

Clinical Phenotypes of Atopy and Asthma in COPD



A Meta-analysis of SPIROMICS and COPDGene

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BACKGROUND: Little is known about the concordance of atopy with asthma COPD overlap. Among individuals with COPD, a better understanding of the phenotypes characterized by asthma overlap and atopy is needed to better target therapies.

RESEARCH QUESTION: What is the overlap between atopy and asthma status among individuals with COPD, and how are categories defined by the presence of atopy and asthma status associated with clinical and radiologic phenotypes and outcomes in the Genetic Epidemiology of COPD Study (COPDGene) and Subpopulation and Intermediate Outcome Measures in COPD Study (SPIROMICS)?

STUDY DESIGN AND METHODS: Four hundred three individuals with COPD from SPIROMICS and 696 individuals from COPDGene with data about specific IgEs to 10 common allergens and mixes (simultaneous assessment of combination of allergens in similar category) were included. Comparison groups were defined by atopic and asthma status (neither, atopy alone, atopic asthma, nonatopic asthma, with atopy defined as any positive specific IgE (≥ 0.35 KU/L) to any of the 10 allergens or mixes and asthma defined as self-report of doctor-diagnosed current asthma). Multivariable regression analyses (linear, logistic, and zero inflated negative binomial where appropriate) adjusted for age, sex, race, lung function, smoking status, pack-years smoked, and use of inhaled corticosteroids were used to determine characteristics of groups and relationship with outcomes (exacerbations, clinical outcomes, CT metrics) separately in COPDGene and SPIROMICS, and then adjusted results were combined using meta-analysis.

RESULTS: The prevalence of atopy was 35% and 36% in COPD subjects from SPIROMICS and COPDGene, respectively, and less than 50% overlap was seen between atopic status with asthma in both cohorts. In meta-analysis, individuals with nonatopic asthma had the most impaired symptom scores (effect size for St. George's Respiratory Questionnaire total score, 4.2; 95% CI, 0.4-7.9; effect size for COPD Assessment Test score, 2.8; 95% CI, 0.089-5.4), highest risk for exacerbations (incidence rate ratio, 1.41; 95% CI, 1.05-1.88) compared with the group without atopy or asthma. Those with atopy and atopic asthma were not at increased risk for adverse outcomes.

INTERPRETATION: Asthma and atopy had incomplete overlap among former and current smokers with COPD in COPDGene and SPIROMICS. Nonatopic asthma was associated with adverse outcomes and exacerbation risk in COPD, whereas groups having atopy alone and atopic asthma had less risk.

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KEY WORDS: asthma COPD overlap; atopy; COPD

Take-home Point

To what degree atopy corresponds to asthma COPD overlap and confers risk to disease morbidity in COPD is not clear. In this study, individuals with COPD and nonatopic asthma had increased adverse respiratory outcomes and COPD exacerbations compared with those with atopic asthma or those without asthma regardless of atopic status. Ascertaining the atopic status of patients with ACO may be necessary to fully identify risk of adverse outcomes and guide therapeutic management.

FOR EDITORIAL COMMENT, SEE PAGE 2239

COPD is a cause of substantial morbidity and mortality in the United States and worldwide.¹ It is a heterogeneous disease, with outcomes and severity differing widely between patients. Efforts have been made to study this heterogeneity with the goal of tailoring treatments to vulnerable subgroups. Accordingly, an expanding body of

literature describes a phenotype of individuals having an overlap of both asthma and COPD features, termed Asthma COPD overlap (ACO).²⁻⁴ The discussion of ACO is not new, but is rather a variation of the age-old debate of the Dutch vs British Hypotheses.⁵⁻⁸ Regardless, the resurgence of literature on the topic has yielded interesting findings, demonstrating a high risk for exacerbations, symptoms, and adverse outcomes in individuals with ACO.^{3,4,9} However, a major limitation of this literature base is the lack of a clear definition for ACO or a clear understanding of what this phenotype represents. Some consensus definitions of ACO have been outlined,¹⁰⁻¹² which suggest definitions for ACO that include characteristics of allergic disease such as sputum eosinophilia, history of atopy, and elevated total IgE, suggesting that ACO is linked to eosinophilic and Th2-type inflammation.

Concurrently with this literature, a few studies of COPD have explored the association of atopy, defined as sensitization to common indoor and outdoor allergens, with adverse outcomes.^{13,14} One small study

ABBREVIATIONS: ACO = asthma chronic obstructive pulmonary disease overlap; ANOVA = analysis of variance; BD = bronchodilator; CAT = COPD Assessment Test; CCL11 = eotaxin 1; CCL3 = macrophage inflammatory protein-1; COPDGene = Genetic Epidemiology of COPD Study; IRR = incidence rate ratio; MMP3 = matrix metalloproteinase 3; MMRC = Modified Medical Research Council dyspnea score; Pi10 = the average wall thickness for a hypothetical airway of 10-mm lumen perimeter on CT; SGRQ = Saint George's Respiratory Questionnaire; SPINK1 = serine protease inhibitor Kazal-type 1; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study

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demonstrated that atopy was associated with increased risk for nocturnal symptoms and exacerbations,¹³ whereas another study demonstrated an association between atopy and higher respiratory symptoms while also noting increased responsiveness to the use of inhaled corticosteroid.¹⁴ Whether this allergic phenotype overlaps fully or partially with ACO remains to be seen. Previous literature in asthma has shown that those with nonatopic asthma appear to have worse outcomes than those with atopic asthma.¹⁵ However, a similar analysis of individuals with ACO to determine the risks associated with nonatopic vs atopic asthma overlapping with COPD has not been performed.

