Online data supplement

Grading Severity of Productive Cough Based on Symptoms and Airflow Obstruction

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Study design, setting, and populations

This study used the Lovelace Smokers Cohort (LSC) conducted in Albuquerque, New Mexico (USA), a city with a population of approximately 700,000 inhabitants. The LSC is an ongoing prospective cohort study. It was recruited starting in 2001 using radio and television advertisement from Albuquerque and its surrounding communities and patients are followed every 18 months. The average follow-up period was 6 year. The characteristics of the cohort have been published previously [1 2]. Briefly, it includes current or former smokers of predominantly female Hispanic and non-Hispanic white ancestry. Inclusion criteria upon study enrollment were at least 20 pack years of smoking and age between 40 and 75 years. This study was approved by the Western Institutional Review Board (No. 20031684).

The validation population was drawn from the COPDGene cohort, with average follow-up for 5 years [3]. In this cohort, patients were recruited from pulmonary clinics at 21 clinical centers across the USA. Its characteristics include current and former smokers with at least 10 pack years, age between 45 and 80 years of age at enrollment, male and female patients in similar proportions, and non-Hispanic Whites and African Americans. More details can be found at http://www.copdgene.org/study-design.

Institutional Review Board approval

The study in the LSC was approved by the Western Institutional Review Board (Olympia, WA; #20031684) and all subjects gave informed consent for their participation. The multi-center study on the COPDGene was approved by the appropriate IRBs at 21 clinical centers and by the ancillary study oversight committee.

Transition probabilities

A multi-state Markov–like model is used to study transition probabilities. We have previously used this methodology to describe transition probabilities between spirometrically defined states in smokers [4]. Some important concepts underlying this methodology are outlined in this supplement.

In the Markov chain literature, going from one state (prior state) to another (current state), or remaining in the same state during each measurement is called a *transition*. All possible transitions to all-possible states must be represented otherwise the resultant transitions would not add up to a score of "1". In longitudinal analyses we added "*Cough Only*" and "*Fixed Airflow Obstruction*" states to the PC states to ensure all possible transitions were represented.

Chronic bronchitis may have a relapsing-remitting natural history. In diseases where patients do not progress steadily from one state to the next, the use of standard statistical analysis such as survival analysis are difficult and do not provide valuable information about the chances of reversal of a disease state. These probabilities of disease reversal or resolution are important in discussions of prognosis for patients and practicing physicians. Multi-state Markov-like modeling is a more appropriate analysis and provides this important information.

Our analysis is described as a multi-state Markov-like process instead of a Markov chain, because our data does not satisfy the Markov property that requires that each transition be dependent only on the prior state and not on any other previous history. In any multi-state model, transition probabilities are conditional probabilities, that is the transitions depend on prior conditions, but within the natural history of CB, transition to a given

severity state may depend not only on the previous severity state but upon other factors that cannot be accounted for in the model such as changes in smoking behavior or diet. Unlike the natural history of CB, a pure multi-state system able to adhere to strict Markov conditions lends itself to projections far into the future, but due to our real world limitations, we are unable to make use of these rigorous concepts in our manuscript. In our analysis the use of a multi-state Markov-like model allowed us to describe the flow of patients from one state into another, with disease resolution occurring at all PC severity stages, but more frequently among subjects with less severe stages (i.e., Productive Cough), and least among those with Chronic Productive Cough with Signs of Airflow Obstruction.

Sensitivity analysis

Following the same strategy of the staging system in the cohorts, we performed a sensitivity analysis defining the groups based on presence and duration of phlegm, wheeze and FAO, while ignoring the presence or duration of cough and another analysis included patients with concomitant asthma or chronic airflow obstruction alone without phlegm (as previously defined).

Results of the sensitivity analysis

When PC severity categories were alternatively defined by ignoring cough, as opposed to the standard cough productive of phlegm criteria, the severity staging classification remained unchanged in both cohorts (Table e3). Further, including subjects with concomitant asthma or with FAO alone without phlegm resulted in the same ranking as the proposed classification, and FAO alone without phlegm ranked between *chronic*

productive cough and *productive cough with signs of airflow obstruction* in the ordinal severity scale (Table e3).

