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Asthma is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline: Five-year Follow-up in Adult Smokers from the COPDGene Study

Lystra P. Hayden, MD, MMSc, Megan E. Hardin, MD, MPH, Weiliang Qiu, PhD, David A. Lynch, MD, Matthew J. Strand, PhD, Edwin J. van Beek, MD, PhD, James D. Crapo, MD, Edwin K. Silverman, MD, PhD, Craig P. Hersh, MD, MPH

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Running Title: **Asthma, Respiratory Exacerbations, and Active COPD**

Lystra P. Hayden, MD, MMSc[1,2], Megan E. Hardin, MD, MPH[3], Weiliang Qiu, PhD[2], David A. Lynch, MD[4], Matthew J. Strand, PhD[5], Edwin J. van Beek MD, PhD[6], James D. Crapo, MD[7], Edwin K. Silverman, MD, PhD[2,8], Craig P. Hersh, MD, MPH[2,8] on behalf of the COPDGene Investigators*.

[1] Division of Respiratory Diseases, Boston Children's Hospital, Boston, MA; [2] Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA; [3] Clinical Discovery Unit, Early Clinical Discovery, AstraZeneca, Waltham, MA; [4] Department of Radiology, National Jewish Health, Denver, CO; [5] Division of Biostatistics and Bioinformatics, National Jewish Health, Denver, CO; [6] Department of Radiology, University of Edinburgh, Edinburgh, Scotland, UK; [7] Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO; [8] Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA.

Corresponding author: Lystra P. Hayden, MD, MMSc, Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, Lystra.Hayden@childrens.harvard.edu

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2) Childhood Pneumonia Is A Risk Factor For COPD Development But Not Disease Progression In The COPDGene Study. Poster discussion. American Thoracic Society International Conference, Washington, DC, May 21, 2017.

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ABSTRACT

Background
Previous investigations in adult smokers from the COPDGene Study have shown that early-life respiratory disease is associated with reduced lung function, COPD, and airway thickening. Using five-year follow-up data we assessed disease progression in subjects with early-life respiratory disease. We hypothesized that there are alternative pathways to reaching reduced FEV_1 and subjects with childhood pneumonia, childhood asthma, or asthma-COPD overlap (ACO), would have less lung function decline than subjects without these conditions.

Methods
Subjects returning for five-year follow-up were assessed. Childhood pneumonia was defined by self-reported pneumonia at <16 years. Childhood asthma was defined as self-reported asthma diagnosed by a health-professional at <16 years. ACO was defined as COPD subjects with self-reported asthma diagnosed by a health-professional at ≤40 years. Smokers with and without these early-life respiratory diseases were compared on measures of disease progression.

Results
Follow-up data from 4,915 subjects was examined, including 407 childhood pneumonia subjects, 323 childhood asthmatics, and 242 ACO subjects. History of childhood asthma or ACO was associated with in increased exacerbation frequency (childhood asthma $p<0.001$;ACO $p=0.006$), and odds of severe exacerbations (childhood asthma OR1.41;ACO OR1.42). History of childhood pneumonia was associated with increased exacerbations in COPD subjects ($\beta=0.17$;$p=0.04$). None of these early-life respiratory diseases were associated with increased rate of lung function decline or progression on CT scan.

Conclusions
Subjects with early-life asthma are at increased risk of developing COPD, and having more active disease with more frequent and severe respiratory exacerbations, without increased rate of lung function decline over a five-year period.

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INTRODUCTION

Early life respiratory conditions, including pneumonia and asthma, increase risk for developing chronic obstructive pulmonary disease (COPD).[1-5] Classically, COPD is thought of as a disease of adult smokers, characterized by rapid lung function decline.[3,6] An emerging subtype of COPD is being defined in a subset of subjects who, due to childhood respiratory disease, never achieve the expected maximal FEV_1 in young adulthood.[1,5,7] These patients are more likely reach the diagnostic threshold for COPD even with normal age-related lung function decline.[3] Understanding progression of COPD in this population will be an important factor in personalizing management and treatment plans.

We have previously examined subjects with childhood pneumonia, childhood asthma, and asthma-COPD overlap (ACO) in Phase 1 of COPDGene, a multicenter observational cohort of adult smokers.[1,8-10] Childhood pneumonia was associated with reduced lung function, COPD, and increased airway disease on chest computed tomography (CT).[1] Childhood asthma was associated with smaller segmental airways.[9] ACO subjects were younger with a lower lifetime smoking intensity, but similar FEV_1 reductions as non-ACO COPD subjects, implying an additional mechanism for their reduced lung function.

The current study used five-year follow-up data from Phase 2 of COPDGene to examine disease progression in three independent subject groups of current and former smokers: childhood pneumonia, childhood asthma, and ACO. We hypothesized that these early life respiratory diseases will identify subjects with less lung function decline at the time of five-year follow-up. To assess this, we have independently compared subjects from this cohort in three separate analyses (1) subjects with versus without childhood pneumonia, (2) subjects with versus without childhood asthma, and (3) subjects with ACO versus those with COPD alone (e-Figure 1).