Methods

SPIROMICS (n = 2,981) and COPDGene (n = 10,199) are multicenter, longitudinal observational studies of individuals with and at risk for COPD. SPIROMICS inclusion criteria for COPD subjects included age 40 to 80, minimum smoking history of 20 pack-years, and FEV₁/FVC < 0.7. COPDGene recruited African American and non-Hispanic white COPD subjects between the ages of 45 and 80 years, with minimum 10-pack-year history of smoking and FEV₁/FVC < 0.7. SPIROMICS collected extensive phenotyping data annually for 3 years.^{16,17} In COPDGene, individuals were assessed at baseline and 5 years, with 10-year follow-up ongoing. Specific IgEs were available on a subset of individuals (n = 403 and 696 in SPIROMICS and COPDGene, respectively) having COPD defined as post-bronchodilator (BD) FEV₁/FVC < 0.7 (selection strategy is shown in e-Appendix 1).

Total and specific IgE levels were measured for 10 indoor and outdoor allergens and mixes (simultaneous assessment of combination of allergens in similar category), including cat dander, dog dander, dust mite (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*, separately), cockroach, mouse urine proteins, ragweed, mold mix, tree mix, grass mix (e-Appendix 1, supplementary methods; Phadia Immunology Reference Laboratory, Thermo Fisher Scientific). In SPIROMICS, total IgE was measured as part of the Myriad-RBM multiplex platform,¹⁸ whereas in COPDGene, total IgE was measured in the Phadia Immunology Reference Laboratory as described in e-Appendix 1, supplementary methods. Specific IgEs for both studies were measured in a subset of randomly selected individuals among those having COPD (equivalent of GOLD spirometry categories II through IV in COPDGene and strata 3 through 4 of SPIROMICS), with existing data from at least one follow-up visit or known to be deceased. We over-sampled individuals from the Johns Hopkins site (to facilitate future ancillary studies of allergen exposures) and otherwise randomly selected from all clinical sites. The sample size was predetermined based on effect size calculations.

Studied outcomes included moderate (change in medications, unscheduled doctors visit) and severe (ED visit, hospitalization) COPD exacerbations (reported over the previous 12 months and collected prospectively), 6-minute walk distance, post-BD FEV₁ percent predicted (and percent change post BD), modified Medical Research Council questionnaire (MMRC), St. George's Respiratory Questionnaire (SGRQ) and COPD assessment test score (CAT). CAT was collected yearly in SPIROMICS but only year 5 for COPDGene.

Participants underwent whole-lung multidetector inspiratory and expiratory CT.¹⁹ Studied parameters included percent emphysema (percent voxels < 950 Hounsfield units, inspiration), percent gas

This study seeks to evaluate subtypes of COPD defined by atopy and asthma overlap and to determine the association of these subtypes with exacerbation risk, symptom scores, and CT phenotypes in COPD. The Genetic Epidemiology of COPD Study (COPDGene) and Subpopulation and Intermediate Outcome Measures in COPD Study (SPIROMICS) are multicenter cohorts of individuals with and at risk for COPD.¹⁶ We hypothesized that the allergic, atopic subtype of COPD would not fully overlap with ACO, but that both atopy and asthma would still be associated with adverse outcomes, including symptoms and exacerbations in the population with COPD.

trapping (percent voxels < 856 Hounsfield units, expiration), and airway wall thickness (Pi10).

A subset from SPIROMICS (n = 1,544) had biomarkers measured using the Myriad-RBM platform.¹⁸

Statistical Methods

Atopy was defined as positive sensitization (≥ 0.35 KU/L) to any of the 10 allergens or allergen mixes. Asthma was defined as self-report of doctor-diagnosed asthma and report of this diagnosis being current (answered in affirmative when asked in addition to having the diagnosis if they still have this diagnosis). A simple definition based on clinical history was used because of the lack of agreement about a definition of ACO in the published literature on the topic and also was chosen for consistency with previous analyses from COPDGene.^{20,21} Atopy and asthma status were included as four distinct categories (neither, atopy, nonatopic asthma, atopic asthma). Exacerbations were modeled dichotomously (no exacerbations vs any exacerbations) for cross-sectional analysis of exacerbations in the past year only, and all other outcomes were modeled continuously.

Analysis of variance (ANOVA) and χ^2 tests were used to assess differences in measurements by atopy/asthma categories. Logistic and linear regression models assessed the cross-sectional associations of atopy/asthma status with outcomes. Zero-inflated negative binomial regression was used for longitudinal models of exacerbations (with offset for days of follow-up). All models were adjusted for age, sex, race (African American vs others), FEV₁ percent predicted, current smoking status, pack-years smoked, and use of inhaled corticosteroids (ICS). Data from COPDGene and SPIROMICS were analyzed separately, and then effect estimates were pooled using inverse variance weighted meta-analysis ("metan" commands in Stata) as used in previous analysis of COPDGene and SPIROMICS^{22,23} and further described in e-Appendix 1, supplementary methods.

Exploratory analysis was performed for 98 (of 115) biomarkers from SPIROMICS having at least 10% of values above the lower limit of quantification (see supplement). ANOVA was used to test differences in biomarker levels by asthma/atopy group. Log base 2 normalized biomarker levels were analyzed for canonical pathways using Ingenuity Pathways Analysis (Qiagen), with each group compared separately with the group without atopy or asthma.