Table e1. General characteristics of the Lovelace Smokers' and COPDGene cohorts.

	Total n=12,573	COPDGene n=10,300	Lovelace Smokers Cohort n=2,271	p
Age in years	59(9.3)	59.6(9)	55.6(9.5)	<0.001
Male (%)	48	53.2	22.9	<0.001
BMI	28.7(6.3)	28.8(6.3)	28.2(6.4)	<0.001
Obese (%)	36.2	37.2	31.8	<0.001
Current smoker (%)	53	52.6	59.4	<0.001
Packs year	43.7(24.4)	44.2(25)	39.7(21.4)	<0.001
Dust and fumes (%)	54.2	59.1	32.3	<0.001
FEV_1 in liters	2.3(0.9)	2.3(0.9)	2.5(0.8)	<0.001
FVC in liters	3.3(1)	3.3(1)	3.5(0.9)	<0.001
FEV_1/FVC	67.3(15.5)	66.9(16.2)	73.1(10.6)	<0.001
FEV_1% predicted	78.6(24.8)	76.6(25.6)	87.4(18.6)	<0.001
FVC% predicted	88.2(17.9)	87.1(18.3)	93.3(15.3)	<0.001
SGRQ Total	26.2(22.6)	27.1(23)	21.8(17.8)	<0.001
SGRQ symptoms	32.3(26)	32.4(26.1)	31.1(23.3)	0.017
SGRQ activity	37.8(29.8)	39.1(30.5)	31.7(25)	<0.001
SGRQ impacts	17.6(20)	18.8(20.8)	11.8(14.2)	<0.001

Comparison of the development (LSC) and validation (COPD Gene) cohorts. Continuous variables are presented as mean (standard deviation) and proportions as percentages.
BMI: body mass index.
FEV_1: forced expiratory volume in liters during the first second.
FVC: forced vital capacity in liters.
SGRQ: St. George's Respiratory Questionnaire.

Table e2a. General health related quality of life (SF-36) differences between rank ordered Productive Cough severity states in the Lovelace Smokers' Cohort

N=1422	Healthy Smokers n=870	Productive Cough n=81	Chronic Productive Cough n=69	Productive Cough with Signs of Airflow Obstruction n=83	Chronic Productive Cough with Signs of Airflow Obstruction n=319	p value
General health perception	72.9(19.6)[d,e]	71.1(21)[e]	66(20.7)	63(23.6)[a]	60.3(21.6)[a,b]	p<0.001
Role Physical	82.6(32.9)[e]	81.2(33)[e]	79.3(35.3)	80.7(33.2)[e]	69(39.6)[a,b,d]	p<0.001
Physical Functioning	83(21.6)[e]	81.2(22.4)[e]	76.4(23.7)	80.4(18.8)[e]	70.2(25.6)[a,b,d]	p<0.001
Bodily pain	70.2(25)[e]	66.7(22.2)	67.6(26.2)	64.4(23.6)	61.2(25.2)[a]	p<0.001
Vitality	60.4(21.6)[c,d,e]	58.3(21.7)	52.7(19.7)[a]	52.4(21.7)[a]	49.2(23.5)[a,b]	p<0.001
Mental health	76.1(17.7)[d,e]	73.2(18.1)	72.2(20.3)	68.6(19.8)[a]	69.7(21.8)[a]	p<0.001
Role emotional	81.6(35.7)[d,e]	73.7(41.4)	74.4(41.7)	61.8(45.1)[a]	68.3(42.1)[a]	p<0.001
Social functioning	84.9(22.3)[d,e]	79.5(24.5)	80.4(25.1)	71.8(27.3)[a]	75.7(27.6)[a]	p<0.001
SGRQ						
Total score	12.8 ± 12.4[c,d,e]	16.3 ± 11.7[d,e]	18.8 ± 11.3[a,e]	24.4 ± 13.0[a,b,e]	32.5 ± 17.4[a,b,c,d]	P<0.001
Symptoms	16.7 ± 16.1[b,c,d,e]	25.0 ± 10.3[a,d,e]	30.9 ± 12.8[a,d,e]	44.9 ± 18.0[a,b,c,e]	52.0 ± 19.3[a,b,c,d]	p<0.001

