 percent predicted, age of onset, and body mass index. Examination of the model in different planes highlights that the obese-comorbid group separates out on body mass index, whereas the remaining 4 clusters are differentiated based on age of onset and disease severity.

DISCUSSION

This study identified 5 phenotypes in adults with symptoms of airflow obstruction. We confirmed the presence of an asthma-COPD overlap group and identified 2 groups of childhood-onset atopic asthma distinguished by severity; a symptomatic adult-onset group associated with obesity, comorbidities and systemic inflammation; and an adult-onset group with mild intermittent disease. The responses to inhaled β-agonist, antimuscarinic, and

corticosteroid treatments differed between phenotypes and might form the basis of phenotype-specific recommendations. In particular, the findings from the ICS trial suggest that the asthma-COPD overlap and obese-comorbid groups might represent steroid-responsive phenotypes.

The asthma-COPD overlap group[7,18,21] has features of atopic asthma, with marked variability in airflow obstruction, emphysema, and chronic bronchitis in current smokers or exsmokers. This group had the most severe airflow obstruction, lies within the spectrum of the asthma-COPD overlap syndrome (ACOS),[22] and is clinically important because it is associated with considerable morbidity and increased health care use, yet there is a limited evidence base for treatment.[3] Typically, those in this overlap group are excluded from major asthma trials based on their smoking history and from major COPD trials because of their marked bronchodilator reversibility.[6,23,24] We have demonstrated that this group benefits from ICS treatment and has marked bronchodilator reversibility to both inhaled β-agonist and antimuscarinic therapy, with β-agonists having a modestly greater bronchodilator efficacy. The novel findings regarding the steroid responsiveness of this overlap group are potentially important because many patients with this phenotype are currently being treated according to COPD guidelines in view of their incompletely reversible airflow obstruction, reduced transfer factor values, and smoking histories. The recent combined statement by the Global Initiative for Asthma and Global Initiative for COPD[22] has recommended that patients with ACOS should all receive ICSs in view of the known risk of severe exacerbations or death in patients with uncontrolled asthma. Our findings support this strategy. However, we would argue that randomized controlled trials to determine the ICS dose response in this group should be a priority for future research.

We also found a phenotype with adult-onset disease, obesity, systemic inflammation, and multiple comorbidities. In contrast to previous cluster analyses, in patients with severe asthma,[10,25] we did not find a marked female predominance. The group had marked respiratory disability discordant with their moderate airflow obstruction and minimal bronchodilator responsiveness to β-agonist and antimuscarinic treatments. We found marked improvement in SGRQ scores but not peak flow variability after 12 weeks of ICS treatment. The improvement in SGRQ scores was observed across all domains and was 2.5-fold greater than the minimal clinically important difference. This finding is consistent with a retrospective analysis that reported a significant ICS response in patients with late-onset asthma with obesity but not early-onset asthma with obesity.[26] The recent report that sputum IL-5 levels and submucosal eosinophil numbers, but not sputum eosinophil numbers, are increased in obese patients with severe asthma is consistent with our findings of a low FENO value yet steroid-responsive disease.[27] High rates of cardiovascular and metabolic comorbidity and symptoms of depression and anxiety suggest that treatment of these comorbidities needs to be considered.

The 2 clusters of childhood-onset disease were consistent with atopic asthma distinguished by severity, with the severe group having a greater response to ICS, β-agonist, and antimuscarinic therapy. The fifth phenotype was consistent with adult-onset disease with mild or intermittent airflow obstruction.

Mean serum IgE levels were increased in all clusters, possibly because of either a central role of atopy in the pathogenesis of the disorders of airways obstruction across the spectrum of phenotypes[28] or the effects of smoking,[29] particularly in the overlap and obese-comorbid groups. However the FENO value, a marker of eosinophilic airways inflammation,[30] and positive Phadiatop results, a marker of atopy,[31] were increased in the 2 childhood-onset clusters but not the 3 adult-onset clusters. Levels of periostin, an IL-13–related marker of T_H2 immune response,[14,32] were highest in the severe childhood-onset asthma phenotype.