MATERIALS AND METHODS

Study Subjects

COPDGene enrolled 10,199 current and former smokers with and without COPD in Phase 1 from 2008–2011. This investigation evaluates the first 4,915 subjects returning for five-year follow-up in Phase 2 (September 24,2016 data set) (e-Figure1). This study was approved by the Institutional Review Boards at each of the twenty-one clinical sites and all participants provided written informed consent.[10] At enrollment subjects were 45–80 years old, non-Hispanic white or African American, and had at least a 10 pack-year smoking history. Subjects were excluded if they had history of lung disease other than COPD or asthma, if they were nonsmokers, or if they had undergone lung transplant or lung volume reduction surgery. Study protocol, enrollment criteria, and data collection forms were previously described and are available at www.copdgene.org.[10,11]

Participants completed a modified American Thoracic Society Respiratory Epidemiology Questionnaire, Modified Medical Research Council dyspnea scale, and questionnaires related to demographics and medical history.[11-13] Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) with permissions obtained for instrument use.[14] Subjects completed a standardized spirometry protocol (ndd EasyOne Spirometer, Zurich, Switzerland) before and after albuterol. Quantitative image analysis used Thirona software (www.thirona.eu). Inspiratory and expiratory chest CT scans were available for 72% and 62% of Phase 2 participants, respectively. Emphysema was quantified by inspiratory scan low-attenuation areas < -950 Hounsfield units (HU), and by the adjusted density of lung HU below which 15% of the voxels had the lowest attenuation numbers at full inspiration. Gas trapping was quantified on expiratory scan at < -856 HU . Parametric response mapping (PRM) paired inspiratory and expiratory CT images to define emphysema, and to assess functional small airways disease as a measure of non-emphysematous air trapping.[15] Airway measurements assessed the square root of the wall

area of a hypothetical airway with 10mm internal perimeter (SRWA-Pi10) and were available for 20% of participants.[16,17]

Statistical Analysis

Childhood pneumonia was defined by self-report of first pneumonia at < 16 years or during childhood.[1] Childhood asthma was defined as self-report of asthma diagnosed by a health professional with age of onset at < 16 years or during childhood.[1,18] ACO was defined as subjects with COPD who self-reported asthma diagnosed by a health professional with age of onset at ≤ 40 years or during childhood.[1,8,18,19] COPD was defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 spirometry grades 2-4, corresponding to post-bronchodilator forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) ratio < 0.7 with FEV_1 < 80% predicted.[20]

Mortality data was compiled using the social security death index through the COPDGene Longitudinal Follow-up Program (September 2016 dataset). Interval development of COPD diagnosis was defined if a subject did not have GOLD grade 2-4 COPD at visit 1 but did at visit 2. Chronic bronchitis was defined by cough and phlegm production lasting at least three months per year for at least two years. Respiratory exacerbations were defined by use of antibiotics and/or systemic steroids for an acute respiratory illness. Severe exacerbations required an emergency room visit or hospitalization.

We performed three independent comparisons: (1) subjects with versus without childhood pneumonia, (2) subjects with versus without childhood asthma, and (3) subjects with ACO versus COPD alone (e-Figure 1). Demographics, respiratory symptoms/diseases, lung function, and chest CT scan measurements were assessed using R v3.1.1. Tests used and covariates adjusted for are detailed in Tables 1-4 and supplement e-Tables 1-2. Multivariable analyses used logistic regression, linear regression, or linear mixed models. Linear mixed models assessed two measures per subject, comparing visits 1 and 2, with intercept computed at the level of subject, the only variable considered as a random effect. Subjects with missing or unclassifiable responses were removed from specific analyses.

To assess association with COPD exacerbations, a sensitivity analysis was performed among only the subset of subjects who had GOLD Stage 2-4 COPD at the time of initial enrollment. Exacerbation severity, frequency, and rate of lung function decline were compared independently in COPD subjects with and without childhood pneumonia, and those with and without childhood asthma.

RESULTS

Subject classification and characteristics

Of 10,199 adult smokers enrolled, 857 (8.4%) had childhood pneumonia, 730 (7.2%) had childhood asthma and 569 (5.6%) had ACO (Table 1, e-Table 1). Five-year follow-up data on 4,915 subjects was examined; 19 subjects who had undergone interval lung transplant or lung volume reduction surgery were excluded. Disease progression analysis in Phase 2 included 407 (47%) of childhood pneumonia subjects, 323 (44%) of childhood asthmatics and 242 (43%) of ACO subjects. Overlap between subject classifications can be seen in Figure 1. Childhood pneumonia subjects were older, more likely to be non-Hispanic white, and had a longer smoking history compared to subjects without childhood pneumonia. Childhood asthma subjects were younger and more likely to be African American than those without childhood asthma. ACO subjects were more likely to be younger, female, African American, and have fewer pack-years smoking than COPD subjects without ACO.