Statistical analysis was performed with Stata version 12.1 (StataCorp, LLC, College Station, TX). SPIROMICS and COPDGene were approved by institutional review boards at each center (e-Tables 1, 2).

Results

The final sample size for analysis in SPIROMICS was $n = 391$ because of missing data on asthma status. In SPIROMICS, 226 (58%) individuals with COPD had neither atopy nor asthma, 101 (26%) had atopy alone, 37 (9%) had nonatopic asthma, and 27 (7%) had atopic asthma. Similarly, in COPDGene, 389 (56%) individuals with COPD had neither atopy nor asthma, 184 (26%) had atopy alone, 69 (10%) had nonatopic asthma, and 54 (8%) had atopic asthma. Overall, there was incomplete overlap between atopy and asthma that was consistent between cohorts, such that approximately 56% to 58% of individuals with asthma were nonatopic, and most subjects with atopy (approximately 77%-79%) did not have asthma (Fig 1). Participants were followed up for an average of 2.8 years in SPIROMICS and 5.9 years in COPDGene at the time of analysis. Individuals in both cohorts with and without available atopy data were compared (e-Tables 3, 4), and were largely similar, with the exception of individuals in COPDGene, with atopy data having slightly lower lung function than those without atopy data, and individuals in SPIROMICS with atopy data having more time followed up than those without atopy data.

Patient Characteristics

A comparison of participant characteristics by asthma and atopy categories for each study is presented in Table 1. Participants with asthma (both nonatopic and atopic) were younger and more likely to be female and African American compared with those without asthma.

FEV₁ percent predicted was lowest in the nonatopic asthma group compared with other groups, but this difference was statistically significant only in SPIROMICS. Nonatopic individuals with asthma had the highest prevalence of several comorbidities compared with other groups such as osteoporosis, obesity, gastroesophageal reflux disease, and congestive heart failure in at least one of the cohorts. The asthma groups (atopic and nonatopic) both had higher prevalence of inhaled corticosteroid compared with non-asthma groups.

Total IgE was highest in the atopic groups compared with the nonatopic groups. In SPIROMICS, absolute blood eosinophils was significantly higher in the atopic groups, whereas percent change in post-BD FEV₁ was higher in the asthma groups. A similar trend for eosinophils but not post-BD FEV₁ was observed in COPDGene.

Associations of Atopy and Asthma Categories With COPD Outcomes

Functional Status and Patient-Reported Outcomes

After adjustment for covariates and pooling effect estimates between COPDGene and SPIROMICS, the nonatopic asthma group had the most impaired MMRC (β , 0.24; 95% CI, 0.13-0.48), SGRQ (β , 4.2; 95% CI, 0.4-7.9) and CAT scores (β , 2.8; 95% CI, 0.09-5.4) when compared with the group without atopy or asthma, where β indicates difference in outcome (MMRC, SGRQ, CAT) when compared with the group without atopy or asthma. Participants with

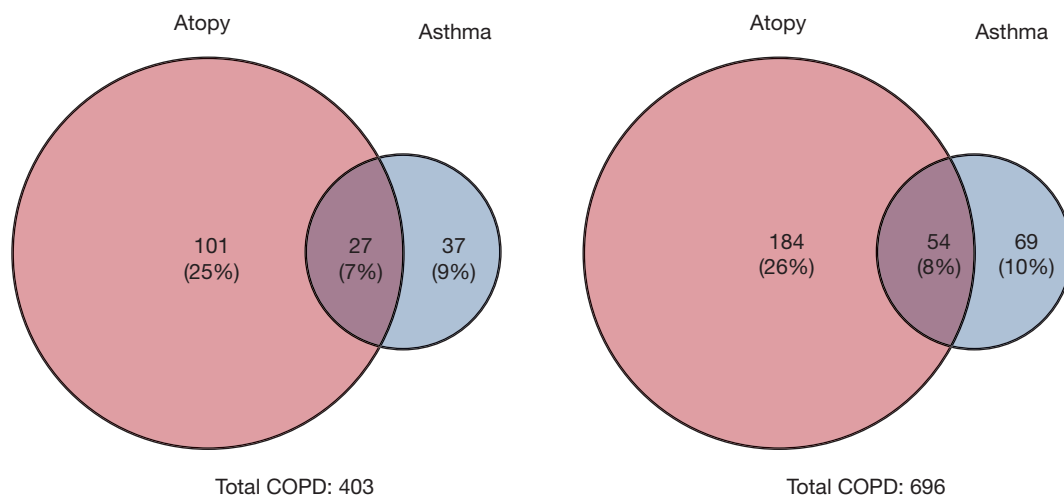


Figure 1 – Distribution of atopy and asthma in SPIROMICS (left panel) and COPDGene (right panel). Size of circles reflects percentage of individuals in the group. 6MWD = 6-minute walk distance; CAT = COPD Assessment test; IRR = incidence rate ratio; MMRC = Modified Medical Research Council dyspnea score; SGRQ = Saint George's Respiratory Questionnaire.

