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Asthma-Copd Overlap Syndrome And Disease Progression In The Copdgene Cohort Study

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by

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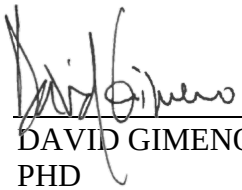

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ASTHMA-COPD OVERLAP SYNDROME AND DISEASE PROGRESSION IN THE COPDGENE COHORT STUDY

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Chronic Obstructive Pulmonary Disease (COPD) is a debilitating and degenerative lung disease characterized by progressive airway obstruction and alveolar destruction. When asthma and COPD co-occur and interact, with asthma having been diagnosed first, the resulting respiratory disease is called Asthma-COPD Overlap Syndrome (ACOS). Current research suggests that persons with ACOS may have more severe respiratory disease and lifestyle limitations than those with either disease alone. The purpose of the current study was to determine if and how disease progression differs in patients with ACOS versus COPD only, using data collected during the COPDGene cohort study. Demographic characteristics and disease outcome measures were compared at baseline and five-year follow-up for patients with ACOS versus COPD only. Changes in these metrics were compared using multiple linear regression and multinomial logistic regression models controlling for BMI, pack-years of smoking, gender, race, age, and current smoking status. The prevalence of ACOS in the current study population was 8.5%. Overall, subjects with ACOS were younger, had less pack-years of smoking, were more likely to be female, and were more likely to be of non-white race

compared with subjects with COPD only. Subjects with ACOS had lower quality of life scores, larger bronchodilator responses and forced vital capacities, less emphysema, and were more likely to experience severe COPD exacerbations at both study visits. However, changes in disease outcomes over a five-year period were very similar between the two groups, with the exception of frequent exacerbation status and bronchodilator response (BDR) status. Subjects with ACOS were less likely to experience frequent COPD exacerbations, and also less likely to display a bronchodilator response after the follow-up period, compared with subjects with COPD alone. The reduction of frequent COPD exacerbations in patients with ACOS suggests that treatment strategies currently used to treat asthma may have a positive effect on COPD, while the reduction in the frequency of BDRs in these patients suggests that understanding the inflammatory response in ACOS and preventing the associated airway remodeling may be important topics for future research.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

BACKGROUND

Literature Review

Industrialization during the 19th and early 20th centuries has been associated with what has come to be known as the epidemiologic transition.[1] According to this model, lifestyle changes associated with industrialization and associated better standards of living, including improved nutrition and hygiene, have been accompanied by a shift in morbidity and mortality.[1,2] This shift is characterized by a transition from mortality among the young from acute, often infectious, conditions to morbidity and mortality primarily among the elderly from chronic, largely "man-made" conditions.[1,2] Prior research has associated these chronic conditions with lifestyle factors such as smoking, exposure to environmental pollution, and sedentary habits.[1,3,4] It should be noted, however, that this transition is neither complete nor static. As evidenced by the current COVID-19 epidemic, infectious conditions are still associated with a large burden of mortality, even in developed regions. Another notable example of this phenomenon is the resurgence of measles in Western countries, where this disease had been eradicated, due to a rise in anti-vaccine sentiment.[5] Nevertheless, with a growing- and aging- global population concentrated in areas that are experiencing increased industrialization, the burden of chronic diseases is still expected to increase substantially in the decades to come.[6]

Chronic obstructive pulmonary disease (COPD) is one such disease with a large, and increasing, global disease burden.[6,7] COPD is a debilitating and degenerative disease

characterized by progressive airway obstruction and alveolar destruction.[7,8] Localized and systemic inflammation interact in COPD, leading to fibrosis and loss of elasticity in the lung parenchyma, which in turn leads to irreversible small airway collapse and gas trapping.[8] A reversible, cholinergic airway narrowing is also frequently seen.[8] COPD has been recognized by the World Health Organization as part of the global epidemic of noncommunicable diseases.[9] COPD has no cure, and current treatment options are limited even where there is advanced healthcare infrastructure.[6,9] In resource poor regions, COPD often goes unrecognized, and treatment is not available.[10] Prevention of COPD is mainly focused on smoking cessation or avoidance, as well as reducing the need for burning biomass fuels and reduction of other airborne pollutants through improving community infrastructure.[9]

Asthma is another chronic respiratory disease characterized by inflammation and obstruction of the airways, although the pathophysiology of asthma is better understood than that of COPD.[8] Most cases of asthma display an allergic pattern of inflammation resulting in airway narrowing and hyperresponsiveness, although different subtypes of disease are increasingly being recognized.[8] Like COPD, asthma has no cure, but there are effective treatments for asthmatics- namely inhaled corticosteroids.[8] Although the potential underlying mechanism is not understood, previous diagnosis with asthma is strikingly common among people diagnosed with COPD.[11–13] For example, Soriano *et al*. reported 43.2% of incident COPD cases from a study in the United Kingdom also had a previous diagnosis of asthma.[12] When the two conditions co-occur and interact, with asthma having been diagnosed first, the resulting respiratory disease is called Asthma-COPD Overlap Syndrome (ACOS).[13–15]

ACOS is increasingly being recognized as a distinct clinical phenotype with features of both asthma and COPD.[8,14,15] Current research suggests that patients with ACOS tend to have more severe respiratory dysfunction than those with either COPD or asthma alone.[8,16–18] Using cross-sectional and longitudinal analyses, Park *et al*. compared patients with ACOS to patients with asthma only in a Korean cohort.[18] The authors found that patients with ACOS were older, more likely to be male, less likely to have atopy, had lower baseline lung function with greater airway obstruction, and lower pre- and post- bronchodilator FEV1/FVC compared to patients with asthma only.[18] ACOS patients also had greater variation in FEV1 over time, a higher rate of exacerbations during follow-up, and a larger decline in pulmonary function after one and three years.[18] These results suggest that ACOS is phenotypically distinct from asthma, and causes a larger degree of respiratory decline over time than asthma alone.[18] However, this study did not compare ACOS to COPD alone.

Hardin *et al*. conducted a cross-sectional study comparing American patients with ACOS to those with COPD alone.[13] They found patients with ACOS were younger, smoked less, were more likely to report a history of hay fever, more likely to be African American, more likely to have had two or more COPD exacerbations in the previous year, and it was more likely that these exacerbations were severe than in patients with COPD alone.[13] The authors also reported that patients with ACOS had increased severity of disease and worse health-related quality of life scores, even after adjustment for potential confounding factors.[13] Direct measures of lung function, however, were similar in the two groups.[13] The authors suggested

that these observations may indicate that airway inflammation, rather than parenchymal destruction, could explain the differences in disease severity and health-related quality of life in ACOS vs COPD only subjects within this cohort.[13]

Public Health Significance

Global prevalence of COPD is currently estimated at 328 million people, with 168 million men and 160 million women affected, although this estimate is certain to be an underestimate due to underdiagnosis, especially in low- and middle-income countries.[6,10] By 2030, COPD is expected to directly account for 7.8% of all deaths, and 27% of smoking-related deaths, making it the third leading cause of death globally, after cancer (33%) and cardiovascular disease (29%).[6,9] Given the tremendous burden and economic impact of COPD, understanding and mitigating disease development and progression represents an important public health concern.[7,9,17]

The economic and social burden of COPD is directly associated with several factors including disease severity, frequency of exacerbations, and presence of comorbidities-including asthma.[11] As mentioned previously, asthma is a frequent comorbid condition in patients with COPD, and patients with ACOS may have worse outcomes.[11,16,17] Historically, however, these patients have been excluded from COPD-targeted studies due to concern that disease etiology or presentation may be different in this population, particularly as a result of previous inhaled corticosteroid use.[8,16,17,19] In studies where dual diagnosis has been allowed, comorbid asthma was associated with poor outcomes and increased healthcare utilization using

cross-sectional analyses.[13,16–18] However, an understanding of disease progression using longitudinal approaches is still needed to determine how asthma and COPD interact to produce a distinct clinical phenotype that may have unique treatment needs.[18]

Specific Aims

The aim of this study was to investigate how disease progression differed in patients with ACOS compared to COPD only. This aim was focused on understanding how measures of lung function and respiratory health changed in the five years between baseline and follow-up in the two patient subgroups. The *rationale* for this investigation was that understanding how COPD progresses in different patient populations could inform healthcare needs and treatment strategies. The *hypothesis* for this study was that patients with ACOS would have greater COPD progression in terms of reduced lung function and worse measures of respiratory health than patients with COPD only.