Mortality

Of 10,199 adult smokers enrolled at Phase 1, mortality data was available for 8,901 (87%). Deceased subjects included 116 (14%) childhood pneumonia subjects, 84 (12%) of childhood asthmatics, and 103 (18%) of ACO subjects (e-Figure 1). There were no statistically significant differences in mortality

among subjects with childhood pneumonia, childhood asthma, or ACO in analysis adjusted for gender, age, race, FEV_1, pack-years smoking, and current smoking ($p>0.5$ for all analyses).

Disease Progression

Supplemental e-Table 1 shows univariate associations with childhood pneumonia, childhood asthma, and ACO. In multivariable models, childhood pneumonia was not associated with disease progression by lung function, clinical symptoms including severity and frequency of respiratory exacerbations, or chest CT scan measurements of emphysema and airway disease (Table 2).

Compared to those without childhood asthma, subjects with childhood asthma had increased frequency of respiratory exacerbations (β=0.22 exacerbations/year; $p<0.001$) and increased odds ratio of having had a severe exacerbation in the prior year (OR 1.41;95%CI 1.00-1.96) (Table 3). Subjects with childhood asthma showed less FVC decline (β=58.44ml;p=0.02) and borderline significance for less FEV_1 decline (β=32.10ml;p=0.053). Childhood asthmatics had a statistically significant, but not clinically significant, improvement in quality of life based on improvement in SGRQ total score (β=-2.40 points;p=0.01).[21] On chest CT, there were no differences in progression of emphysema and airway disease.

Compared to subjects with COPD only, ACO subjects had increased frequency of exacerbations (β=0.20 exacerbations/year;p=0.006) and increased odds of a severe exacerbation (OR 1.42;95%CI 1.00-2.00) (Table 4). They had a statistically but not clinically significant improvement in SGRQ total score (β=-2.89 points;p=0.007). There was no difference in the rate of decline in FEV_1 or FVC. On chest CT, ACO subjects had less progression of emphysema and air trapping compared to COPD subjects, but no difference in progression of airway wall thickening.

Sensitivity Analysis

There were 1,613 subjects with GOLD stage 2-4 COPD at enrollment who returned for five-year follow-up. Among COPD subjects, a history of childhood pneumonia was associated with increased frequency of respiratory exacerbations (β=0.17;p=0.04) when compared to subjects without childhood pneumonia (e-Table 2); there was no significant increase in severe exacerbations or the rate of lung function decline. COPD subjects with childhood asthma did not have increased frequency or severity of respiratory exacerbations when compared to those without childhood asthma; there was an association with slower rate of decline in FVC (β=91.64ml;p=0.04).

DISCUSSION

This investigation used five-year follow-up data from 4,915 adult smokers to examine disease activity and progression independently in those with childhood pneumonia, childhood asthma, and ACO. Childhood asthma and ACO were associated with increased disease activity, with more frequent and severe exacerbations, but not with disease progression defined by lung function decline and chest CT changes. Childhood asthmatics had less lung function decline, and ACO subjects had less progression of CT emphysema and air trapping. Childhood pneumonia was associated with increased respiratory exacerbations among COPD subjects, with no increase in the rate of lung function decline.

We have previously established that, in adult smokers from COPDGene, early life respiratory diseases are associated with reduced lung function and COPD.[1,8,9,18] Childhood pneumonia was associated with increased odds of developing COPD (OR 1.40;95%CI 1.17-1.66), with the greatest risk among those with asthma and pneumonia in childhood (OR 1.85;95%CI 1.10-3.18).[1] Childhood asthma was associated with smaller segmental airways, which was a risk for decreased FEV_1 and chronic airflow obstruction.[9] ACO subjects, compared to those with COPD alone, were younger, with lower lifetime smoking intensity, and increased exacerbation frequency.[8,18]

Other cohorts have shown that asthma and wheezy bronchitis are associated with COPD risk.[22] In the Childhood Asthma Management Program, 11% of 1,041 participants met spirometric criteria for COPD by age 30, and analysis of lung growth trajectories showed a subset with reduced lung growth.[5] The Aberdeen WHEASE cohort followed 330 subjects to age 61, showing that childhood asthma and wheeze were associated with COPD development.[23] The Melbourne Asthma Cohort found that childhood asthma conferred a thirty-two-fold adjusted odds of developing COPD. In 45 year follow-up among 1,389 Tasmanian children, low childhood lung function was associated with COPD and ACO.[24] These associations are likely due to reduced lung growth in patients with childhood respiratory disease causing a decrease in maximally attained lifetime FEV_1, and increasing probability that natural decline in lung function will lead to diagnostic levels of COPD. This concept is supported by prior description of lung function trajectories, which showed that current and former smokers with low FEV_1 in early adulthood can develop COPD based only on natural lung function decline.[7]