St George's Respiratory Questionnaire (SGRQ) and Medical Outcomes Study 36-Item Short Form Health Survey (SF36) measures' mean score ± standard deviation for each rank- ordered chronic bronchitis severity stage.
p values for ANOVA results.
[a, b, c, d, e]: different from a) Healthy Smokers, b)Productive Cough , c) Chronic Productive Cough, d)Productive Cough with Signs of Airflow Obstruction, and e)Chronic Productive Cough with Signs of Airflow Obstruction, respectively in post hoc Tukey's tests

Table e2b. General health related quality of life (SF-36) differences between rank ordered Productive Cough severity states in the COPDGene cohort

N=4488	Healthy smokers, n=2717	Productive Cough n=278	Chronic Productive Cough n=137	Productive Cough with Signs of Airflow Obstruction n=444	Chronic Productive Cough with Signs of Airflow Obstruction n=912	p value
General health perception	73(19.5)[b,c,d,e]	64.2(20.2)[a,e]	57.7(23.2)[a,e]	59.6(20.7)[a,e]	48.8(23)[a,b,c,d]	p<0.001
Role physical	84(23.6)[b,c,d,e]	75.1(28.4)[a,d,e]	73.9(28.3)[a,e]	66.5(28.6)[a,b,e]	57.3(30.9)[a,b,c,d]	p<0.001
Physical functioning	80.7(22.7)[b,c,d,e]	69.1(27.3)[a,e]	68.4(27.4)[a,e]	62.3(26.4)[a,e]	53.2(27.8)[a,b,c,d]	p<0.001
Bodily pain	74.3(24)[b,c,d,e]	67.1(28.3)[a,d,e]	60.1(29.3)[a]	55.9(24.9)[a,b]	58.2(26.5)[a,b]	p<0.001
Vitality	66.3(19.2)[c,d,e]	60.8(19.9)[d,e]	55.4(22.5)[a]	54.1(20.4)[a,b,e]	48.5(22.2)[a,b,d]	p<0.001
Mental health	77.8(17)[c,d,e]	72.8(17.6)[d,e]	70.5(18.8)[a]	65.9(20.7)[a,b]	64.7(21.8)[a,b]	p<0.001
Role emotional	86.8(21.4)[b,c,d,e]	75.8(27.4)[a,e]	77.2(28.9)[a,e]	70.1(28.6)[a]	67.2(30.6)[a,b,c]	p<0.001
Social functioning	86.3(21)[b,c,d,e]	76.9(25.2)[a,e]	77.3(28.8)[a,e]	69.5(26.1)[a,e]	66.1(29.2)[a,b,c]	p<0.001
SGRQ						
Total score	9.7 ± 12.3[b,c,d,e]	18.7 ± 15.8[a,d,e]	21.2 ± 16.0[a,d,e]	31.0 ± 18.3[a,b,c,e]	42.6 ± 21.4[a,b,c,d]	p<0.001
Symptoms	10.7 ± 13.3[b,c,d,e]	27.9 ± 16.5[a,c,d,e]	34.8 ± 14.5[a,c,d,e]	41.7 ± 20.6[a,b,c,e]	57.0 ± 20.0[a,b,c,d]	p<0.001

St George's Respiratory Questionnaire (SGRQ) and Medical Outcomes Study 36-Item Short Form Health Survey (SF36) measures' mean score ± standard deviation for each rank- ordered chronic bronchitis severity stage.
p values for ANOVA results

[a, b, c, d, e]: different from a) Healthy Smokers, b)Productive Cough , c) Chronic Productive Cough, d)Productive Cough with Signs of Airflow Obstruction, and e)Chronic Productive Cough with Signs of Airflow Obstruction, respectively in post hoc Tukey's tests

Table e3: Symptom and Spirometric Predictors of CT-assessed Airway Remodeling.