METHODS

Study Design

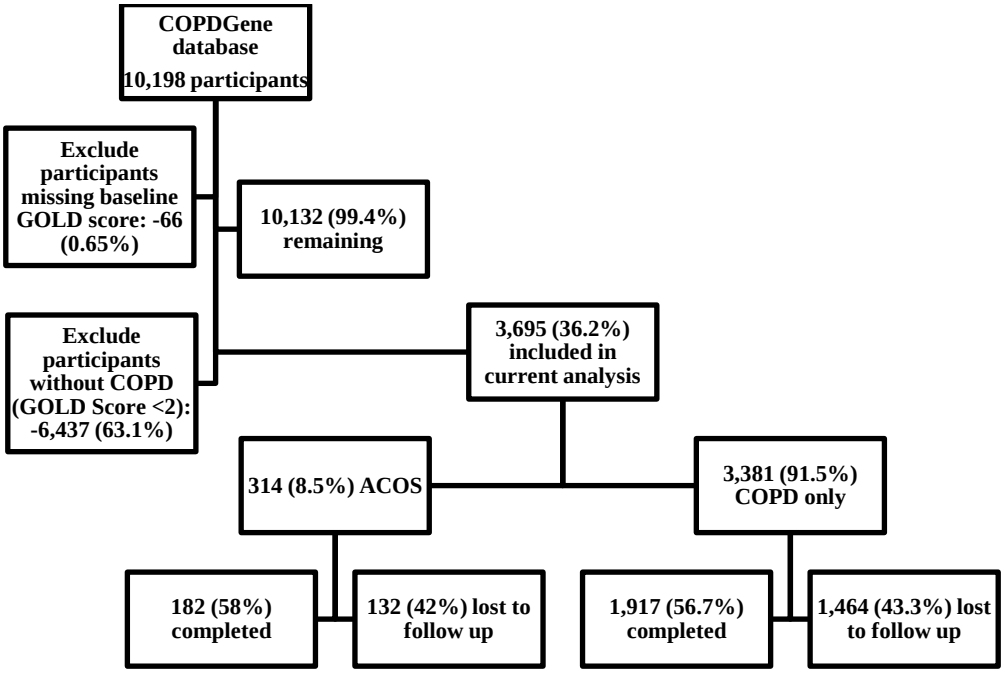
This study represents a secondary data analysis of data collected during the first two phases of the Genetic Epidemiology of COPD Study. The Genetic Epidemiology of COPD Study (COPDGene) is a multi-site observational, longitudinal cohort study investigating the underlying genetic factors that are associated with COPD development and progression.[7,20] COPDGene has enrolled over 10,000 participants since beginning in 2007 and is expected to complete the ten-year follow-up phase of data collection in 2022.[7,20] Participants in the original

COPDGene study were non-Hispanic whites (66.5%) and African-Americans (33.5%) aged 45 to 80 years (mean 59.5) with a history of smoking (at least 10 pack-years), with (36.2%) or without (63.8%) a diagnosis of COPD at baseline.[7] Healthy never-smokers were also included as controls.[20] Both men (53.5%) and women (46.5%) were included.[7] Current smoking was reported by 53.1% of participants, and use of supplemental oxygen was reported by 11.5% of participants.[7] At baseline and follow-up, participants completed comprehensive symptom and comorbidity questionnaires, lung spirometry measurements, chest computed tomography (CT) scans, and provided samples for genetic and biomarker profiling.[7,20] The COPDGene study also collected data on patient demographics, medical history, lifestyle factors, and healthcare utilization, with the goal of developing a phenotype for patients with COPD.[7,20] COPDGene is currently in the third phase of the study, following up with patients ten years after their initial study visit.[7,20]

For the current study, the first two study phases (i.e., baseline and five year follow-up) were included for analysis as these data are the most complete.[7] The COPDGene data set used for the current study consisted of 16,482 observations, representing 10,198 individual participants. After excluding individuals without COPD, as indicated by a baseline GOLD score of less than two (n=6,437), (or with missing baseline GOLD scores, n=66) 3,695 participants remained in the study population.[13,17] At the time of the current study, 2,099 individuals had completed the 5-year follow-up visit, leaving 1,596 individuals lost to follow up. Using the ACOS definition described below, 314 (8.5%) individuals in the baseline study population were identified as having ACOS, while the remaining 3,381 individuals had COPD

only. Of those individuals with completed follow-up visits, 182 had ACOS and 1,917 had COPD only. A schematic view of the study population is presented in Figure 1 below.

Figure 1: Schematic view of the study population.



Asthma-COPD Overlap Syndrome

The first step of the current study was to identify the subset of patients in the COPDGene cohort that had ACOS. This study used the ACOS definition proposed by Sin *et al* (see Figure 2 for a visual depiction of this definition).[14] Previous studies of ACOS have largely been limited to using either self-reported asthma diagnosis or documentation of a physician's diagnosis of asthma as the only criterion for determining ACOS.[11,17–19] Therefore,

using Sin *et al.'s* new consensus definition in this study represents a novel and objective strategy for identifying patients with ACOS in the COPDGene cohort study data.

This definition requires that a patient be over 40 years of age, have a post bronchodilator forced expiratory volume to forced vital capacity ratio (FEV1/FVC) less than 0.70 or the lower limit of normal (LLN), have an exposure to tobacco or environmental pollution greater than or equal to ten pack years of cigarette smoking, and documentation of asthma before the age of 40 or a bronchodilator response greater than 400mL in FEV1.[14] In addition to these "major" criteria, at least one of the following "minor" criteria must also be present for a patient to be considered as having ACOS: documentation of allergic rhinitis or another atopic disease, two or more instances of having a bronchodilator response of at least 200mL and 12% of baseline, or having peripheral eosinophil counts of at least 300 cells per microliter.[14] Because presence of ACOS was not directly assessed during the COPDGene study, this information was abstracted from the clinical data that was collected in order to determine the ACOS status of each subject.

To achieve the classification of ACOS using the COPDGene data, three new ACOS indicator variables were created and initially given a value of "missing" for each subject. These variables were used to track the presence of the "major" and "minor" ACOS criteria as described above, and to assign the final ACOS classification. All participants enrolled in the COPDGene study were between the ages of 45 and 80 at the time of enrollment, thus the first criterion was met for all subjects. Age of subjects was determined by the difference of the date

of enrollment and the subject's date of birth, and recorded in years. Any subject with an age less than 40 was assigned a value of "0" for the ACOS indicator variable. Pre- and post-bronchodilator spirometry was performed on each participant at each study visit using a standardized study protocol and equipment[20]. Spirometry measurements including the FEV1/FVC ratio and the calculated LLN were recorded as part of this study data. For subjects with a recorded FEV1/FVC ratio less than 0.70, or below the LLN for the subject, a value of "1" was given to the ACOS major criteria score. For subjects not meeting these spirometry measurements, a value of "0" was assigned. Subjects documented to have at least ten pack years of cigarette smoking, were given an additional "1" to the ACOS major criteria score, and a "0" otherwise. Lastly, a final "1" was added to the ACOS major criteria score if documentation of asthma before the age of 40 or a bronchodilator response greater than 400mL in FEV1 was present for each subject. Bronchodilator response was directly measured as part of the standardized spirometry assessment, while documentation of asthma was self-reported in the Respiratory Disease Questionnaire completed by each subject.[20] Similarly, the ACOS "minor" criteria score was assessed by assigning a score of "1" for the presence of each criterion, and a "0" for its absence. Documentation of allergic rhinitis or atopic disease was self-reported in the Respiratory Disease Questionnaire.[20] Instances of having a bronchodilator response of at least 200mL and 12% of baseline were assessed as part of the spirometry, and peripheral eosinophil counts were measured on the blood sample obtained at each study visit.[20] Thus, each subject was assigned a final classification of ACOS if the major criteria score was four points, and the minor criteria score was at least one point. Presence of ACOS was coded

as a "1" in the indicator variable, and absence was coded as a "0". All subjects had sufficient exposure data to make an ACOS determination.