In this study, childhood asthmatics and ACO subjects were frequent exacerbators, yet did not have significantly increased rate of lung function decline or emphysema progression at five-year follow-up. This is contrary to previous descriptions of frequent exacerbators in COPDGene where there was an association between frequent exacerbations and excess FEV_1 decline.[25] This difference is likely due to the fact that in our current study we examined frequent exacerbators who were early life asthmatics. Asthmatic subjects may have different drivers of exacerbations than usual COPD subjects, as well as a slower rate of lung function decline. Our current investigation of disease progression in asthmatics supports work from the European Community Respiratory Health survey examining 218 ACO subjects and showing they had less FEV_1 decline than COPD subjects at 4-12 year follow-up, but higher hospitalization rates.[26] Similarly, in 55 subjects from an Australian cohort, ACO was not associated with longitudinal lung function decline over four years.[27]

This study expands our understanding of the natural history of COPD in smokers with childhood respiratory disease, and highlights the significance of early life asthma. Early life asthma is a known risk factor for developing COPD. Our study reveals that disease progression is distinctly different for these subjects, who experience more frequent and severe exacerbations, but without significantly increased rate of lung function decline. In fact, these subjects appeared to be protected from decline in lung function (childhood asthma) or progression of emphysema (ACO). In a sensitivity analysis looking at only subjects with COPD, childhood pneumonia was associated with more frequent exacerbations without any difference in rate of lung function decline, and childhood asthma was associated with less FVC decline.

This study is limited by the use of self-reported history of pneumonia and asthma. Ideally, medical records of diagnoses would be available; however, in this large study of adult subjects, this would have required childhood records, which was not feasible. Self-reported diagnosis has been shown to be effective at revealing meaningful subsets of subjects with early life respiratory disease in our prior investigations in this cohort, which have included sensitivity analysis for recall bias.[1,8,9,28] It would be optimal to examine disease progression in non-smokers, however, this COPDGene investigation did not include data on non-smokers. This is an important area for future investigation.

This study examines disease progression at five-year follow-up in approximately half of the original cohort. A limitation in this population with significant morbidity is a concern for selection bias. Ideally, we would include all original subjects in longitudinal analysis. Of the original 10,199 subjects enrolled, 6,056 (59%) have been accounted for, including 1,141 deaths, and 4,915 subjects with Phase 2 data; additional efforts are ongoing to bring back more subjects. The CT analysis is limited by data being available only for a subset of Phase 2 subjects, which particularly affected SRWA-Pi10 data.

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CONCLUSIONS

We demonstrate that among a population of adult smokers, early life asthmatics have more active respiratory disease, with increased frequency and severity of exacerbations, but without increased rate of lung function decline or disease progression on chest CT.[22] Early life respiratory diseases are known risk factors for developing COPD.[1-5] COPD in these populations is likely due to lung development progressing along a reduced lung growth trajectory, with maximal expected FEV_1 never being achieved. Thus, these subjects are at risk for reaching the level of COPD even with only typical lung function decline associated with aging. This investigation elucidates the expected course of COPD in at-risk populations, showing that early life respiratory diseases are risk factors for active disease without lung function decline. This supports the idea that there is an alternative pathway to reach COPD in smokers with early life respiratory disease, suggesting a subtype of COPD with a different mechanism of reduced FEV_1. These asthmatic subjects additionally may have different drivers of respiratory exacerbations, and a better understanding this relationship could promote different therapeutic considerations, allowing increased precision in COPD treatment.

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***Collaborating investigators for the COPDGene® Study:** *Administrative Center:* James D. Crapo, MD (PI); Edwin K. Silverman, MD, PhD (PI); Barry J. Make, MD; Elizabeth A. Regan, MD, PhD. *Genetic Analysis Center:* Terri Beaty, PhD; Ferdouse Begum, PhD; Robert Busch, MD; Peter J. Castaldi, MD, MSc; Michael Cho, MD; Dawn L. DeMeo, MD, MPH; Adel R. Boueiz, MD; Marilyn G. Foreman, MD, MS; Eitan Halper-Stromberg; Nadia N. Hansel, MD, MPH; Megan E. Hardin, MD; Lystra P. Hayden, MD, MMSc; Craig P. Hersh, MD, MPH; Jacqueline Hetmanski, MS, MPH; Brian D. Hobbs, MD; John E. Hokanson, MPH, PhD; Nan Laird, PhD; Christoph Lange, PhD; Sharon M. Lutz, PhD; Merry-Lynn McDonald, PhD; Margaret M. Parker, PhD. Dandi Qiao, PhD; Elizabeth A. Regan, MD, PhD; Stephanie Santorico, PhD; Edwin K. Silverman, MD, PhD; Emily S. Wan, MD; Sungho Won *Imaging Center:* Mustafa Al Qaisi, MD; Harvey O. Coxson, PhD; Teresa Gray; MeiLan K. Han, MD, MS; Eric A. Hoffman, PhD; Stephen Humphries, PhD; Francine L. Jacobson, MD, MPH; Philip F. Judy, PhD; Ella A. Kazerooni, MD; Alex Kluiber; David A. Lynch, MB; John D. Newell, Jr., MD; Elizabeth A. Regan, MD, PhD; James C. Ross, PhD; Raul San Jose Estepar, PhD; Joyce Schroeder, MD; Jered Sieren; Douglas Stinson; Berend C. Stoel, PhD; Juerg Tschirren, PhD; Edwin Van Beek, MD, PhD; Bram van Ginneken, PhD; Eva van Rikxoort, PhD; George Washko, MD; Carla G. Wilson, MS. *PFT QA Center, Salt Lake City, UT:* Robert Jensen, PhD. *Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO:* Douglas Everett, PhD; Jim Crooks, PhD; Camille Moore, PhD; Matt Strand, PhD; Carla G. Wilson, MS. *Epidemiology Core, University of Colorado Anschutz Medical Campus, Aurora, CO:* John E. Hokanson, MPH, PhD; John Hughes, PhD; Gregory Kinney, MPH, PhD; Sharon M. Lutz, PhD; Katherine Pratte, MSPH; Kendra A. Young, PhD.