	Wall area % sub-segmental	Wall area % segmental	Pi10
Self-Reported Wheeze*	0.49(0.25, 0.74)	0.99(0.81, 1.18)	0.02(0.01, 0.03)
FEV1/FVC*	-5.59(-6.18, -5.01)	-4.94(-5.43, -4.46)	-0.09(-0.11, -0.07)

Multivariable linear regression analyses with CT-assessed airway wall thickness measures (i.e., airway wall area % at the sub-segmental and segmental level and Pi10) as outcomes and wheeze and FEV1/FVC as predictors. All models are additionally adjusted for productive cough severity states.
Wall area %segmental and sub-segmental= (Total airway surface – Airway lumen surface/ Total airway surface x 100), averaged for all measured airways at the segmental and sub-segmental levels respectively.
Pi10= root square of the surface of a hypothetical airway with an interior diameter of 10mm.
FEV1/FVC= Forced expiratory volume in the first second/ forced vital capacity.
*= results have a significance level < 0.001.

Table e4. Sensitivity analysis

The effects of (1) asthma defined as a patient reported history of asthma or a positive bronchodilator response – improvement of FEV1 or FVC of 200ml or 12%-, (2) FAO without phlegm and the requirement for the presence of cough for most days of three months for more than 2 consecutive years. Rank ordered the different severity stages according to St George's Respiratory Questionnaire Impact and Activity Sub-scales scores.

	→→→ Increasing SGRQ Impact and Activity Sub-Scales Scores→→→					
LSC proposed classification*	Healthy smokers	Productive Cough	Chronic Productive Cough	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction	
COPD Gene proposed classification*	Healthy smokers	Productive Cough	Chronic Productive Cough	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction	
LSC phlegm only	Healthy smokers	Productive Cough	Chronic Productive Cough	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction	
COPD Gene phlegm only	Healthy smokers	Productive Cough	Chronic Productive Cough	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction	
LSC asthma and CAO	Healthy smokers	Productive Cough	Chronic Productive Cough	Chronic airway obstruction	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction
COPD Gene asthma and CAO	Healthy smokers	Productive Cough	Chronic Productive Cough	Chronic airway obstruction	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction

LSC: Lovelace Smokers Cohort

*Proposed classification: *Healthy smokers* do not produce phlegm or cough; *Productive Cough* and produce phlegm for most days of three month for less than 2 years; *Chronic Productive Cough* and produce phlegm for most days of three months for at least 2 years; *Productive Cough with Signs of Airflow* Obstruction cough and produce phlegm for most days of three month for less than 2 years and have wheeze or fixed airway obstruction; *Chronic Productive Cough with Signs of Airflow Obstruction* cough

and produce phlegm for most days of three month for at least 2 consecutive years and have wheeze or fixed airway obstruction.
Phlegm only: same as proposed classification irrespective of the presence of cough.
Asthma and FAO: same as the proposed classification but does not exclude patients with a reported history of asthma or presence of chronic airway obstruction without phlegm production

Table e5a. Baseline medication use in the Lovelace Smokers Cohort. Percentages are non-exclusive.

N=1422	Healthy Smokers n=870	Productive Cough n=81	Chronic Productive Cough n=69	Productive Cough with Signs of Airflow Obstruction n=83	Chronic Productive Cough with Signs of Airflow Obstruction n=319	p value
LABA	5(0.6%)	1(1.2%)	1(1.4%)	1(1.2%)	17(5.3%)	p<0.001
SABA	3(0.3%)	0	0	1(1.2%)	4(1.3%)	p=0.087
ICS	31(3.6%)	3(3.7%)	3(4.3%)	2(2.4%)	27(8.5%)	p=0.003
SAMA	11(1.3%)	1(1.2%)	1(1.4%)	3(3.6%)	36(11.3%)	p<0.001
LAMA	4(0.5%)	0	0	2(2.4%)	4(1.3%)	p=0.110
ICS +LABA	4(0.5%)	1(1.2%)	1(1.4%)	1(1.2%)	12(4.1%)	p<0.001

Table e5b. Baseline medication use in the COPD Gene. Percentages are non-exclusive.