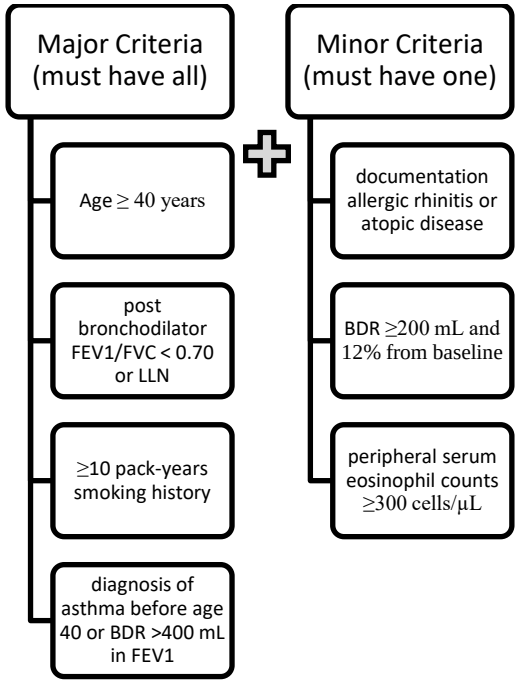


Figure 2: Diagnostic criteria for ACOS (LLN: lower limit of normal; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; BDR: bronchodilator response)

Outcome Measures

There were ten outcome measures that were used to determine disease progression: the body-mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index, the Global Initiative for Obstructive Lung Disease (GOLD) score, the St. George's Respiratory Questionnaire (SGRQ) score, self-reported health status, the presence and severity of COPD exacerbations, distance walked during a standard six-minute walk test, lung spirometry results,

and CT based measures of emphysema, airway wall thickness, and gas trapping. These indices will be described in turn below and are summarized in Table 1.

The BODE index is a multidimensional grading system used to predict the risk of death from any cause and the risk of death from respiratory causes in subjects with COPD.[21] This index is calculated using a point-value system based on a subject's FEV1(% of predicted), distance walked in a standard six-minute walk test, score on the Medical Research Council dyspnea scale (self-reported assessment of breathlessness), and body-mass index (BMI).[21] The BODE index ranges from zero to ten, with higher scores indicating a greater risk of death.[21] In the original cohort used to develop the BODE index, the hazard ratio for all-cause mortality was 1.34 per one-point increase in BODE index, and the hazard ratio for respiratory disease-related mortality was 1.62 per one-point increase.[21] The BODE index has since been validated in several studies, and was found to be more accurate at predicting death and reduced quality of life in COPD patients than its component measurements alone.[22,23] Furthermore, these studies indicated that a change in the BODE index can be used to track progress associated with disease treatment.[22] In the COPDGene study, data collected from the clinical examination and patient questionnaires completed at each study visit were used to calculate the BODE score for each participant at each visit. This score was reported as an integer between one and ten.

Table 1: Description of outcomes and scoring systems used in the COPDGene study.

Respiratory Outcome or Score	**Description**
BODE index	1-10, higher score means more airway limitation
GOLD 0	"Control" FEV1 ≥ 80%, FEV1/FVC ≥ 0.7
GOLD 1	FEV1 ≥ 80% and FEV1/FVC < 0.7
GOLD 2	50% ≤ FEV1 < 80% and FEV1/FVC < 0.7
GOLD 3	30% ≤ FEV1 < 50% and FEV1/FVC < 0.7
GOLD 4	FEV1 < 30% and FEV1/FVC < 0.7
GOLD -1	"PRISm" Preserved Ratio, Impaired Spirometry
St. George's Respiratory Questionnaire (SGRQ)	0-100, Higher scores mean lower quality of life
Self-reported general health question (SRGHQ)	1: Poor, 2: Fair, 3: Good, 4: Very Good, 5: Excellent; self-reported overall health
Frequent Exacerbations	0: less than two exacerbations per year 1: two or more exacerbations per year
Severe Exacerbations	0: no severe exacerbations reported 1: severe exacerbations reported
Forced expiratory volume in 1 second (FEV1)	Amount of air, in liters, exhaled in one second
Forced vital capacity (FVC)	Maximum total amount of air exhaled, in liters
FEV1/FVC	FEV1 to FVC ratio, normal range: 0.7-0.8
6-Minute Walk Test	Distance (in feet) walked during standardized 6-minute walk test
Percent emphysema (-950 Hu)	CT-quantified emphysema distribution
Percent Gas Trapping (-856 Hu)	CT- quantified gas trapping distribution
Pi10 SRWA	CT- quantified airway wall thickness, square root of wall area of a 10mm (luminal perimeter) airway
CT: Computed Tomography; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity; GOLD: global initiative for obstructive lung disease; Pi10 SRWA: 10mm luminal perimeter, square root wall area; Hu: Hounsfield units	

The GOLD score is another multidimensional grading system used to categorize disease severity in COPD.[24] The original GOLD scoring system uses an A-B-C-D based ranking that considers symptom severity and exacerbation history of a patient to determine their COPD stage.[24] The COPD Foundation produced a modified version of the GOLD scoring system, which uses spirometry measurements to track disease progression. The COPD Foundation GOLD score ranges from negative one to four, with higher scores indicating more severe respiratory impairment.[20] This modified GOLD scoring system was used during the COPDGene study.[20] As of 2011, the GOLD Foundation has also switched to this numeric scoring system based on airflow limitation as measured by spirometry.[25] The alphabetic scoring system is still used to assess symptom severity, due to a lack of correlation between the spirometry assessment and patient health status.[25,26] Overall, the modified system appears to be as valid as the original, but it may still need refinement (AUC 0.623 vs 0.634, respectively).[26–28]

St. George's Respiratory Questionnaire (SGRQ) is a survey style questionnaire widely used to evaluate quality of life in individuals with COPD and other airway diseases.[29] SGRQ scores range from zero to 100, with higher scores indicating worse quality of life.[29] Like the BODE index, the SGRQ allows for comparison of scores before and after initiation of a treatment regimen, or other follow-up period.[30] The SGRQ has been validated for use in both adults (18+) and older adults (65+) with obstructive airway disease (including COPD in particular), making it well suited to this cohort.[31–33] The test-retest intraclass correlations for the SGRQ-B (American version) were 0.795 to 0.900.[33]

During the COPDGene study, participants were also asked to rate their overall health (In general, how would you describe your health?) on a scale of one to five, with five meaning they felt they were in excellent health and one meaning they felt they were in poor health.[20] Participant responses are referred to as the self-reported general health question (SRGHQ) throughout the current study. The question was asked without a reference period, and thus may be subject to recall bias. However, other studies have found that this type of question can still be valid in a variety of contexts, thus it was chosen that the question should remain in the current analysis.[34]

The presence and severity of COPD exacerbations was assessed as follows. COPDGene participants were recorded as having frequent COPD exacerbations if they reported having at least two exacerbations in the previous year.[17,20] A dichotomous indicator variable was created and given a value of "1" if the participant reported two or more COPD exacerbations on the Respiratory Disease Questionnaire and a "0" otherwise. Similarly, presence of severe exacerbations was concluded if participants reported having a respiratory complication that resulted in a hospital or emergency department visit.[17,20] This response was coded in a second indicator variable, using a "1" to indicate an emergency department visit and a "0" otherwise, again using the participant response from the Respiratory Disease Questionnaire.

As mentioned previously, pre- and post-bronchodilator pulmonary function testing was completed in compliance with the American Thoracic Society guidelines, using a standardized study protocol and spirometer.[20,35] Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were recorded in liters, and the FEV1/FVC ratio was recorded as a decimal. ATS guidelines were also followed in the administration of the standardized six-minute walk test.[20,36] Results of the six-minute walk test (distance walked) were recorded in feet. Computed tomography (CT) scans were used to compute the percent area of the lung with tissue densities indicative of emphysematous changes or gas trapping (density thresholds of -950 and -856 Hounsfield units, respectively).[37] CT scans were also used to calculate airway wall thickness by measuring the square root of the wall area of small airways (airways with a 10mm luminal perimeter). Greater values of this metric have previously been associated with increased levels of airway disease.[37] Detailed protocols for these assessments, as well as the protocol for the acquisition of CT scans can be found in the study protocol appendices linked in Reagan EA, Hokanson JE, Murphy JR, *et al.* 2010.[20]

Covariates

Covariates included factors that have already been associated with worse outcomes in COPD: age, gender, race, BMI, and pack-years of smoking.[17] Older patients with COPD (65+) have demonstrated worse lung function and exercise tolerance, as well as increased frequency of comorbidities when compared to younger patients in previous studies.[7] Female sex has also previously been associated with higher disease severity, independently of other relevant factors.[7] Racial differences in COPD outcomes have also been found, with African American

subjects experiencing lower quality of life scores during COPD exacerbations and hospitalizations as compared to non-Hispanic Whites.[7] Adjusting for pack-years of smoking allows the current analysis to evaluate the effects of asthma on COPD progression independently of potential differences in exposure to tobacco products. Lastly, BMI has been associated with reduced 6-minute walk test performance and greater dyspnea, independently of COPD status, so the current analysis needs to take measures to reduce the potential effect of obesity on ACOS related outcomes.[7]

Study Power

The COPDGene study contains records for over 10,000 participants. According to the study by Hardin *et al.*[17] using preliminary baseline data from the COPDGene cohort, of 915 subjects with COPD, 119 were identified as having comorbid asthma and 796 subjects had COPD only. As reported in the results section below, the current study identified 3,695 subjects with COPD only and 314 subjects with ACOS. Of these subjects, 1,917 and 182 completed the five year follow up study, respectively. Focusing the power analysis on the SGRQ score, as this measure has had the minimal meaningful difference determined and validated[38], we see that patients with COPD alone had an average change in SGRQ score of 1.77±15.75 points, while patients with ACOS had an average change in SGRQ score of -1.57±15.94 points (p=0.009, Table 5, below). Using the population sizes at follow-up, an alpha level of 0.05, setting the effect size to the minimal meaningful difference of 4 points, and the student's *t* test for two independent sample means, this study had a power of 0.77 to detect this difference.