COPDGene® Study Clinical Centers *Ann Arbor VA:* Jeffrey L. Curtis, MD; Carlos H. Martinez, MD, MPH; Perry G. Pernicano, MD. *Baylor College of Medicine, Houston, TX:* Nicola Hanania, MD, MS; Philip Alapat, MD; Mustafa Atik, MD; Venkata Bandi, MD; Aladin Boriek, PhD; Kalpatha Guntupalli, MD; Elizabeth Guy, MD; Arun Nachiappan, MD; Amit Parulekar, MD. *Brigham and Women's Hospital, Boston, MA:* Dawn L. DeMeo, MD, MPH; Craig Hersh, MD, MPH; Francine L. Jacobson, MD, MPH; George Washko, MD. *Columbia University, New York, NY:* R. Graham Barr, MD, DrPH; John Austin, MD; Belinda D'Souza, MD; Gregory D.N. Pearson, MD; Anna Rozenshtein, MD, MPH, FACR; Byron Thomashow, MD. *Duke University Medical Center, Durham, NC:* Neil MacIntyre, Jr., MD; H. Page

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McAdams, MD; Lacey Washington, MD. *HealthPartners Research Institute, Minneapolis, MN:* Charlene McEvoy, MD, MPH; Joseph Tashjian, MD. *Johns Hopkins University, Baltimore, MD:* Robert Wise, MD; Robert Brown, MD; Nadia N. Hansel, MD, MPH; Karen Horton, MD; Allison Lambert, MD, MHS; Nirupama Putcha, MD, MHS. *Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA:* Richard Casaburi, PhD, MD; Alessandra Adami, PhD; Matthew Budoff, MD; Hans Fischer, MD; Janos Porszasz, MD, PhD; Harry Rossiter, PhD; William Stringer, MD. *Michael E. DeBakey VAMC, Houston, TX:* Amir Sharafkhaneh, MD, PhD; Charlie Lan, DO. *Minneapolis VA:* Christine Wendt, MD; Brian Bell, MD. *Morehouse School of Medicine, Atlanta, GA:* Marilyn G. Foreman, MD, MS; Eugene Berkowitz, MD, PhD; Gloria Westney, MD, MS. *National Jewish Health, Denver, CO:* Russell Bowler, MD, PhD; David A. Lynch, MB. *Reliant Medical Group, Worcester, MA:* Richard Rosiello, MD; David Pace, MD. *Temple University, Philadelphia, PA:* Gerard Criner, MD; David Ciccolella, MD; Francis Cordova, MD; Chandra Dass, MD; Gilbert D'Alonzo, DO; Parag Desai, MD; Michael Jacobs, PharmD; Steven Kelsen, MD, PhD; Victor Kim, MD; A. James Mamary, MD; Nathaniel Marchetti, DO; Aditi Satti, MD; Kartik Shenoy, MD; Robert M. Steiner, MD; Alex Swift, MD; Irene Swift, MD; Maria Elena Vega-Sanchez, MD. *University of Alabama, Birmingham, AL:* Mark Dransfield, MD; William Bailey, MD; Surya Bhatt, MD; Anand Iyer, MD; Hrudaya Nath, MD; J. Michael Wells, MD. *University of California, San Diego, CA:* Joe Ramsdell, MD; Paul Friedman, MD; Xavier Soler, MD, PhD; Andrew Yen, MD. *University of Iowa, Iowa City, IA:* Alejandro P. Comellas, MD; John Newell, Jr., MD; Brad Thompson, MD. *University of Michigan, Ann Arbor, MI:* MeiLan K. Han, MD, MS; Ella Kazerooni, MD; Carlos H. Martinez, MD, MPH. *University of Minnesota, Minneapolis, MN:* Joanne Billings, MD; Abbie Begnaud, MD; Tadashi Allen, MD. *University of Pittsburgh, Pittsburgh, PA:* Frank Sciurba, MD; Jessica Bon, MD; Divay Chandra, MD, MSc; Carl Fuhrman, MD; Joel Weissfeld, MD, MPH. *University of Texas Health Science Center at San Antonio, San Antonio, TX:* Antonio Anzueto, MD; Sandra Adams, MD; Diego Maselli-Caceres, MD; Mario E. Ruiz, MD.