N=4488	Healthy smokers, n=2717	Productive Cough n=278	Chronic Productive Cough n=137	Productive Cough with Signs of Airflow Obstruction n=444	Chronic Productive Cough with Signs of Airflow Obstruction n=912	p value
LABA	4(0.1)	0	0	3(0.7)	52(5.8)	p<0.001
SABA	100(3.7)	10(3.6)	9(6.6)	72(16.3)	372(41.5)	p<0.001
ICS	13(0.5)	2(0.7)	1(0.7)	8(1.8)	70(7.9)	p<0.001
SAMA	6(0.2)	1(0.4)	1(0.7)	5(1.1)	55(6.2)	p<0.001
LAMA	35(1.3)	7(2.5)	1(0.7)	20(4.5)	224(25)	p<0.001
ICS + LABA	42(1.6)	5(1.8)	3(2.2)	25(5.6)	231(25.8)	p<0.001
SABA + SAMA	19(0.7)	2(0.7)	2(1.5)	22(5)	116(13)	P<0.001

LABA: long acting beta agonist
SABA: Short acting beta agonist
ICS: inhaled corticosteroid
SAMA: short acting muscarinic antagonist
LAMA: long acting muscarinic antagonist
ICS +LABA : an inhaled corticosteroid and a long acting beta agonist in the same inhaler device

Cohort	Healthy smokers,	Productive Cough	Chronic Productive Cough	Productive Cough with Signs of Airflow Obstruction	Chronic Productive Cough with Signs of Airflow Obstruction
LSC FEV1/FVC<LLN, n (%)	5(0.2%)	2(0.7%)	1(0.7%)	11(2.5%)	469(51.4%)
COPD Gene FEV1/FVC<LLN, n (%)	13(1.5%)	0	1(1.4%)	1(1.2%)	124(38.9%)

Table e6. Number and percentage of subjects within each group meeting the fixed airflow obstruction criteria based on the lower limit of normal criteria. LSC: Lovelace Smokers Cohort; FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; LLN: Lower limit of normal calculated as the 5^{th} percentile of NHANES III.

Figure e1: Lovelace Smokers' Cohort population flow diagram.