Thus, we may anticipate that the current study was adequately powered to detect meaningful differences.

Data Analysis

Subjects that participated in both study visits were included in the final (change values and multivariable) analysis. For the cross-sectional comparisons, subjects who were lost to follow up were included to allow for the comparison of the lost cohort to the retained cohort. For the cross-sectional analyses, missing values for individual outcome measures were allowed at each timepoint. However, for the longitudinal analysis, only subjects with complete data at both visits were included. Markers of disease outcomes for COPD vs ACOS subjects were compared at baseline and follow-up using descriptive statistics (mean ± standard deviation, median ± interquartile range, mode, and range as appropriate). Chi-squared tests were used to detect differences in categorical variables, which included BODE index, GOLD score, self-reported health status, smoking status, presence of severe exacerbations, presence of frequent exacerbations, and bronchodilator response, between the two groups at baseline and follow-up. Independent samples T-tests were used to detect differences among the continuous variables, which included BMI, pack years of smoking, SGRQ score, six-minute walk test, forced vital capacity- percent predicted, forced expiratory volume -percent predicted, volume of bronchodilator response as a percent of FEV1, percent gas trapping on CT, percent emphysema on CT, and airway wall thickness, between the two groups at baseline and follow-up. For all statistical tests, p-values of ≤ 0.05 were considered significant differences.

To account for the correlation of outcomes between phase 1 and phase 2, and to adjust for other covariates, the multiple linear regression for continuous outcomes (e.g. SGRQ score, six-minute walk test results, and CT-derived measures of emphysema and airway wall thickness), or the multinomial logistic regression model for categorical outcomes (e.g., presence of a bronchodilator response, presence of frequent exacerbations, presence of severe exacerbations, and BODE index) was used to compare ACOS versus COPD only patients. These models were applied to change variables representing the difference in disease outcomes between baseline and follow-up measurements. Categorical change variables were coded as "increased," "decreased," or "no change" for variables representing scores (ex. BODE and GOLD scores), and "developed," "lost," or "no change" for variables representing the presence or absence of a condition (ex. BDR, severe exacerbations, frequent exacerbations). For example, if a participant reported the presence of severe exacerbations at baseline, but reported the absence of severe exacerbations at follow-up, the change variable for severe exacerbations would be coded as "lost" for this participant. By contrast, if a participant did not have a BDR at baseline, but did have a BDR at follow-up, the change variable for BDR would be coded as "developed" for this participant. Multiple regression model assumptions were checked using the Breusch-Pagan test for heteroskedasticity, Shapiro-Wilk's test for normality of residuals, variance inflation factors for multicollinearity, the link test to check for model specification problems, the Ramsey Regression Equation Specification Error Test to check for the use of an appropriate functional form, and Cook's distance to check for influential points. The Independence of Irrelevant Alternatives (IIA) assumption for the multinomial logistic regression model was checked, and the data were also checked for case specificity. All

multivariable models were adjusted for differences in *baseline* outcome measures (age, gender, race, BMI, current smoking status, and pack-years of smoking).

To investigate the potential for differential loss to follow-up, baseline characteristics of participants who completed the five-year follow-up visit were compared to those participants who were lost to follow-up. These data are summarized in Table 2, below. While ACOS status, age, smoking status, and BDR (% FEV1) were similar between completers and lost participants, differences were detected for the remaining measures. Loss to follow up was more frequent among African Americans (20.6% vs 25.4% African Americans, $X^2(1, N=3695) = 9.64$, $p=0.002$) and males (52.8% vs 59.0% males, $X^2(1, N=3695) = 15.68$, $p<0.001$). Participants who were lost to follow up also had lower BMI (mean ±SD: 28.63 ±6.14 vs 27.32 ±6.40, $p<0.001$), greater pack-years of smoking (mean ±SD: 51.25 ±25.54 pack-years vs 55.14 ±29.84 pack-years, $p<0.001$), higher SGRQ scores (mean ±SD: 36.39 ±21.32 points vs 46.79 ±21.26 points, $p<0.001$), and lower self-reported general health than participants who completed the study (31.2% vs 45.9% scored 1 or 2 points, $X^2(4, N=3693) = 153.46$, $p<0.001$). They also performed worse on the six-minute walk test (mean ±SD: 1263.28 ±363.15 feet vs 1052.48 ±408.70 feet, $p<0.001$), had lower FVC (% predicted) (mean ±SD: 79.20 ±15.98% vs 72.59 ±18.04%, $p<0.001$), lower FEV1 (% predicted) (mean ±SD: 54.12 ±16.30% vs 45.15 ±18.80%, $p<0.001$), greater percent gas trapping (mean ±SD: 36.01 ±19.20% vs 42.24 ±21.66%, $p<0.001$), greater percent emphysema (mean ±SD: 11.69 ±11.57% vs 15.60 ±14.29%, $p<0.001$), and greater airway wall thickness than study completers (mean ±SD: 2.68 ±0.56 units vs 2.84 ±0.56 units, $p<0.001$). Finally, participants who were lost to follow up had

higher baseline GOLD (39.4% vs 58.5% scored 3 or 4, $X^2(2, N=3695) = 241.72$, $p<0.001$) and BODE (6.2% vs 20.7% scored over 5 points, $X^2(10, N=3597) = 300.56$, $p<0.001$) scores, and were more likely to have reported experiencing severe COPD exacerbations (19% vs 27.3%, $X^2(1, N=3695) = 40.29$, $p<0.001$), frequent COPD exacerbations (15.2% vs 21.7%, $X^2(1, N=3695) = 27.71$, $p<0.001$), and inhaled corticosteroid use ($X^2(1, N=3563) = 16.16$, $p<0.001$) compared to participants who were not lost to follow-up. However, loss to follow-up was independent of ACOS status (8.7% vs 8.3%, $X^2(1, N=3695) = 0.187$, $p=0.666$), and is thus not expected to change the observed associations of the exposure and outcomes under investigation.

Table 2: Demographic and health characteristics of the study cohort, complete cases versus lost to follow up, at baseline.

	Baseline (N= 3695)		
	Complete Cases	Lost to Follow up	
	(N = 2099)	(N = 1596)	p-value*
Mean (SD)			
BMI	28.63 (6.14)	27.32 (6.40)	<0.001
Age at baseline	63.16 (8.30)	63.52 (8.83)	0.208
Pack years of smoking	51.25 (25.54)	55.14 (29.84)	<0.001
SGRQ score (total)	36.39 (21.32)	46.79 (21.26)	<0.001
6-minute walk test distance	1263.28 (363.15)	1052.48 (408.70)	<0.001
FVC (% predicted)	79.20 (15.98)	72.59 (18.04)	<0.001
FEV1 (% predicted)	54.12 (16.30)	45.15 (18.80)	<0.001
BDR (% FEV1)	9.04 (12.72)	8.70 (13.90)	0.439
% Gas trapping	36.01 (19.20)	42.24 (21.66)	<0.001
% Emphysema	11.69 (11.57)	15.60 (14.29)	<0.001
Airway wall thickness	2.68 (0.56)	2.84 (0.56)	<0.001
N (%)			
ACOS (yes)	182 (8.7%)	132 (8.3%)	0.666
Gender (male)	1107 (52.7%)	946 (59.3%)	<0.001