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TABLES

Table 1: COPDGene Phase 2 Subject Characteristics

	Childhood Pneumonia	No Childhood Pneumonia	P-value	Childhood Asthma	No Childhood Asthma	P-value	Asthma-COPD Overlap	COPD	P-value
Phase 1 Subjects (%)	N = 857	N = 9306		N = 730	N = 9417		N = 569	N = 3110	
Phase 2 Subjects (%)	407 (47%)	4491 (48%)	0.69	323 (44%)	4563 (48%)	0.03	242 (43%)	1359 (44%)	0.64
Male gender (%)[a]	202 (50%)	2269 (51%)	0.77	157 (49%)	2312 (51%)	0.51	107 (44%)	760 (56%)	0.001
Mean age, year (SD)[c]	67 (8)	65 (9)	<0.001	64 (8)	66 (9)	<0.001	65 (8)	69 (8)	<0.001
Non-Hispanic white (%)[a]	350 (86%)	3165 (70%)	<0.001	200 (62%)	3305 (72%)	<0.001	157 (65%)	1099 (81%)	<0.001
African American (%)[a]	57 (14%)	1326 (30%)		123 (38%)	1258 (28%)		85 (35%)	260 (19%)	
Pack-years of smoking (SD)[b]	50 (27)	44 (24)	<0.001	43 (23)	44 (24)	0.21	46 (24)	53 (26)	<0.001
Current smoking (%)[a]	134 (33%)	1698 (38%)	0.06	125 (39%)	1707 (37%)	0.69	82 (34%)	390 (29%)	0.12
COPD at enrollment (%)[a]	175 (54%)	1429 (41%)	<0.001	152 (61%)	1446 (40%)	<0.001	242 (100%)	1359 (100%)	NA

Abbreviations: *COPD* Chronic Obstructive Pulmonary Disease, *SD* standard deviation. Univariate analysis with [a] Chi-square [b] Wilcoxon rank sum test [c] t-test.

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Table 2: Disease Progression in Childhood Pneumonia

	Childhood Pneumonia	No Childhood Pneumonia	Impact of Childhood Pneumonia[a] OR	95% CI	P-value
	N = 407	N = 4491			
Developed COPD (%)[b,e,f]	30 (7%)	313 (7%)	1.04	(0.69, 1.52)	0.84
Developed oxygen requirement (%)[b.e.f]	32 (8%)	286 (6%)	1.09	(0.73, 1.59)	0.66
Developed chronic bronchitis (%)[b,e,f,h]	31 (8%)	359 (8%)	0.92	(0.61, 1.33)	0.66
Had a severe COPD exacerbation in prior yr (%)[b,e,f,g,h]	48 (12%)	411 (9%)	1.23	(0.87, 1.71)	0.23
			β	SE	P-value
Number of COPD exacerbations in prior yr, mean (SD)[c,e,f,g,h]	0.42 (0.86)	0.30 (0.79)	0.06	0.04	0.10
FEV1 post-BD % predicted, mean Δ (SD)[d,e]	-1.64 (11)	-1.98 (11)	0.33	0.55	0.54
FEV_1 post-BD mL, mean Δ (SD)[d,e,f,i]	-196 (279)	-202 (287)	8.32	15.03	0.58
FVC post-BD % predicted, mean Δ (SD)[d,e]	-1.83 (12)	-2.11 (12)	0.30	0.62	0.63
FVC post-BD mL, mean Δ (SD)[d,e,f,i]	-250 (417)	-248 (424)	3.56	22.52	0.87
St. George's Respiratory Questionnaire score, mean Δ (SD)[d,e,f,g]	-0.57 (17)	0.29 (15)	model does not converge		
Modified Medical Research Council dyspnea scale, mean Δ (SD)[d,e,f,g]	-0.05 (1.13)	0.07 (1.24)	-0.11	0.06	0.09
6 minute walk distance in feet, mean Δ (SD)[d,e,f,g]	-154 (333)	-129 (363)	-23.90	18.85	0.21
CT Scan Measures[k]					
<u>Emphysema Progression</u>					
PRM Emphysema % at -950 HU, mean Δ (SD)[d,e,f,h,j]	0.45 (4)	0.71 (3)	-0.03	0.20	0.86
Adjusted density, mean Δ (SD)[d,e,f,h,j]	-0.05 (12)	-0.83 (11)	-0.33	0.50	0.51
<u>Air Trapping Progression</u>					
Gas Trapping %, expiratory scan at -856 HU, mean Δ (SD)[d,e,f,h,j]	1.14 (9)	1.21 (9)	0.48	0.51	0.34
PRM functional small airway disease, mean Δ (SD)[d,e,f,h,j]	1.09 (7)	0.92 (7)	0.56	0.43	0.19
<u>Airway Thickening Progression</u>					
SRWA-Pi10 (SD), mean Δ (SD)[d,e,f,h,j]	0.06 (0.29)	0.04 (0.30)	0.02	0.03	0.57