TABLE 1] Participant Characteristics

Characteristic	COPDGene					SPIROMICS				
	Neither n = 389 (56%)	Atopy Alone n = 184 (26%)	Nonatopic Asthma n = 69 (10%)	Atopic Asthma n = 54 (8%)	P	Neither n = 226 (58%)	Atopy Alone n = 101 (26%)	Nonatopic Asthma n = 37 (9%)	Atopic Asthma n = 27 (7%)	P
Demographics, smoking										
Age, y	64.7 (8.1)	63.3 (8.9)	60.2 (7.9)	60.1 (9.0)	<.001	66.3 (7.6)	64.4 (7.5)	61.5 (7.9)	63.4 (9.8)	.001
Female, No. (%)	179 (46%)	48 (26%)	49 (71%)	30 (56%)	<.001	110 (49%)	32 (32%)	25 (68%)	15 (56%)	.001
African American, No. (%)	51 (13%)	47 (26%)	19 (28%)	23 (43%)	<.001	30 (13%)	19 (19%)	10 (27%)	9 (33%)	.019
Current smoking, No. (%)	148 (38%)	82 (45%)	32 (46%)	22 (41%)	.377	82 (36%)	34 (34%)	12 (32%)	8 (30%)	.873
Pack-years smoked	55.7 (25.3)	51.9 (27.5)	50.8 (28.2)	47.7 (29.5)	.0922	51.9 (22.7)	52.4 (22.8)	46.9 (20.2)	45.8 (19.2)	.332
>HS education, No. (%)	332 (86%)	164 (89%)	56 (81%)	42 (78%)	.133	153 (68%)	75 (74%)	14 (38%)	17 (65%)	.001
Severity of disease, physiologic measures										
FEV ₁ , % pred	50.6 (17.0)	51.3 (17.5)	46.3 (16.8)	50.3 (16.7)	.2180	60.9 (22.9)	66.8 (20.1)	55.5 (18.5)	61.7 (22.8)	.035
Post-BD Pct change FEV ₁	9.9 (12.8)	8.6 (14.4)	9.9 (12.5)	11.7 (12.9)	.4558	9.7 (6.8)	11.2 (8.2)	13.3 (7.6)	13.9 (9.4)	.003
BMI	27.7 (6.2)	27.3 (5.0)	29.2 (6.9)	29.6 (7.7)	.0249	26.9 (5.3)	28.6 (5.6)	27.6 (5.5)	26.9 (5.9)	.093
Oxygen use, No. (%)	125 (32%)	46 (25%)	24 (35%)	12 (22%)	.144	44 (19%)	15 (15%)	9 (24%)	6 (22%)	.585
Current use of oral steroids, No. (%)	18 (5%)	11 (6%)	4 (6%)	6 (13%)	.192	4 (2%)	1 (1%)	3 (8%)	2 (7%)	.035
Current use of ICS, No. (%)	40 (11%)	18 (10%)	16 (24%)	7 (14%)	.014	87 (39%)	34 (34%)	25 (68%)	17 (63%)	<.001
Comorbidities										
History of allergic disease, No. (%)	75 (19%)	45 (24%)	24 (35%)	30 (56%)	<.001	48 (21%)	37 (37%)	9 (24%)	13 (48%)	.002
CHD, No. (%)	59 (15%)	34 (19%)	14 (20%)	8 (15%)	.600	8 (4%)	1 (1%)	2 (6%)	0 (0%)	.331
CHF, No. (%)	15 (4%)	10 (5%)	9 (13%)	4 (7%)	.019	4 (2%)	1 (1%)	2 (6%)	1 (4%)	.366
Diabetes, No. (%)	51 (13%)	26 (14%)	10 (14%)	7 (13%)	.981	29 (13%)	13 (13%)	5 (14%)	2 (7%)	.861
OSA, No. (%)	74 (19%)	30 (16%)	16 (23%)	12 (22%)	.568	45 (20%)	19 (19%)	11 (29%)	6 (22%)	.545

(Continued)

TABLE 1] (Continued)

Characteristic	COPDGene				SPIROMICS				P
	Neither n = 389 (56%)	Atopy Alone n = 184 (26%)	Nonatopic Asthma n = 69 (10%)	Atopic Asthma n = 54 (8%)	Neither n = 226 (58%)	Atopy Alone n = 101 (26%)	Nonatopic Asthma n = 37 (9%)	Atopic Asthma n = 27 (7%)	
GERD or PUD, No. (%)	130 (34%)	54 (29%)	34 (49%)	15 (28%)	72 (32%)	32 (32%)	12 (33%)	6 (22%)	.747
Obesity, No. (%)	124 (32%)	56 (30%)	28 (41%)	22 (41%)	60 (27%)	44 (44%)	13 (35%)	9 (33%)	.024
Osteoporosis, No. (%)	80 (21%)	17 (9%)	15 (22%)	9 (17%)	25 (11%)	7 (7%)	9 (25%)	2 (7%)	.028
Biomarkers									
Total IgE	64.8 (136.3)	385.4 (698.9)	101.9 (360.2)	592.7 (1,197.9)	22.1 (37.9)	145.5 (253.4)	11.4 (8.4)	53.5 (62.9)	< .001
Absolute eosinophils	0.19 (0.14)	0.22 (0.17)	0.18 (0.12)	0.22 (0.22)	0.18 (0.12)	0.23 (0.17)	0.18 (0.16)	0.23 (0.21)	.0392

All values listed as mean (SD) unless otherwise specified. BD = bronchodilator; CHD = coronary heart disease; CHF = congestive heart failure; GERD = gastroesophageal reflux disease; HS = high school; ICS: inhaled corticosteroids; PUD = peptic ulcer disease.

atopy alone or atopic asthma did not have substantially different MMRC, SGRQ, or CAT scores compared with the group without atopy or asthma. No significant differences were seen in 6-minute walk distance and FEV₁ percent predicted between groups (Fig 2A).

