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Silent airway mucus plugs in COPD and clinical implications

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Abstract

Background: Airway mucus plugs are frequently identified on computed tomography (CT) scans of patients with COPD with a smoking history without mucus-related symptoms, i.e., cough and phlegm ("silent mucus plugs").

Research Questions: In patients with COPD, what are risk and protective factors associated with silent airway mucus plugs? Are silent mucus plugs associated with functional, structural, and clinical measures of disease?

Study Design and Methods: We identified mucus plugs on chest CT scans of participants with COPD from the COPDGene study. The mucus plug score was defined as the number of pulmonary segments with mucus plugs, ranging from 0 to 18, and categorized into three groups (0, 1-2, and 3+). We determined risk and protective factors for silent mucus plugs and the associations of silent mucus plugs with measures of disease severity using multivariable linear and logistic regression models.

Results: Of 4,363 participants with COPD, 1,739 had no cough or phlegm. Among the 1,739 participants, 627 (36%) had airway mucus plugs identified on CT. Risk factors of silent mucus plugs (compared to symptomatic mucus plugs) were older age (Odds ratio, OR=1.02), female sex (OR=1.40), and Black race (OR=1.93) (all P values < 0.01). Among those without cough or phlegm, silent mucus plugs (vs. absence of mucus plugs) were associated with worse 6-MWD, resting SpO2, FEV1% predicted, greater emphysema, thicker airway walls, and higher odds of severe exacerbation in the past year in adjusted models.

Interpretation: Mucus plugs are common in COPD patients without mucus-related symptoms. Silent mucus plugs are associated with worse functional, structural and clinical measures of disease. CT-identified mucus plugs can complement the evaluation of patients with COPD.

Keywords: COPD, mucus plug, airway, silent mucus plug, chronic bronchitis, chronic mucus hypersecretion, cough, phlegm, emphysema, COPDGene, CT

Mucus plugs are a manifestation of airway pathology, and up to 67% of COPD patients have airway mucus plugs identified on chest computed tomography (CT) scans.[1,2] The presence of mucus plugs on CT is associated with airflow limitation, worse quality of life, and higher all-cause mortality.[1-3]

While it may be intuitive to assume that mucus plugs coincide with chronic bronchitis (also known as chronic mucus hypersecretion), chronic cough and sputum production are frequently absent in individuals with mucus plugs.[4,5] Recent studies found that about 30% of current or former smokers who report no cough or phlegm have airway mucus plugs on CT.[1,2,6] However, the clinical implications of radiographically identified mucus plugs in the absence of cough and phlegm (hereafter termed “silent mucus plugs”) in patients with COPD have not been systematically studied.

In this study, we aimed to identify which participants are more likely to have silent mucus plugs as opposed to symptomatic mucus plugs, and to determine the clinical significance of silent mucus plugs, i.e., associations with outcomes. We used the COPDGene study,[7] a well-characterized cohort of former and current smokers with the full spectrum of COPD severity with CT-based assessment of mucus plugs. We hypothesized that there may be differences in participant characteristics between those with silent mucus plugs and those with symptomatic mucus plugs, and that certain participants characteristics (e.g., age, sex, race, history of asthma) may be associated with silent mucus plugs. We also hypothesized that for participants without cough or phlegm, a higher burden of mucus plugs would be associated with clinical, functional, and structural measures of disease.

Methods

Study design and population

We performed cross-sectional analyses of selected participants of the COPDGene study. The study design and protocols of the COPDGene study have been described previously and can be accessed at www.COPDGene.org (Clinical trial identifier: NCT00608764).[7] Briefly, the COPDGene study is an observational prospective cohort study which included 45- to 80-year-old non-Hispanic White or non-Hispanic Black with a ≥10-pack-year smoking history with or without COPD. Participants were enrolled between 2008 and 2011 (phase 1) and completed questionnaires, pulmonary function tests, and chest CT imaging. The institutional review board at each participating clinical center approved the COPDGene study, and all participants gave written informed consent. All 4,363 participants who had a diagnosis of COPD at the baseline visit, defined by Global Initiative for Obstructive Lung Disease (GOLD) grades 1 (mild) through 4 (very severe), and whose CT imaging quality was adequate to assess mucus plugs were included in this study (Figure 1).

CT assessment

The COPDGene imaging protocols and CT assessment of mucus plugging have been described previously.[1,7] Briefly, baseline CT scans were assessed for mucus plugs by readers who had at least two years of experience in lung imaging and airway mucus plug assessment. Each CT scan was assessed for airway mucus plugs by a first reader. Then all CT scans positive for mucus plugs as well as 20% of the negative scans were independently scored by a second reader. When mucus plug scores were discrepant between the two readers, the images were assessed by a third reader. Middle-to-large airways (i.e., ~2-10-mm lumen diameter) were surveyed. A mucus plug was defined as an opacity that completely occluded the lumen of an airway. Lung parenchyma within 2 cm from the costal or diaphragmatic pleura was excluded, as the airways in those regions are too small to accurately ascertain occlusive luminal plugs. A final mucus plug score for each study participant was assigned based on the number of pulmonary segments with mucus plugs according to Netter's bronchial anatomy nomenclature. The mucus

plug score ranged from 0 (no mucus plugs evident on CT) to 18 (mucus plugs in all pulmonary segments). Participants were categorized into three groups based on their mucus plug scores: 0,1-2, and ≥3 pulmonary segments with mucus plugs, as previously described. The grouping was based on the distribution of mucus plugs in participants with COPD,[3] showing a similar percentage falling into 1-2 and 3+ categories. Further analysis demonstrated an association between 1-2 and 3+ categories and all-cause mortality,[3] supporting its use for the current analysis.