Abbreviations: *COPD* chronic obstructive pulmonary disease; *yr* year; *SD* standard deviation; *FEV_1* forced expiratory volume in the first second; *BD* bronchodilator; *FVC* forced vital capacity; *CT* computed tomography; *PRM* parametric response mapping; *HU* Hounsfield units; *SRWA-Pi10* square root wall area of a hypothetical airway with 10mm internal perimeter. [a] Each row is a separate model: [b] Logistic regression with odds ratio (OR), 95 % confidence interval (CI); [c] Linear regression and [d] Linear mixed model with beta coefficient (β), standard error (SE). Adjusted for: [e] pack-years of smoking; [f] gender, age, race; [g] FEV_1 % predicted; [h] current smoking; [i] height; [j] scanner model, BMI; [k] data available for only a portion of the population.

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Table 3: Disease Progression in Childhood Asthma

	Childhood Asthma	No Childhood Asthma	Impact of Childhood Asthma[a]		
			OR	95% CI	P-value
	N = 323	N = 4563			
Developed COPD (%)[b,e,f]	27 (8%)	317 (7%)	1.22	(0.80, 1.81)	0.34
Developed oxygen requirement (%)[b.e.f]	23 (7%)	295 (6%)	1.26	(0.78, 1.92)	0.31
Developed chronic bronchitis (%)[b,e,f,h]	28 (9%)	359 (8%)	1.26	(0.82, 1.87)	0.27
Had a severe COPD exacerbation in prior yr (%)[b,e,f,g,h]	52 (16%)	406 (9%)	1.41	(1.00, 1.96)	0.04
			β	SE	P-value
Number of COPD exacerbations in prior yr, mean (SD)[c,e,f,g,h]	0.59 (1.08)	0.29 (0.77)	0.22	0.04	<0.001
FEV1 post-BD % predicted, mean Δ (SD)[d,e]	-1.48 (12)	-1.98 (10)	0.47	0.60	0.44
FEV_1 post-BD mL, mean Δ (SD)[d,e,f,i]	-168 (303)	-204 (284)	32.10	16.61	0.05
FVC post-BD % predicted, mean Δ (SD)[d,e]	-0.73 (13)	-2.15 (12)	model does not converge		
FVC post-BD mL, mean Δ (SD)[d,e,f,i]	-188 (432)	-252 (421)	58.44	24.84	0.02
St. George's Respiratory Questionnaire score, mean Δ (SD)[d,e,f,g]	-2.22 (18)	0.39 (15)	-2.40	0.88	0.01
Modified Medical Research Council dyspnea scale, mean Δ (SD)[d,e,f,g]	-0.02 (1.26)	0.07 (1.23)	-0.08	0.07	0.25
6 minute walk distance in feet, mean Δ (SD)[d,e,f,g]	-151 (385)	-130 (360)	-27.21	20.93	0.19
CT Scan Measures[k]					
Emphysema Progression					
PRM Emphysema % at -950 HU, mean Δ (SD)[d,e,f,h,j]	0.61 (4)	0.68 (3)	-0.29	0.23	0.20
Adjusted density, mean Δ (SD)[d,e,f,h,j]	-1.33 (12)	-0.72 (11)	0.17	0.58	0.77
Air Trapping Progression					
Gas Trapping %, expiratory scan at -856 HU, mean Δ (SD)[d,e,f,h,j]	1.19 (9)	1.19 (9)	-0.78	0.60	0.20
PRM functional small airway disease, mean Δ (SD)[d,e,f,h,j]	0.97 (8)	0.93 (7)	-0.41	0.51	0.42
Airway Thickening Progression					
SRWA-Pi10 (SD), mean Δ (SD)[d,e,f,h,j]	0.07 (0.33)	0.04 (0.30)	0.03	0.04	0.41

Abbreviations: *COPD* chronic obstructive pulmonary disease; *yr* year; *SD* standard deviation; *FEV_1* forced expiratory volume in the first second; *BD* bronchodilator; *FVC* forced vital capacity; *CT* computed tomography; *PRM* parametric response mapping; *HU* Hounsfield units; *SRWA-Pi10* square root wall area of a hypothetical airway with 10mm internal perimeter. [a] Each row is a separate model: [b] Logistic regression with odds ratio (OR), 95 % confidence interval (CI); [c] Linear regression and [d] Linear mixed model with beta coefficient (β), standard error (SE). Adjusted for: [e] pack-years of smoking; [f] gender, age, race; [g] FEV_1 % predicted; [h] current smoking; [i] height; [j] scanner model, BMI; [k] data available for only a portion of the population.