Exacerbation Risk

After adjustment, compared with the group without atopy or asthma, the nonatopic asthma group had the highest odds of reporting at least one exacerbation (OR, 2.52; 95% CI, 1.58-4.03) or severe exacerbation (OR, 2.80; 95% CI, 1.63-4.82) in the prior year, and higher incidence rate of any exacerbations over follow-up (incidence rate ratio [IRR], 1.41; 95% CI, 1.05-1.88). Compared with the group without atopy or asthma, the atopy and atopic asthma groups had similar odds of exacerbation in the prior year and incidence rate of exacerbations over follow-up (Fig 2B).

CT Outcomes

Percent emphysema was lower in atopy alone (β , -2.02; 95% CI, -3.48 to -0.56), nonatopic asthma (β , -4.66; 95% CI, -6.08 to -3.23) and atopic asthma groups (β , -4.33; 95% CI, -6.75 to -1.92), with β indicating difference in corresponding CT metric in each group compared with the group having neither atopy nor asthma. Percent gas trapping was not significantly different in atopy alone, but it was lower in the nonatopic (β , -4.39; 95% CI, -7.58 to -1.20) and atopic asthma groups (β , -5.11; 95% CI, -8.68 to -1.54) compared with the group without atopy or asthma. Airways wall thickness measured by Pi10 was higher in the atopy-alone group (β , 0.02; 95% CI, 0.003-0.036) but not significantly different in the non-atopic and atopic asthma group compared with those having neither atopy nor asthma (Fig 2 C, Table 2, e-Fig 1)

Sensitivity Analyses

Sensitivity analysis was performed of asthma and atopy status with clinical and CT outcomes, with additional adjustment for comorbidity burden using count of comorbidities (previously demonstrated to be a valid approach, particularly in the context of SPIROMICS and COPDGene²⁴). Results were mostly unchanged except for the loss of significance of the association with SGRQ in the nonatopic asthma group (e-Table 5).

Measures of Heterogeneity in Meta-analyses

Given that some differences did exist between cohorts in characteristics and severity, heterogeneity

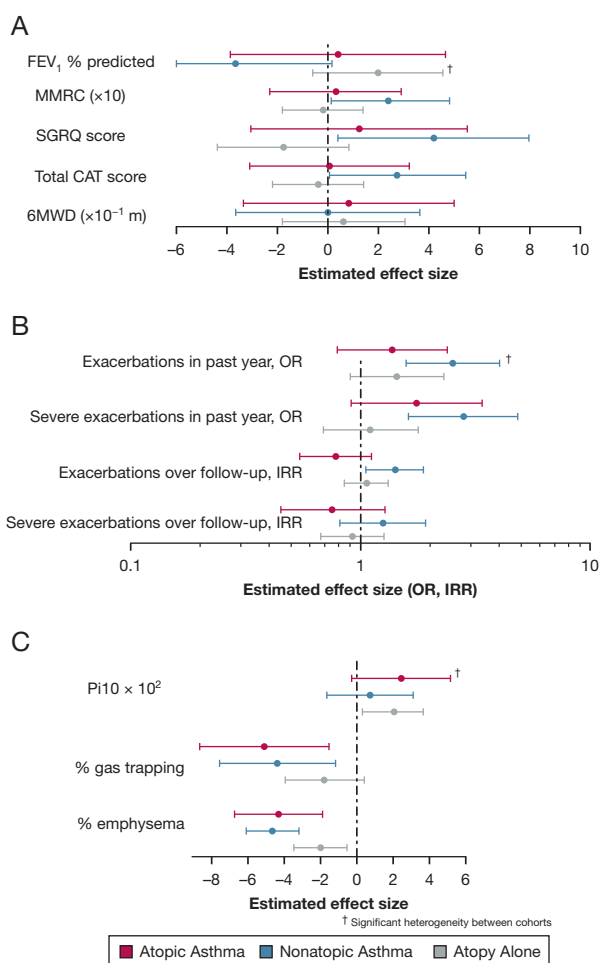


Figure 2 – Pooled associations of atopy, nonatopic asthma, and atopic asthma categories with clinical outcomes, CT metrics, exacerbations from SPIROMICS ($n = 403$) and COPDGene ($n = 696$). Analysis of CAT includes SPIROMICS data only. A, FEV_1 analyzed in units of percent predicted. MMRC, SGRQ, and CAT scores analyzed using points of total score, with MMRC scaled by 10^{-1} . 6MWD analyzed in meters and measurements scaled by 10 meters. Accordingly, a change in 1 unit on the pictured axis corresponds to the following changes for the pictured outcomes: 1% change in FEV_1 % predicted, 0.1-point change on the MMRC scale, 1-point change in SGRQ, 1-point change in CAT, and 10-m change in 6MWD. B, Results depicted on log scale. C, Pi10 scaled by 10^2 , Gas trapping and emphysema analyzed as percentages. Accordingly, a change in 1 unit of the pictured axis corresponds to the following changes for the pictured outcomes: 0.01 change in Pi10, 1% change in percent gas trapping, 1% change in percent emphysema. Gray represents atopy alone. Blue represents nonatopic asthma. Red represents atopic asthma. Comparison group (not pictured) with neither atopy nor asthma. CCL11 = eotaxin 1; CCL3 = macrophage inflammatory protein-1; CXCL5 = C-X-C motif chemokine ligand 5; KLK3_F = human plasma prekallikrein; MMP3 = matrix metalloproteinase 3; SERPINA3 = alpha-1-antichymotrypsin; SPINK1 = serine protease inhibitor Kazal-type 1. See Figure 1 legend for expansion of other abbreviations.

measures from meta-analysis were examined (e-Table 6). Three P values for heterogeneity were significant, including analysis of FEV_1 percent predicted outcome in the atopy-alone group, dichotomous exacerbation outcome in the nonatopic asthma group, and Pi10 outcome in the atopic

asthma group. In secondary analysis, atopic status (without regard to presence of asthma) was analyzed alone for associations with functional status, patient-reported outcomes, exacerbation risk, and CT outcomes. Results demonstrated association of atopic status with more preserved lung function, lower risk for exacerbations in SPIROMICS, and differences only in airway wall thickness in COPDGene (e-Tables 7-10).