Race (Caucasian)	1661 (79.1%)	1194 (74.8%)	0.002
SRGH score 1	102 (4.9%)	197 (12.3%)	<0.001
2	555 (26.5%)	540 (33.8%)	
3	886 (42.3%)	644 (40.4%)	
4	475 (22.7%)	189 (11.8%)	
5	79 (3.8%)	26 (1.6%)	
Smoking status (current)	1266 (60.3%)	925 (58.0%)	0.149
GOLD score 2	1265 (60.3%)	660 (41.4%)	<0.001
3	653 (31.1%)	511 (32.0%)	
4	181 (8.6%)	425 (26.6%)	
BODE score 0	390 (18.8%)	142 (9.3%)	<0.001
1	353 (17.1%)	173 (11.3%)	
2	370 (17.9%)	174 (11.4%)	
3	339 (16.4%)	221 (14.5%)	
4	287 (13.9%)	239 (15.7%)	
5	205 (9.9%)	253 (16.6%)	
6	100 (4.8%)	229 (15.0%)	
7	24 (1.2%)	72 (4.7%)	
8	2 (0.1%)	14 (0.9%)	
9	0 (0.0%)	8 (0.5%)	
10	0 (0.0%)	2 (0.1%)	
Severe Exacerbations (yes)	396 (18.9%)	442 (27.7%)	<0.001
Frequent Exacerbations (yes)	319 (15.2%)	350 (21.9%)	<0.001
Inhaled Corticosteroids (yes)	214 (10.6%)	231 (15.0%)	<0.001

**p-value for completed vs lost, t-test (means) or chi-square test (proportions)*
BMI: body-mass index; SGRQ: Saint George's respiratory questionnaire; FVC: forced vital capacity; FEV1: Forced expiratory volume in one second; BDR: bronchodilator response; SRGH: self-reported general health; GOLD: global initiative for obstructive lung disease; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity

Data Handling and Informed Consent

All study data are previously collected data from an IRB approved study (UTHSCSA protocol number HSC20070644H). Written informed consent was obtained from all participants before study initiation. Additional UTHealth Committee for the Protection of

Human Subjects (CPHS) approval for this project was also obtained (protocol number HSC-SPH-20-0850). These data do not contain any personally identifying health information, as they have been stripped of all personal identifiers as defined by the UTHealth CPHS and UTHSCSA Institutional Review Board. Nevertheless, study data was transferred to the student using a password protected, fully encrypted USB drive and stored on a password protected, secure computer. All study data stored by the student was destroyed upon completion of the current project.

RESULTS

Cross-Sectional Analyses

Table 3, below, contains the demographic and health status information for the study population at baseline. Compared to participants with COPD only, patients with ACOS were younger (mean ±SD: 63.56 ±8.44 years vs 60.66 ±9.13 years, respectively $p<0.001$), more likely to be female (56.3% vs 47.8% males, $X^2(1, N=3695) = 8.44$, $p=0.004$), less likely to be Caucasian (78.1% vs 68.5% Caucasian, $X^2(1, N=3695) = 15.11$, $p<0.001$), and smoked less (mean ±SD: 53.39 ±27.49 pack-years vs 47.98 ±27.71 pack-years, respectively $p=0.001$). Participants with ACOS also scored higher on the SGRQ (mean ±SD: 40.36 ±21.90 points vs 46.52 ±21.25 points, $p<0.001$), and reported lower self-perceived general health than participants with COPD only (37.1% vs 44.6% scored 1 or 2 points, $X^2(4, N=3693) = 10.98$, $p=0.027$). Several measures of pulmonary structure and function were also different between the two groups, with participants with ACOS having higher FVC (% predicted) (mean ±SD: 76.07 ±17.17% vs 79.33 ±17.43%, $p=0.001$), higher BDR (% FEV1) (mean ±SD: 8.31

±12.64% vs 15.07 ±17.30%, p<0.001), greater airway wall thickness (mean ±SD: 2.73 ±0.56 units vs 2.92 ±0.64 units, p<0.001), and less percent emphysema (mean ±SD: 13.60 ±13.09% vs 10.58 ±10.74%, p<0.001). Lastly, participants with ACOS were more likely to report experiencing severe COPD exacerbations (21.9% vs 30.6%, $X^2(1, N=3695) = 12.19$, p<0.001) and more likely to report experiencing frequent COPD exacerbations (16.9% vs 30.6%, $X^2(1, N=3695) = 35.98$, p<0.001) than participants with COPD only. Participants with ACOS tended to report inhaled corticosteroid use more frequently and current smoking less frequently than participants with COPD only, but these trends did not reach statistical significance. Baseline BMI, GOLD scores, BODE scores, 6-minute walk test results, FEV1 (% predicted), and percent gas trapping on CT scans were all similar between the two groups.

Table 3: Demographic and health characteristics of the study cohort at baseline.

	Baseline (N= 3695)		
	COPD only	ACOS	
	(N = 3381)	(N = 314)	p-value*
Mean (SD)			
BMI	28.01 (6.25)	28.62 (6.70)	0.101
Age (in years)	63.56 (8.44)	60.66 (9.13)	<0.001
Pack years of smoking	53.39 (27.49)	47.98 (27.71)	0.001
SGRQ score (total)	40.36 (21.90)	46.52 (21.25)	<0.001
6-minute walk test distance	1171.28 (397.62)	1200.83 (390.07)	0.213
FVC (% predicted)	76.07 (17.17)	79.33 (17.43)	0.001
FEV1 (% predicted)	50.15 (18.07)	51.26 (16.94)	0.296
BDR (% FEV1)	8.31 (12.64)	15.07 (17.30)	<0.001
% Gas trapping	38.70 (20.56)	37.36 (19.66)	0.316
% Emphysema	13.60 (13.09)	10.58 (10.74)	<0.001
Airway wall thickness	2.73 (0.56)	2.92 (0.64)	<0.001
N (%)			
Gender (male)	1903 (56.3%)	150 (47.8%)	0.004
Race (Caucasian)	2640 (78.1%)	215 (68.5%)	<0.001

SRGH score 1	268 (7.9%)	31 (9.9%)	0.027
2	986 (29.2%)	109 (34.7%)	
3	1403 (41.5%)	127 (40.4%)	
4	626 (18.5%)	38 (12.1%)	
5	96 (2.8%)	9 (2.9%)	
Smoking status (current)	2019 (59.7%)	172 (54.8%)	0.088
GOLD score 2	1753 (51.8%)	172 (54.8%)	0.367
3	1065 (31.5%)	99 (31.5%)	
4	563 (16.7%)	43 (13.7%)	
BODE score 0	498 (15.1%)	34 (11.1%)	0.274
1	484 (14.7%)	42 (13.7%)	
2	487 (14.8%)	57 (18.6%)	
3	507 (15.4%)	53 (17.3%)	
4	485 (14.7%)	41 (13.4%)	
5	411 (12.5%)	47 (15.4%)	
6	308 (9.4%)	21 (6.9%)	
7	86 (2.6%)	10 (3.3%)	
8	15 (0.5%)	1 (0.3%)	
9	8 (0.2%)	0 (0.0%)	
10	2 (0.1%)	0 (0.0%)	
Severe Exacerbations (yes)	742 (21.9%)	96 (30.6%)	<0.001
Frequent Exacerbations (yes)	573 (16.9%)	96 (30.6%)	<0.001
Inhaled Corticosteroids (yes)	397 (12.2%)	48 (16.0%)	0.055

**p-value for COPD only vs ACOS, t-test (means) or chi-square test (proportions)*
BMI: body-mass index; SGRQ: Saint George's respiratory questionnaire; FVC: forced vital capacity; FEV1: Forced expiratory volume in one second; BDR: bronchodilator response; SRGH: self-reported general health; GOLD: global initiative for obstructive lung disease; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity

Similarly, univariate demographic and health status information for study participants at the 5-year follow-up visit is summarized below in Table 4. At follow-up, participants with ACOS were again younger (mean ±SD: 69.04 ±8.25 years vs 66.16 ±8.52 years, respectively $p<0.001$), more likely to be female (53.6% vs 43.4% males, $X^2(1, N=2099) = 6.96$, $p=0.008$), less likely to be Caucasian (79.8% vs 72.5% Caucasian, $X^2(1, N=2099) = 5.27$, $p=0.022$), and

smoked less (mean ±SD: 53.00 ±25.87 pack-years vs 47.18 ±24.42 pack-years, p=0.004) than participants with COPD only. Participants with ACOS again scored higher on the SGRQ than participants with COPD only (mean ±SD: 36.88 ±21.01 points vs 40.84 ±21.85 points, p=0.021) but self-reported general health was similar between the two groups (unlike at baseline). As with the baseline visit, measures of pulmonary structure and function were also different between the two groups at follow-up, with participants with ACOS having higher FVC (% predicted) (mean ±SD: 75.30 ±16.89% vs 78.39 ±17.37%, p=0.028), higher BDR (% FEV1) (mean ±SD: 9.15 ±11.04% vs 12.77 ±13.60%, p<0.001), greater airway wall thickness (mean ±SD: 2.68 ±0.55 units vs 2.85 ±0.62 units, p<0.001), and less percent emphysema (mean ±SD: 12.90 ±12.89% vs 10.56 ±11.09%, p=0.034). At follow-up, participants with ACOS were still more likely to report experiencing severe COPD exacerbations than participants with COPD only (19.4% vs 28.7%, $X^2(1, N=2080) = 8.85$, p=0.003), but the two groups were equally likely to report experiencing frequent COPD exacerbations, making this the only other measurement (along with SRGH score) that changed in terms of the presence of a statistically significant difference between baseline and follow-up. Inhaled corticosteroid use, smoking status, BMI, GOLD scores, BODE scores, 6-minute walk test results, FEV1 (% predicted), and percent gas trapping on CT scans were all similar between the two groups at follow-up, just as they were at baseline. A summary of these demographic and health characteristics at baseline using only the follow-up cohort (n=2,099) is included in the appendices.

Table 4: Demographic and health characteristics of the study cohort at follow-up.

	Follow-up (N= 2099)	

	COPD only	ACOS	
	(N = 1917)	(N = 182)	p-value*
Mean (SD)			
BMI	28.12 (6.37)	28.92 (6.93)	0.130
Age (in years)	69.04 (8.25)	66.16 (8.52)	<0.001
Pack years of smoking	53.00 (25.87)	47.18 (24.42)	0.004
SGRQ score (total)	36.88 (21.01)	40.84 (21.85)	0.021
6-minute walk test distance	1094.14 (432.65)	1146.54 (420.43)	0.149
FVC (% predicted)	75.30 (16.89)	78.39 (17.37)	0.028
FEV1 (% predicted)	51.71 (18.76)	53.09 (17.64)	0.374
BDR (% FEV1)	9.15 (11.04)	12.77 (13.60)	<0.001
% Gas trapping	38.70 (20.41)	36.06 (20.68)	0.153
% Emphysema	12.90 (12.89)	10.56 (11.09)	0.034
Airway wall thickness	2.68 (0.55)	2.85 (0.62)	<0.001
N (%)			
Gender (male)	1028 (53.6%)	79 (43.4%)	0.008
Race (Caucasian)	1529 (79.8%)	132 (72.5%)	0.022
SRGH score 1	113 (6.7%)	10 (6.0%)	0.226
2	466 (27.4%)	60 (35.9%)	
3	755 (44.5%)	68 (40.7%)	
4	302 (17.8%)	24 (14.4%)	
5	62 (3.7%)	5 (3.0%)	
Smoking status (current)	1351 (71.1%)	124 (68.5%)	0.456
GOLD score 2	686 (42.6%)	72 (45.3%)	0.333
3	515 (32.0%)	49 (30.8%)	
4	227 (14.1%)	18 (11.3%)	
BODE score 0	277 (18.0%)	28 (18.8%)	0.327
1	253 (16.4%)	17 (11.4%)	
2	281 (18.2%)	26 (17.4%)	
3	235 (15.2%)	26 (17.4%)	
4	230 (14.9%)	27 (18.1%)	
5	165 (10.7%)	21 (14.1%)	
6	69 (4.5%)	2 (1.3%)	
7	26 (1.7%)	1 (0.7%)	
8	7 (0.5%)	1 (0.7%)	
Severe Exacerbations (yes)	369 (19.4%)	52 (28.7%)	0.003
Frequent Exacerbations (yes)	273 (14.2%)	29 (15.9%)	0.534
Inhaled Corticosteroids (yes)	147 (8.0%)	17 (9.7%)	0.445

**p-value for COPD only vs ACOS, t-test (means) or chi-square test (proportions)*
BMI: body-mass index; SGRQ: Saint George's respiratory questionnaire; FVC: forced vital capacity; FEV1: Forced expiratory volume in one second; BDR: bronchodilator response; SRGH: self-reported general health; GOLD: global initiative for obstructive lung disease; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity

Longitudinal Analyses

Changes in disease progression between participants with ACOS and COPD only are summarized in Table 5, below. Change in BMI, pack-years of smoking, six-minute walk test results, FVC (% predicted), and FEV1 (% predicted) were similar for the two groups. CT based measures of percent gas trapping, percent emphysema, and airway wall thickness were also similar between participants with ACOS and COPD only. Frequency of increases or decreases in BODE scores, GOLD scores, and self-reported general health scores were approximately the same in participants with ACOS compared to participants with COPD only. Both groups were also equally like to quit or re-start smoking, or to develop or lose severe COPD exacerbations. By contrast, participants with ACOS were more likely to lose frequent COPD exacerbations ($X^2(2, N=2099) = 26.44$, $p<0.001$), more likely to lose a BDR ($X^2(2, N=1757) = 28.53$, $p<0.001$), and more likely to discontinue or initiate inhaled corticosteroid use ($X^2(2, N=1951) = 6.36$, $p=0.042$) than participants with COPD only. Change in BDR (% FEV1) (mean ±SD: 0.60 ±15.42% vs -3.18 ±18.98%, p=0.004) and SGRQ scores (mean ±SD: 1.77 ±15.75 vs -1.57 ±15.94, p=0.009) were also different between the two groups.

Table 5: Change in demographic characteristics of the study cohort from baseline to follow-up with descriptive statistics.

	Follow-up (N= 2099)	

	COPD Only (N=1917)	ACOS (N=182)	p-value*
Mean (SD)			
Change in BMI	-0.39 (3.17)	-0.36 (3.88)	0.937
Change in pack years	1.29 (2.31)	1.16 (1.89)	0.463
Change in SGRQ score	1.77 (15.75)	-1.57 (15.94)	0.009
Change in 6 min walk distance	-187.11 (370.03)	-149.35 (349.48)	0.226
Change in FVC (% predicted)	-4.06 (14.12)	-4.16 (14.61)	0.932
Change in FEV1 (% predicted)	-3.09 (11.09)	-2.77 (10.37)	0.723
Change in BDR (%FEV1)	0.60 (15.42)	-3.18 (18.98)	0.004
Change in % gas trapping	3.98 (10.20)	3.96 (10.71)	0.986
Change in % emphysema	1.75 (5.42)	1.40 (4.92)	0.451
Change in airway wall thickness	0.02 (0.42)	-0.01 (0.43)	0.376
N (%)			
Change in BODE score (increase)	508 (33.3%)	30 (20.1%)	0.742
(decrease)	296 (19.4%)	45 (30.2%)	
Change in GOLD score (increase)	312 (19.4%)	26 (16.4%)	0.611
(decrease)	266 (16.5%)	29 (18.2%)	
Change in SRGH score (increase)	505 (29.8%)	48 (28.7%)	0.922
(decrease)	325 (19.2%)	31 (18.6%)	
Develop severe exacerbations	254 (13.4%)	30 (16.6%)	0.393
Lose severe exacerbations	229 (12.1%)	24 (13.3%)	
Develop frequent exacerbations	185 (9.7%)	15 (8.2%)	<0.001
Lose frequent exacerbations	178 (9.3%)	39 (21.4%)	
Initiate inhaled corticosteroids	93 (5.2%)	13 (7.6%)	0.042
Discontinue inhaled corticosteroids	130 (7.3%)	20 (11.7%)	
Quit smoking	244 (12.8%)	25 (13.8%)	0.726
Re-start smoking	38 (2.0%)	5 (2.8%)	
Develop BDR	308 (19.3%)	13 (8.2%)	<0.001
Lose BDR	328 (20.5%)	59 (37.1%)	

**p-value for COPD only vs ACOS, t-test (means) or chi-square test (proportions)*
BMI: body-mass index; SGRQ: Saint George's respiratory questionnaire; FVC: forced vital capacity; FEV1: Forced expiratory volume in one second; BDR: bronchodilator response; SRGH: self-reported general health; GOLD: global initiative for obstructive lung disease; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity

As shown in Table 6, beta coefficients for ACOS were not different from zero for the models predicting change in percent emphysema, change in percent gas trapping, change in airway wall thickness, or change in six-minute walk test scores. However, the beta coefficient

for ACOS in the model predicting change in SGRQ score (β coefficient (95% confidence interval): -2.81 (-5.33, -0.282), p=0.029) was different from zero. For each model, variance inflation factors were all less than 5.0, the link test p-value was greater than 0.05, the Ramsey Regression Equation Specification Error Test p-value was greater than 0.05, and Cook's distance was less than 1.0. The Breusch-Pagan test and Shapiro-Wilk's both rejected the null hypothesis for each of the models tested, however when the residual plots were examined it was determined that the rejection of these tests was likely due to the large sample size in the study, as the plots did not display large deviations from the model assumptions.