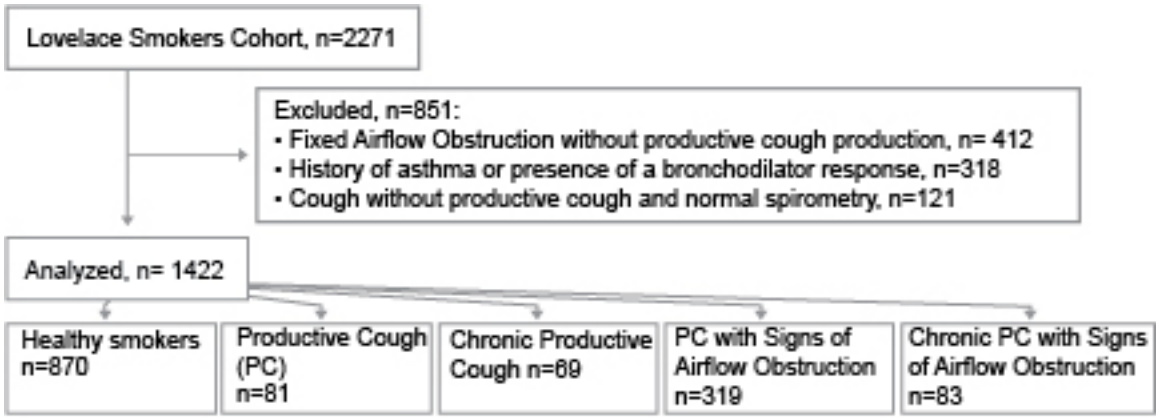
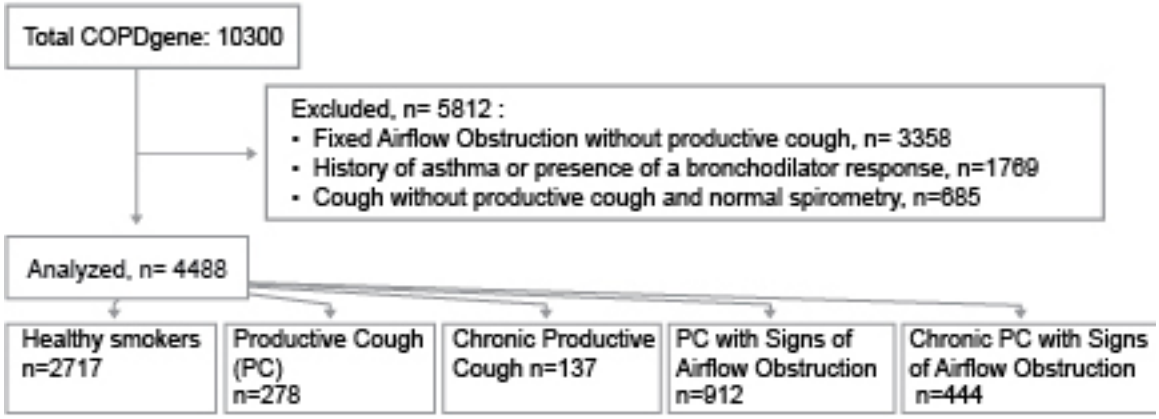


Figure e2: COPDGene population flow diagram.



Flow diagram. Patients were classified according to their answers to the ATS –DLD1978 Questionnaire in: *Healthy smokers* if they answered: Do you bring up phlegm on most days for 3 consecutive months or more during the year? *No* Do you usually cough on most days for 3 consecutive months or more during the year? *No*; *Productive cough* if they answered: Do you bring up phlegm on most days for 3 consecutive months or more during the year? *Yes*, Do you usually cough on most days for 3 consecutive months or more during the year? *Yes* For how many years have you had this trouble? *Less than two*; *Chronic productive cough* if: Do you bring up phlegm on most days for 3 consecutive months or more during the year? *Yes* Do you usually cough on most days for 3 consecutive months or more during the year? *Yes*; For how many years have you had this trouble? *At least two*. *Productive cough with signs of airflow obstruction* if they answered: Do you bring up phlegm on most days for 3 consecutive months or more during the year? *Yes* Do you usually cough on most days for 3 consecutive months or more during the year? *Yes* For how many years have you had this trouble? *Less than two* AND/OR complained of wheeze or had chronic airway obstruction; *Chronic productive cough with signs of airflow obstruction* if they answered: Do you bring up phlegm on most days for 3 consecutive months or more during the year? *Yes* Do you usually cough on most days for 3 consecutive months or more during the year? *Yes* For how many years have you had this trouble? *More than two* AND complained of wheeze and/or had chronic airway obstruction.

Figure e3: The percentage of participants who reported of productive cough or chronic productive cough and had CAO or wheeze only or had combined CAO and wheeze.