Serum Biomarkers

Most mean biomarker levels were relatively similar between asthma-atopy groups, although several biomarkers differed significantly between groups in unadjusted analysis, and biomarkers having $P \leq .1$ for ANOVA ($n = 9$) are pictured in Figure 3. Total IgE appeared to be highest in the atopy alone and atopic asthma groups compared with all other groups. The atopy alone group also had higher levels of IgA and human plasma prekallikrein compared with other groups. The group with atopic asthma had higher levels of matrix metalloproteinase 3 (MMP3), alpha-1-antichymotrypsin, C-X-C motif chemokine ligand 5, and macrophage inflammatory protein-1 (CCL3) levels compared with all other groups. The nonatopic asthma group had higher levels of eotaxin 1 (CCL11) and serine protease inhibitor Kazal-type 1 (SPINK1) levels compared with all other groups. Canonical pathway analysis showed that the atopy alone and atopic asthma groups had more predominant IL-17 signaling, whereas the nonatopic asthma group appeared to have more indication of nuclear factor erythroid 2-related factor 2-mediated oxidative stress response and IL-23 signaling pathways compared with other groups. P values for pathways analysis did not meet statistical significance but reflect observed trends in the data.

Discussion

This pooled analysis of SPIROMICS and COPDGene demonstrated that atopy, though common and present in roughly one third of individuals with COPD, has poor overlap with doctor-diagnosed asthma and likely does not clearly represent the phenotype of ACO. Specifically, more than half of the patients with asthma do not have atopy, and most patients with COPD and atopy do not have doctor-diagnosed asthma. Additionally, individuals with nonatopic asthma appear to have the worst outcomes, including more severe lung function impairment, worse symptom scores, and highest risk for exacerbations. Thus, our study results suggest that

TABLE 2] Pooled Effect Size Estimates of Categories of Atopy Alone, Nonatopic Asthma, and Atopic Asthma With Outcomes Compared With Group Without Asthma or Atopy: SPIROMICS and COPGene

Outcomes	Pooled Effect Size	95% CI	P
FEV ₁ % predicted	1.99	(-0.60 to 4.57)	.132
	-3.66	(-7.48 to 0.16)	.06
	0.40	(-3.86 to 4.66)	.854
MMRC	-0.018	(-0.18 to 0.14)	.826
	0.24	(0.013 to 0.48)	.039
	0.030	(-0.23 to 0.29)	.820
SGRQ	-1.76	(-4.37 to 0.84)	.185
	4.20	(0.40 to 7.99)	.030
	1.24	(-3.05 to 5.53)	.572
CAT score (reflects only SPIROMICS)	-0.39	(-2.18 to 1.40)	.672
	2.76	(0.089 to 5.44)	.043
	0.058	(-3.10 to 3.21)	.971
6MWD	6.20	(-18.23 to 30.63)	.619
	0.063	(-36.25 to 36.38)	.997
	8.39	(-33.27 to 50.06)	.693
FEV ₁ % change post BD	0.73	(-0.72 to 2.17)	.323
	2.39	(0.26 to 4.53)	.028
	3.43	(1.04 to 5.82)	.005
Exacerbations			
Exacerbations in past year, OR	1.43	(0.90 to 2.29)	.131
	2.52	(1.58 to 4.03)	< .001
	1.37	(0.79 to 2.37)	.262
Severe exacerbations in past year, OR	1.10	(0.69 to 1.77)	.682
	2.80	(1.63 to 4.82)	< .001
	1.75	(0.91 to 3.38)	.094
Exacerbations over follow-up, IRR	1.06	(0.85 to 1.32)	.585
	1.41	(1.05 to 1.88)	.020
	0.78	(0.54 to 1.11)	.166
Severe exacerbations over follow-up, IRR	0.92	(0.67 to 1.26)	.592
	1.25	(0.81 to 1.92)	.307
	0.75	(0.45 to 1.28)	.293
CT metrics			
% Emphysema	-2.02	(-3.48 to -0.56)	.007
	-4.66	(-6.08 to -3.23)	< .001
	-4.33	(-6.75 to -1.92)	< .001
% Gas trapping	-1.79	(-3.94 to 0.37)	.104
	-4.39	(-7.58 to -1.20)	.007
	-5.11	(-8.68 to -1.54)	.005

(Continued)

TABLE 2] (Continued)

Outcomes	Pooled Effect Size	95% CI	P
Pi10	0.02	(0.003 to 0.036)	.018
	0.007	(-0.017 to 0.031)	.561
	0.024	(-0.003 to 0.051)	.080

Adjusted for age, sex, race, FEV₁ % predicted, current smoking status, pack-years smoked, inhaled corticosteroid use, and follow-up time only for models with longitudinal exacerbation data. The first row in each category is comparison between the group with atopy alone compared with the group without atopy or asthma; the second row in each category is comparison between group with nonatopic asthma compared with the group without atopy or asthma; and the third row in each category represents comparison between group with atopic asthma and group without atopy or asthma. 6MWD = 6-minute walk distance; CAT = COPD Assessment Test; IRR = incidence rate ratio; MMRC = Modified Medical Research Council (dyspnea questionnaire); Pi10 = bronchial wall thickness of inner perimeter of a 10-mm diameter airway; SGRQ = St George's Respiratory Questionnaire. See Table 1 footnote for expansion of other abbreviation.

although several definitions of ACO focus on allergic markers to define patients with asthma-COPD overlap, the nonatopic asthma subgroup may represent a high-risk population. These findings were noted in analysis of two separate, well-characterized cohorts of COPD, further highlighting the strength and consistency of these results.