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Table 4: Disease Progression in Asthma-COPD Overlap (ACO)

			Impact of ACO[a]		
	ACO	COPD	OR	95% CI	P-value
	N = 242	N = 1359			
Developed oxygen requirement (%)[b.e.f]	33 (14%)	207 (15%)	0.97	(0.64, 1.45)	0.90
Developed chronic bronchitis (%)[b,e,f,h]	24 (10%)	155 (11%)	0.90	(0.55, 1.42)	0.67
Had a severe COPD exacerbation in prior yr (%)[b,e,f,g,h]	60 (25%)	237 (17%)	1.42	(1.00, 2.00)	0.05
			β	SE	P-value
Number of COPD exacerbations in prior yr, mean (SD)[c,e,f,g,h]	0.81 (1.23)	0.56 (1.03)	0.20	0.07	0.006
FEV1 post-BD % predicted, mean Δ (SD)[d,e]	-2.53 (11)	-2.64 (11)	0.10	0.76	0.89
FEV_1 post-BD mL, mean Δ (SD)[d,e,f,i]	-160 (313)	-188 (306)	22.70	21.73	0.30
FVC post-BD % predicted, mean Δ (SD)[d,e]	-2.81 (14)	-3.69 (14)	0.84	0.97	0.39
FVC post-BD mL, mean Δ (SD)[d,e,f,i]	-239 (466)	-314 (506)	65.68	35.85	0.07
St. George's Respiratory Questionnaire score, mean Δ (SD)[d,e,f,g]	-1.09 (17)	1.84 (15)	-2.89	1.06	0.007
Modified Medical Research Council dyspnea scale, mean Δ (SD)[d,e,f,g]	0.09 (1.26)	0.22 (1.29)	-0.13	0.09	0.16
6 minute walk distance in feet, mean Δ (SD)[d,e,f,g]	-156 (356)	-189 (370)	23.60	25.94	0.36
CT Scan Measures[k]					
<u>Emphysema Progression</u>					
PRM Emphysema % at -950 HU, mean Δ (SD)[d,e,f,h,j]	1.14 (5)	2.14 (5)	-0.97	0.41	0.02
Adjusted density, mean Δ (SD)[d,e,f,h,j]	-2.05 (11)	-3.32 (11)	1.27	0.67	0.06
<u>Air Trapping Progression</u>					
Gas Trapping %, expiratory scan at -856 HU, mean Δ (SD)[d,e,f,h,j]	1.57 (11)	3.72 (10)	-2.19	0.89	0.01
PRM functional small airway disease, mean Δ (SD)[d,e,f,h,j]	0.96 (9)	2.12 (8)	-1.20	0.77	0.12
<u>Airway Thickening Progression</u>					
SRWA-Pi10 (SD), mean Δ (SD)[d,e,f,h,j]	0.08 (0.36)	0.03 (0.34)	0.04	0.06	0.54

Abbreviations: *COPD* chronic obstructive pulmonary disease; *yr* year; *SD* standard deviation; *FEV_1* forced expiratory volume in the first second; *BD* bronchodilator; *FVC* forced vital capacity; *CT* computed tomography; *PRM* parametric response mapping; *HU* Hounsfield units; *SRWA-Pi10* square root wall area of a hypothetical airway with 10mm internal perimeter. [a] Each row is a separate model: [b] Logistic regression with odds ratio (OR), 95 % confidence interval (CI); [c] Linear regression and [d] Linear mixed model with beta coefficient (β), standard error (SE). Adjusted for: [e] pack-years of smoking; [f] gender, age, race; [g] FEV_1 % predicted; [h] current smoking; [i] height; [j] scanner model, BMI; [k] data available for only a portion of the population.

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FIGURES

Figure 1 - Overlapping numbers of subjects as categorized for this study by history of childhood pneumonia, childhood asthma or asthma-COPD overlap (ACO).

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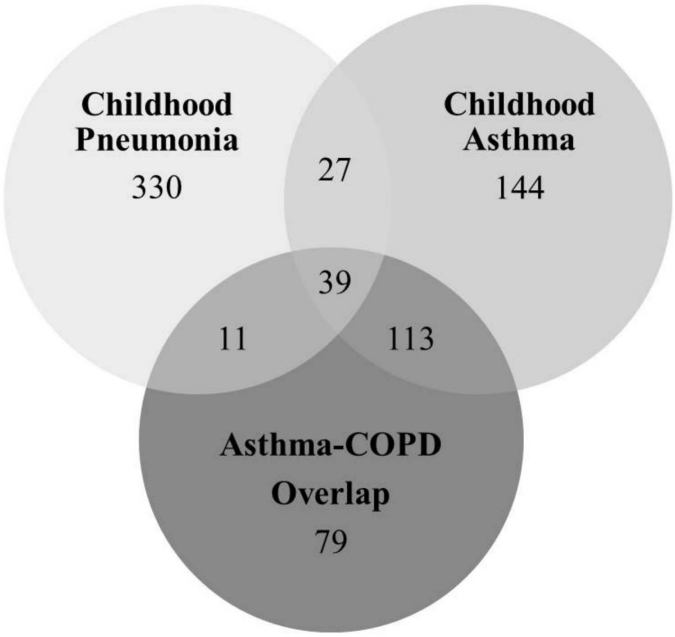

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