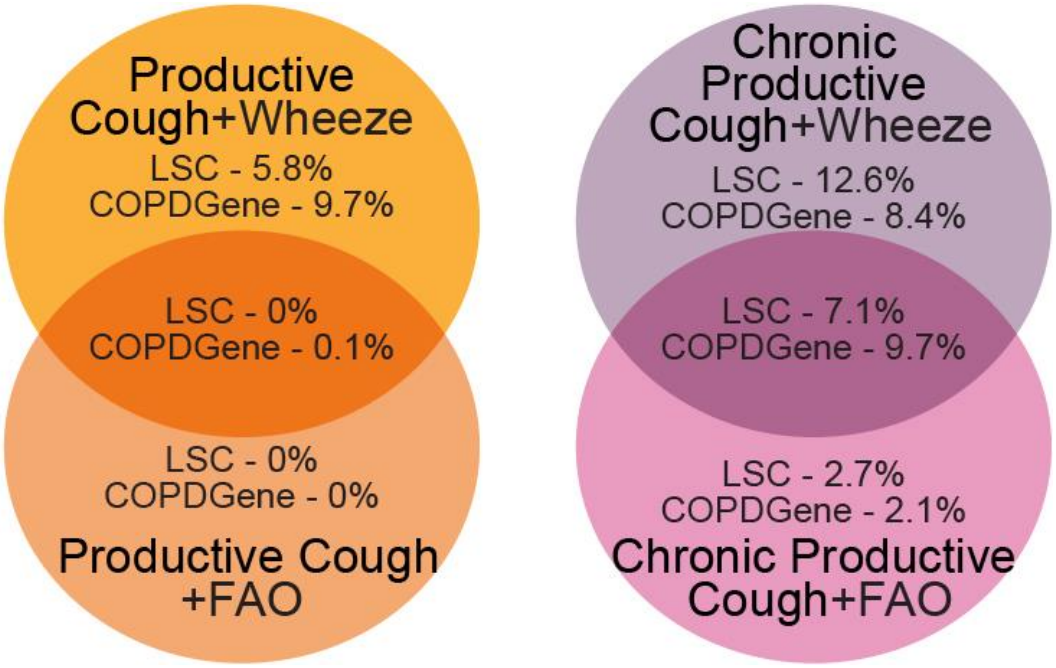
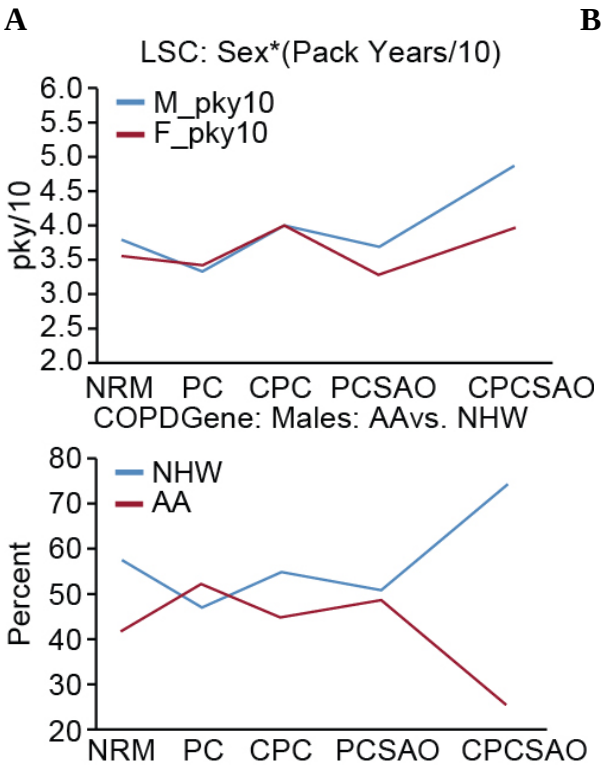


Figure e4: **(A)** Analysis of the interaction between pack-years of smoking and sex on severity of PC states. **(B)** Analysis of the interaction between percent of males and African American or non-Hispanic white ancestry on severity of PC states.
NRM: healthy smokers; PC: Productive Cough; CPC: chronic Productive Cough; PCAR: Productive Cough with Airway Remodeling; CPCAR: Chronic Productive Cough with Airway Remodeling; pky/10: pack decade; M: male; F: female; LSC: Lovelace Smokers Cohort; NHW: non-Hispanic white; AA: African American.



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