Our allocation rule suggests that simple clinical features can allocate most adults with airflow obstruction to identified clusters. Our allocation rule has a similar performance to that of Moore et al[25] and shared 2 of the 3 variables, FEV_1 and age of onset, that discriminated between different patterns of disease. The modest cluster separation, as seen in Fig 2, is also consistent with phenotypes identified in this study representing groupings within a continuum of disease rather than clear-cut entities.

Methodological decisions might affect the results of cluster analyses and are relevant to the interpretation of the study findings.[33] Cluster analysis is an exploratory technique that will define groups in any data set regardless of the underlying structure,[8] and the extent to which our clusters represent meaningful phenotypes must be judged from their clinical coherence, differences in treatment outcomes, longitudinal stability, and the consistency with which they are reproduced in studies of different populations.[1-4,34] For example, differences in reversibility to salbutamol between groups are to be expected given the use of percentage of reversibility as a cluster variable. That these differences are of clinical relevance rather than chance findings is determined by examining the broader characteristics of each cluster and recognizing a clinically consistent pattern, such as atopic asthma. We studied a large random population sample of adults aged 18 to 75 years reporting recent wheeze and breathlessness. This approach reduces bias from predetermined diagnostic labels of asthma and COPD and ensured findings generalizable to a primary care population. Limiting the number of specific cluster variables to 13 avoided use of multiple related variables measuring similar characteristics. We used more than 1 clustering methodology, and the description of similar patterns with the different approaches suggests that these represent robust phenotypes in our population. However, phenotype identification using our methods is limited to the extent that different genetic and pathophysiologic mechanisms might lead to the same or similar phenotypic expression.[35] We have demonstrated a difference in treatment responsiveness between phenotypes; however, these findings require replication in randomized controlled trials.

The ICS-responsiveness phase of the study in steroid-naive subjects was open label. Therefore our estimates of ICS response are potentially open to bias, such as regression to the mean, in the absence of a treatment control. We attempted to reduce the potential effects of bias by masking investigators and participants to cluster allocation, which was only determined at study's end. In the ICS trial, 800 μg/d budesonide was administered because this represents the dose that achieves the maximum obtainable therapeutic benefit in asthmatic patients.[36] A range of clinical outcome variables was assessed, encompassing measures of lung function, asthma control, and airways inflammation. Although the 12-week therapeutic trial was not designed to allow assessment of the effect on severe exacerbations in the different phenotypes, the clinical outcome variables used are validated predictors of future exacerbation risk.[37] A related issue inherent in cluster analyses is the influence of previous and concurrent ICS treatment on some of the key variables used in the cluster analysis, illustrating the potentially dynamic nature of grouping into phenotypes in

response to both treatment and the natural history of disease. The similar mean age of subjects between phenotypes suggests different patterns of disease rather than the same phenotype tested at different stages in its natural history.

We did not assess responses to novel mAb therapies developed for the treatment of patients with severe asthma identified based on specific clinical features or a specific biomarker profile.[5,31,38-40] The decision to assess the responsiveness to ICS, β-agonist, and antimuscarinic treatments recognized their fundamental role in the treatment of both asthma and COPD across the severity spectrum. This approach enabled us to demonstrate that both the asthma-COPD overlap and obese-comorbid phenotypes responded to ICS therapy and that bronchodilation after short-acting β-agonist treatment was similar to or greater than that after short-acting antimuscarinic treatment for all phenotypes. The novel finding of steroid responsiveness in the asthma-COPD overlap and obese-comorbid phenotypes requires validation in randomized controlled trials but would suggest that patients with these phenotypes might benefit from treatment along asthma pathways.

In conclusion, our cluster analysis of patients with symptoms of airflow obstruction identified 5 disease phenotypes, including an asthma-COPD overlap and an obesity-comorbid phenotype. We provide data on their responsiveness to ICS, β-agonist, and antimuscarinic treatments. Our findings provide support for the recommendation to prescribe ICSs in patients with ACOS.

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Clinical implications: This study provides evidence that supports the Global Initiatives for Asthma and COPD recommendation to treat patients with the asthma-COPD overlap syndrome with ICSs.

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