Individuals with ACO may have a higher burden of Th2 or eosinophilic inflammation, and the higher burden of such inflammation could be the cause of an increased risk of respiratory morbidity observed in this group. This belief is reflected in the Spanish consensus statement regarding ACO,¹¹ which includes sputum eosinophilia, history of atopy, and elevated total IgE in their diagnostic criteria. However, in the current

analyses, those with atopic asthma (which would better fit this definition) did not have higher exacerbation risk and did not fare as poorly as those with nonatopic asthma regarding other outcomes, suggesting that perhaps allergic or Th2-type inflammation is not the predominant cause for adverse outcomes in the group with ACO. Our results show that those with nonatopic asthma have worse outcomes across a range of measures, including worse dyspnea, worse respiratory symptoms, and quality of life as measured by CAT and SGRQ, in addition to higher risk of previous and future exacerbations even after adjustment for lung function and other covariates. These results are analogous to what is known about nonatopic asthma without the presence of COPD in adults. A cluster analysis of participants in the Severe Asthma Research Program demonstrated that individuals with nonatopic asthma had lower lung function, increased health care utilization, and frequent use of oral corticosteroids, particularly when compared with individuals with early-onset atopic asthma.^{25,26} These individuals were also more likely to be female and obese, parallel with the higher prevalence of females of the nonatopic individuals with asthma also having COPD in this study.

Although this study shows that individuals with atopy, with or without asthma, had nominally higher risk for future exacerbations and higher airway wall thickness on CT, contrary to the prespecified hypothesis of the study, this group did not show excess risk compared with those without atopy or asthma. Individuals with atopy even showed lower total percent emphysema and strong trends toward less gas trapping. One could hypothesize that ongoing allergic, Th2 inflammation in individuals with COPD could be the predominant influence over Th1 inflammation in these individuals; however, why that would be associated with less decrements in lung

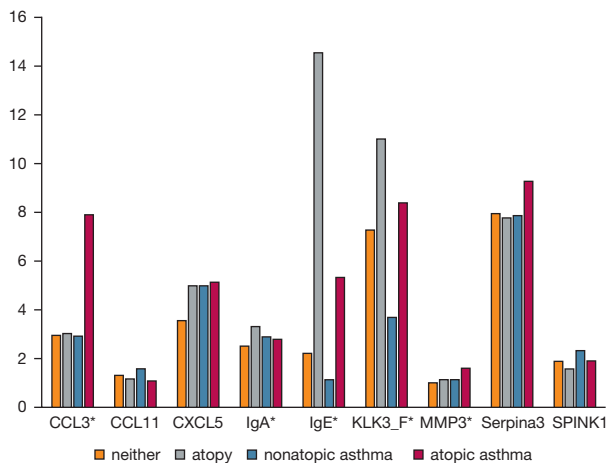


Figure 3 – Differences in selected biomarker levels between atopy and asthma groups (SPIROMICS only). $P < .10$ for all biomarkers listed. $P < .05$ for CCL3 ($P = .0034$), IgE ($P < .0001$), MMP3 ($P = .0327$), IgA ($P = .0007$), human plasma prekallikrein ($P = .0447$), each noted with asterisk (*). Y-axis represents biomarker levels, with units for biomarkers as follows: C-X-C motif chemokine ligand 5, ng/mL; CCL11, pg/mL; SPINK1, ng/mL; CCL3, pg/mL; alpha-1-antichymotrypsin, μ g/mL; IgE, U/mL; MMP3, ng/mL; IgA- mg/mL; KLK3_f, ng/mL; CD11, Serpina3 depicted as $\times 10^2$. SPINK1, CD3, IgE, MMP depicted as $\times 10$. KLK_F depicted as $\times 10^2$. See Figure 2 legend for expansion of abbreviations.

function and CT features in the atopic groups as seen in this study is not entirely clear. Notably, these results demonstrating that atopy alone is not as strongly associated with adverse outcomes and exacerbations are contrary to findings of previous studies.^{13,14} These differences could be explained by differing characteristics of the cohorts. For example, the cohort studied by Jamieson et al¹³ were strictly former smokers, whereas the current study includes current and former smokers with COPD. Additionally, the analysis by Fattahi et al¹⁴ was a sub-analysis of a trial, and therefore inclusion criteria were more stringent than in the current study, which was observational. The current results also differ from the results of cohort studies of the general population, which have shown the association of atopic diseases with adverse outcomes in some settings.²⁷ Furthermore, in light of these findings, quite possibly the key to understanding the relevance of allergic disease with outcomes in COPD may be in the environmental exposures experienced by individuals. This is a relevant point in the context of studies showing the importance of indoor air pollutants to COPD outcomes,^{28,29} which may be heightened among individuals with atopy.³⁰ Comparable findings have been reported among individuals with asthma, in which exposures to allergens are a major contributor to asthma morbidity in those with atopy.³¹ Therefore, understanding atopy alone without understanding environmental exposures is inadequate and highlights the necessity for future work to fill this gap in our understanding.