Table 6: Beta coefficients for the effect of ACOS versus COPD only on the changes in continuous outcomes from baseline to follow-up.

Outcome	β coefficient (95% CI)
change in % emphysema	-0.21 (-1.12, 0.71)
change in % gas trapping	-0.05 (-1.99, 1.90)
change in airway wall thickness	-0.02 (-0.01, 0.05)
change in SGRQ score	-2.81 (-5.33, -0.28)
change in 6-min walk test score	23.8 (-37.8, 85.3)
All models adjusted for the following baseline covariates: BMI, pack-years of smoking, gender, race, age, and current smoking status. (BMI: body-mass index; SGRQ: St. George's respiratory questionnaire)	

As shown in Table 7 below, relative risk ratios (RRRs) for changes in BODE scores, GOLD scores, the development or loss of severe COPD exacerbations, and the development of frequent COPD exacerbations were not different in participants with ACOS compared to participants with COPD only. However, the RRRs for the loss of frequent COPD exacerbations (RRR (95% CI): 2.43 (1.63, 3.63)) and the loss (RRR= 2.00 (1.40, 2.86)) or development (RRR= 0.47 (0.26, 0.87)) of a BDR were different in participants with ACOS compared to

participants with COPD only. For each model, the IIA assumption was met, and the data were determined to be case- specific, thus meeting the assumptions necessary for using the multinomial logistic regression model.

Table 7: Relative risk ratio (RRR) estimates for the effects of ACOS versus COPD only on the change in categorical outcomes from baseline to follow-up.

Outcome (*vs no change*)	RRR (95% CI)
BODE score	
Decrease in BODE score	0.89 (0.57, 1.40)
Increase in BODE score	0.85 (0.57, 1.26)
GOLD score	
Decrease in GOLD score	0.97 (0.63, 1.50)
Increase in GOLD score	0.82 (0.52, 1.30)
Exacerbations	
Loss of frequent exacerbations	2.43 (1.63, 3.63)
Development of frequent exacerbations	0.85 (0.48, 1.49)
Loss of severe exacerbations	1.05 (0.67, 1.67)
Development of severe exacerbations	1.34 (0.88, 2.06)
BDR	
Loss of BDR	2.00 (1.40, 2.86)
Development of BDR	0.47 (0.26, 0.87)
All models adjusted for the following baseline covariates: BMI, pack-years of smoking, gender, race, age, and current smoking status. (BMI: body-mass index; BDR: bronchodilator response; GOLD: global initiative for obstructive lung disease; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity)	

DISCUSSION

The current study used data collected during the COPDGene cohort study to investigate the presence and magnitude of differences in disease progression between subjects with ACOS and those with COPD only. Prior research has failed to reach a consensus regarding whether

people with ACOS represent a distinct patient subgroup, with different disease trajectories from patients with COPD only.[39,40] Overall, the current study suggested that, at a particular point in time, subjects with ACOS do have reduced quality of life and greater evidence of reactive airway disease compared to subjects with COPD only. However, the magnitude of changes in disease outcomes over time were very similar between the two groups, with the exceptions of SGRQ scores, frequent exacerbation status, and BDR status.

Rates of ACOS in the current study (using Sin *et al.'s* definition) were lower than those reported in previous studies using only self-reported history of asthma to define ACOS (current study: 8.5%, previous studies 12.6%[13] - 13%[17], $p<0.001$). However, because there is no "gold standard" test to assess ACOS, it is impossible to say whether the current rate represents less misclassification, or is merely different from previous studies. Subject characteristics in the current study were consistent with previous research indicating female gender, non-Caucasian race, lower pack-years of smoking, and younger age were significantly associated with ACOS compared to COPD only.[13,17] These subject characteristics remained consistently different between the study groups at the five-year follow-up visit, further suggesting that a causal mechanism may be at play. Similarly, SGRQ scores were consistently higher in subjects with ACOS across the study timepoints, meaning that ACOS was associated with lower quality of life throughout the five-year follow-up period. ACOS was further associated with higher FVC (% predicted), higher BDR (% FEV1), greater airway wall thickness, and less percent emphysema at both baseline and follow-up, suggesting that clinical parameters of airway disease are different in these patients. Specifically, these patients appear to have both a

restrictive and reactive lung disease rather than a purely obstructive lung disease. Not surprisingly perhaps, subjects with ACOS were more also likely to report experiencing severe COPD exacerbations and a history of chronic bronchitis than their COPD only counterparts at both timepoints. This observation further enhances the idea of ACOS as a mixed phenotype of reactive, restrictive, and obstructive airway disease that, when exacerbated, may be expected to produce severe respiratory distress.

As mentioned previously, the primary hypothesis of the current study was that ACOS patients would display disease *progression* characteristics that were distinct from patients with COPD only. Specifically, ACOS patients were expected to have greater decreases in measures of lung function, be more likely to develop frequent or severe COPD exacerbations, and experience greater reductions in quality of life compared to patients with COPD only. Indeed, the current study found that the magnitude of change in BDR (% FEV1) and SGRQ scores was different in subjects with ACOS versus COPD only. On average, subjects with ACOS experienced a 3.18% decrease in BDR (%FEV1), meaning that the degree of irreversible airway limitation increased over the study period. Such progression has been associated with increased risk of severe asthma perturbations and declines in lung function due to inflammation- mediated structural remodeling of the airways.[41]

SGRQ scores for participants with ACOS declined by an average of 1.57 points, while scores for participants with COPD alone increased by 1.77 points on average. However, as mentioned previously, the minimum meaningful difference for the SGRQ metric is 4 points.[38] Therefore, while these differences may be statistically significant, their practical significance

may be limited. Such a difference could be explained by normal variations in SGRQ scores across different settings. Participants with ACOS were also more likely to lose frequent COPD exacerbations, more likely to lose a BDR, and more likely to discontinue or initiate inhaled corticosteroid use than participants with COPD only. Similar to the observed decline in the magnitude of patients' BDR, the loss of a BDR entirely represents a significant advancement of disease, as airflow limitation is no longer reversible in these patients. Changes in the use of inhaled corticosteroids may also be indicative of increasing disease severity, as these drugs are useful for controlling bronchial hyperreactivity and their cessation may be due to the development of steroid resistant lung disease or comorbidities for which the use of steroids is contraindicated.[42] The significance of the loss of frequent COPD exacerbations in subjects with ACOS is less clear. This trend does not appear to be due to differential loss to follow-up, as subjects with ACOS who experienced frequent exacerbations at baseline were not more likely to be lost to follow up than those who did not experience frequent exacerbations. Possibly this effect was caused by an unmeasured confounding variable. Because the effects of potential confounding variables cannot be accounted for using univariate methods, this trend was investigated further in the multivariable models described below.

For the multivariable models, adjustment for covariates was done using the *baseline* BMI, pack-years, gender, race, age, and smoking status. Although some authors have raised concerns that adjustment using baseline measurements when the outcome is a change variable may introduce bias, the current study does not meet the criteria identified by these authors as concerning for bias.[43] Furthermore, when adjustment using the change in covariates rather than

baseline covariates was used, the estimated coefficients were nearly identical, suggesting that bias was not a concern in this study. Therefore, the baseline measurements were used for model adjustment, as these variables are more easily interpreted in the context of the current study than the change measurements would have been.

In these longitudinal models, changes in SGRQ score, loss of frequent COPD exacerbations, and the loss or development of a BDR remained significantly different between participants with ACOS compared to participants with COPD only. Changing from COPD only to ACOS status was associated with a 2.81-point decrease in SGRQ score, while controlling for the mentioned covariates. While this average change is less than the minimal important difference of four points, the 95% CI (-5.33, -0.282) includes this value, meaning that it is plausible for ACOS to be associated with a meaningful decrease in SGRQ score.[38] However, most of the 95% CI is less than the minimal important difference, suggesting that we should be cautious about over- interpreting the decrease in SGRQ scores observed in the current study.