Additionally, the current findings further highlight the necessity to understand the process that underlies the higher risk observed in this and other studies of individuals with ACO. The biomarker analysis may provide preliminary insight into the pathophysiology of disease in those with the traditional definition of ACO as well as those with atopy. The findings of this study demonstrate that individuals with highest risk are those with nonatopic asthma who do not have a higher burden of Th2-type inflammation, suggesting that Th2 inflammatory pathways are not the primary driver of adverse outcomes in ACO. Previous literature surrounding allergic and eosinophilic inflammation have highlighted the importance of identification of these phenotypes to tailor therapies such as ICS. Furthermore, GOLD 2019³² treatment guidelines suggest the use of blood eosinophils in the decision-making algorithm for determining which COPD

patients to start on ICS. Christenson et al³³ studied airway epithelial gene expression in a COPD cohort and showed that Th2 gene expression signatures were shown to be associated with airway and blood eosinophilia, bronchodilator reversibility, lower FEV₁, and improvement of airway hyperinflation with ICS treatment.³³ Notably, an analysis of sputum and blood eosinophils from SPIROMICS showed that sputum eosinophilia was more predictive of exacerbation risk than blood eosinophils, further demonstrating this point.³⁴ ICS, or other targeted therapies such as anti-IgE or anti-IL-5, may still be an appropriate treatment for those with eosinophilic, systemic inflammatory, or Th2-high phenotypes of COPD; however, the use of such therapies may not have as strong a utility in the ACO group as a whole, but may instead be used to individualize therapy based on more specific disease phenotypes. Studies of anti-IL-5 therapies in eosinophilic COPD based on blood eosinophil counts have shown mixed results, highlighting group heterogeneity and supporting the need for additional characteristics to differentiate responsive subsets of COPD patients.^{35,36} In the biomarker and canonical pathway analysis, the nonatopic asthma group had suggestive increases in the IL-23 and nuclear factor erythroid 2-related factor 2-mediated inflammation pathways and also had higher eotaxin-1 levels, suggesting that this group also may have heterogeneity regarding inflammation. Accordingly, possibly the potential pathways leading to higher morbidity in the group with ACO may be not just be heterogeneous but also distinct from allergic inflammation. Overall, the results of this study and others appear to demonstrate that the group with ACO likely represents a diverse group that requires a deeper understanding. Additionally, the consistent association of ACO with exacerbation outcomes also raises the question of whether the characterization of ACO itself is subject to diagnostic selection bias (individuals are labeled as “ACO” because they exacerbate more).

As noted, metrics of heterogeneity for the meta-analysis were for the most part not statistically significant; however, there were three cases of significant *P* values. Of these, only the analysis of dichotomous exacerbations among nonatopic individuals with asthma was demonstrated to be a significant effect size through meta-analysis, consistent with the overall trend for slightly more heterogeneity in analyses of the nonatopic asthma group for exacerbation outcomes. Accordingly,

this finding should be interpreted with caution and likely reflects overall a higher degree of heterogeneity in the makeup of the nonatopic asthma group, further demonstrating the necessity to gain a deeper and better understanding of this group.

This study is subject to some limitations. First, the design and recruitment strategies for SPIROMICS and COPDGene were centered on understanding a population with and at risk for COPD; therefore, drawing conclusions about asthma in the framework of ACO should be approached with caution. The prevalence of ICS use among those with ACO was low, reflecting the lack of clear consensus about appropriate inhaler treatment regimen for individuals with ACO and also highlighting the difficulty in defining the population of individuals with ACO. In addition, all multivariable models were adjusted for ICS use. Additionally, recruitment of SPIROMICS and COPDGene relied on volunteers and therefore may not fully represent those who are more severely ill, bedbound, or less mobile. For the analysis of atopy, the panel of allergens tested was limited to 10, which one would expect to have high sensitivity for capturing atopy based on previous literature³⁷; however, some cases of atopy could have been missed. Also, oral corticosteroid use can reduce the production of IgE, which could have some impact on the ability to identify individuals with atopy, which is an additional limitation of the current analysis.

Additionally, the sample size of individuals with atopy data, although large for studies of COPD, was small in comparison with the full SPIROMICS and COPDGene studies, and the number of individuals with sputum cell

counts was even smaller, limiting the ability to analyze sputum eosinophils and other sputum data from SPIROMICS in the current analysis. The sample sizes for nonatopic and atopic asthma groups was small; therefore, conclusions from the analysis should be interpreted with this limitation in mind. Finally, the analysis of biomarkers was limited by the small sample size of individuals with available biomarkers. The biomarker analysis was exploratory in nature and intended to be hypothesis generating; however, the results of this analysis should be read with this consideration.

Interpretation

This study demonstrates that ACO includes both atopic and nonatopic individuals, which may have heterogeneous presentation and underlying mechanistic pathways. In meta-analysis of two independent cohorts, we show that those with COPD and overlapping nonatopic asthma have highest risk for adverse outcomes, including lower lung function, worse respiratory symptoms, and higher moderate and severe exacerbation risk, despite having lower emphysema and gas trapping. Accordingly, subjects with COPD and nonatopic asthma are a high-risk subgroup, which merits further studies to identify targeted therapies. Despite having similar morbidity across symptom outcomes, subjects with atopic asthma and COPD have increased prospective exacerbation risk, and further investigation into whether environmental exposures may contribute to this increased risk in sensitized individuals with COPD is warranted.

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