Consistent with the unadjusted model, study participants with ACOS had a relative risk for losing frequent COPD exacerbations that was 2.43 (95% CI: 1.63, 3.63) times the relative risk of experiencing no change in frequent exacerbations, when the covariates were included. This consistency lends weight to the idea that there is something about having ACOS that reduces the risk of experiencing two or more COPD exacerbations per year. Possibly it is just differential classification of exacerbation events in these subjects as related to the patient's

asthma diagnosis rather than their concurrent COPD diagnosis, leading to the (incorrect) appearance of a reduction in COPD exacerbations. However, it is also possible that one or more of the treatments used to mitigate asthma may also be having a positive effect on COPD severity in these patients. Indeed, current research investigating the use of anti-eosinophil therapies (currently used to treat severe eosinophilic asthma) for the prevention of exacerbations and mortality in patients with COPD supports this idea.[8,44]

Lastly, participants with ACOS were 2.00 (95% CI: 1.40, 2.86) times more likely to experience the loss of a BDR, and 0.474 (95% CI 0.258, 0.869) times less likely to develop a BDR during the follow up period compared to experiencing no change in their BDR status. This is perhaps the most important finding of the current study because it suggests a trend in patients with ACOS to become more "COPD-like" over time, lending credence to the idea that COPD and ACOS may represent a continuous spectrum of a single disease rather than two distinct patient subtypes.[19] Persistence of airflow limitation in both ACOS and COPD patients could be linked to structural remodeling of the lungs caused by increased activity of the proteolytic enzymes known as matrix metalloproteinases, specifically matrix metalloproteinase 9 (MMP-9). MMP-9 has been associated with disease severity in independent studies of patients with asthma and COPD.[45–47] Thus, the MMP-9/ tissue inhibitor of MMP (TIMP) axis may represent a future avenue of treatment that warrants further investigation. Taken together, these data suggest that ACOS, rather than being a distinct pathophysiological phenotype, may instead represent an imperfect proxy for an unrecognized

underlying inflammatory response that perhaps accounts for the wide variation in symptom severity seen in patients with COPD.

Limitations and Future Directions

The current study does have a few limitations to consider. First, to ensure enough subjects in each category to allow race to be used as a covariate, the COPDGene study only enrolled non-Hispanic Caucasian and African American subjects, and therefore may not be generalizable to populations with greater racial or ethnic diversity. Future studies are thus still needed to determine the prevalence of ACOS in populations that are more racially diverse than the current study. Additionally, as with all longitudinal studies, this study suffered from loss to follow-up. Comparison of participants who were lost to follow up with participants who completed the study revealed many significant differences between these two study populations. Specifically, participants who were lost to follow up appeared to be those most severely affected in terms of both quality of life and symptom severity. While this phenomenon is not uncommon in epidemiologic studies, it represents a potential source of bias and should be acknowledged.[48]

Lastly, ACOS status had to be retrospectively abstracted from data that were not collected for the purpose of making this determination. It is likely that this process resulted in some unknown degree of misclassification, and the observed effects might have been different if the study had used data where ACOS status was assessed directly. Direct methods of exposure assessment are generally more reliable than indirect methods, and any improvement

in the reliability of exposure assessment can reduce bias and improve statistical power of a study.[49] For example, if ACOS misclassification occurred due to imperfect data abstraction in the current study, and was non-differential with respect to the outcome(s), the observed trends will have been underestimated. Further studies using direct assessment of ACOS are still needed to determine if such biases have clouded the current understanding of ACOS and COPD.

In the future, it will also be important to investigate whether the observed trends are continued long-term. Phase three of the COPDGene study (the ten-year follow-up visits) will give us an opportunity to examine whether or not, and to what degree, the trends observed in this study persist. Expanding on the idea of an unrecognized inflammatory perturbation underlying COPD severity, the impact of adaptive (Th2) immunity in chronic diseases has come under increasing scrutiny, and the contribution of such Th2- driven inflammation to disease progression in COPD and ACOS should be investigated.[4,8,50] For example, $CD4^+/CD8^+$ T-cell ratios, cytokines, and chemokines could be measured in peripheral blood and/ or bronchoalveolar lavage fluid.[51] Such studies could inform the potential use of emerging biologic therapies to improve quality of life and reduce the burden of COPD and ACOS.[52,53]

CONCLUSION

The current study addressed an important gap in the literature, namely how COPD *progression* differs in patients with ACOS versus COPD only. The data presented here are

largely consistent with the previous study by Hardin *et al.* examining differences between patients with ACOS versus COPD only. However, Hardin *et al.*'s study was only able to include baseline data for the first 2,500 subjects enrolled in the COPDGene cohort, and defined ACOS simply as having COPD and a prior physician's diagnosis of asthma.[13] As such, the current study represented an innovative approach by using the new consensus definition of ACOS and by including all patients enrolled at baseline, as well as including patients with five-year follow-up data. This study identified many differences in cross-sectional disease severity between subjects with ACOS compared with COPD only. The longitudinal approaches applied in the current study also identified a reduction of frequent COPD exacerbations in patients with ACOS, suggesting that treatment strategies currently reserved for asthmatics may benefit those with COPD as well, while the loss of a BDR in these patients suggests that prevention of airway remodeling may also be an important topic for future research.

APPENDICES

Table A.1: Demographic and health characteristics of the follow-up cohort at baseline.

	Baseline (N= 2099)		
	COPD only	ACOS	
	(N = 1917)	(N = 182)	p-value*
Mean (SD)			
BMI	28.57 (6.11)	29.23 (6.49)	0.165
Age (in years)	63.41 (8.22)	60.52 (8.67)	<0.001
Pack years of smoking	51.69 (25.50)	46.65 (25.53)	0.011
SGRQ score (total)	35.77 (21.21)	42.99 (21.44)	<0.001
6-minute walk test distance	1260.10 (364.00)	1297.14 (353.23)	0.193
FVC (% predicted)	78.92 (15.90)	82.14 (16.53)	0.009
FEV1 (% predicted)	54.05 (16.41)	54.79 (15.12)	0.559
BDR (% FEV1)	8.39 (12.03)	15.80 (17.07)	<0.001
% Gas trapping	36.10 (19.23)	35.06 (18.90)	0.522
% Emphysema	11.88 (11.71)	9.76 (9.93)	0.020
Airway wall thickness	2.66 (0.55)	2.87 (0.66)	<0.001
N (%)			
Gender (male)	1028 (53.6%)	79 (43.4%)	0.008
Race (Caucasian)	1529 (79.8%)	132 (72.5%)	0.022
SRGH score 1	91 (4.8%)	11 (6.0%)	0.115
2	494 (25.8%)	61 (33.5%)	
3	814 (42.5%)	72 (39.6%)	
4	444 (23.2%)	31 (17.0%)	
5	72 (3.8%)	7 (3.8%)	
Smoking status (current)	1161 (60.6%)	105 (57.7%)	0.449
GOLD score 2	1151 (60.0%)	114 (62.6%)	0.564
3	597 (31.1%)	56 (30.8%)	
4	169 (8.8%)	12 (6.6%)	
BODE score 0	362 (19.1%)	28 (15.7%)	0.507
1	325 (17.2%)	28 (15.7%)	
2	331 (17.5%)	39 (21.9%)	
3	308 (16.3%)	31 (17.4%)	
4	267 (14.1%)	20 (11.2%)	
5	184 (9.7%)	21 (11.8%)	
6	93 (4.9%)	7 (3.9%)	

7	20 (1.1%)	4 (2.2%)	
8	2 (0.1%)	0 (0.0%)	
Severe Exacerbations (yes)	349 (18.2%)	47 (25.8%)	0.012
Frequent Exacerbations (yes)	266 (13.9%)	53 (29.1%)	<0.001
Inhaled Corticosteroids (yes)	191 (10.3%)	23 (13.1%)	0.055

**p-value for COPD only vs ACOS, t-test (means) or chi-square test (proportions)*
BMI: body-mass index; SGRQ: Saint George's respiratory questionnaire; FVC: forced vital capacity; FEV1: Forced expiratory volume in one second; BDR: bronchodilator response; SRGH: self-reported general health; GOLD: global initiative for obstructive lung disease; BODE: body-mass index, airflow obstruction, dyspnea, and exercise capacity

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