The quantitative assessment of airway wall thickness was performed with Thirona software (Nijmegen, Netherlands). Airway wall thickness was defined as the square root of the wall area of an ideal 10-mm-inner-perimeter airway.[8] We also used parametric response modeling (PRM) estimates of emphysema and functional small airway disease (fSAD).[9,10] Emphysema was defined as low attenuation areas under -950 HU on inspiration and under -856 HU on expiration and small airway disease was defined as low attenuation areas less than -856 HU on expiration but greater than -950 HU on inspiration.[7,10,11] PRM measures of emphysema and fSAD represent the percentage of inspiratory-expiratory matched voxels meeting criteria for those features. Higher values indicate higher burden of emphysema and fSAD.[11] Participants were considered to have emphysema when the affected lung volume was greater than 5%.[9]

Clinical assessment

Participants of the COPDGene study completed standardized questionnaires pertaining to their demographic (age, sex, race, body mass index [BMI]) and clinical information (smoking history, comorbidities, respiratory symptoms).[7,12] Typically, participants completed questionnaires and chest CT scans on the same day. Race was self-reported by participants.

Symptom assessment Symptoms were assessed using the St. George's Respiratory Questionnaire (SGRQ)[13,14] and the American Thoracic Society Division of Lung Disease (ATS-DLD) 1978 Questionnaire.[15] The SGRQ questions are divided into symptom, activity, and

impact components. Each component score ranges from 0 to 100 with higher scores indicating worse health-related quality of life.

History of Asthma and congestive heart failure (CHF) Participants were considered to have a history of asthma if they responded “yes” to the question “have you ever had asthma?”, and a history of CHF if they responded “yes” to the question “have you ever been told by a physician that you have congestive heart failure?”.

Episodes of exacerbation An exacerbation was defined as a new onset of or increase in cough, phlegm, or dyspnea. Participants were also asked whether they had severe COPD exacerbations, defined as episodes requiring hospitalizations, in the past 12 months.

Pulmonary function tests Spirometry was performed before the administration of inhaled bronchodilator (albuterol 180 mcg) and repeated 20 to 30 minutes afterwards. Post-bronchodilator FEV1 % predicted and post-bronchodilator FEV1/FVC ratio are calculated. The third National Health and Nutrition Examination Survey predicted spirometry values were used as reference values for predicted FEV1.[16] COPD was defined as post-bronchodilator FEV1/FVC ratio below 0.70. GOLD grades 1-4 were determined based on FEV1 % predicted values.[17] Our study included participants with COPD with GOLD grades 1 through 4 (Figure 1).

Six-minute walk test The 6-minute walk test measured the distance participants were able to walk in 6 minutes (6-minute walk distance, or 6-MWD) in meter. If participants used supplemental oxygen at baseline, they were allowed to use it during the walk test.

Arterial oxygen saturation Resting arterial oxygen saturation was measured with pulse oximetry (resting SpO2) while participants were at rest in a seated position. If participants used supplemental oxygen at rest, oxygen was withheld, and participants breathed room air for 10 minutes prior to recording SpO2. Supplemental oxygen was restarted if SpO2 fell below 82%.

Definition of silent mucus plug and symptomatic mucus plug

We defined silent mucus plugs as the presence of mucus plugs despite absence of symptoms of chronic mucus hypersecretion, i.e., cough or phlegm, using the SGRQ questions. Participants were considered to have cough or phlegm if they coughed (excluding clearing of the throat) or brought up phlegm almost every day or several days a week in the past 4 weeks (SGRQ questionnaires). Conversely, we defined symptomatic mucus plugs as the presence of mucus plugs on CT imaging along with participant-reported cough and phlegm. We performed the same analysis using cough and phlegm symptoms defined by ATS-DLD questions (see e-Table 1-3). Cough and phlegm questions in the ATS-DLD 1978 questionnaire were “do you usually have a cough excluding clearing of the throat?” and “do you usually bring up phlegm from your chest?”.

Outcomes

Outcomes of interest included 6-MWD, resting arterial oxygen saturation (SpO2), SGRQ scores, post-bronchodilator FEV1% predicted, post-bronchodilator FEV1/FVC ratio, structural changes on CT (e.g., emphysema, wall thickness, small airway disease), and participant-reported severe exacerbations requiring hospitalizations in the past 12 months. These outcomes were measured during the phase 1 visit concurrently with the CT assessment.

Statistical analysis

We compared demographics (age, sex, race), BMI, smoking status, pack year, comorbidities (congestive heart failure or asthma), baseline GOLD stages and lung functional measures between participants with silent mucus plugs and those with symptomatic mucus plugs. We used two sample t-tests when comparing continuous variables between participants with silent vs. symptomatic mucus plugs, univariable linear regression models with the mucus plug score category (0, 1-2, and 3+) as an ordinal variable when comparing continuous

variables between mucus plug score categories, and chi-square tests when comparing categorical variables between groups. To identify risk factors of silent mucus plugs (vs. symptomatic mucus plugs), we performed a multivariable logistic analysis with demographics, BMI, smoking status, pack year, congestive heart failure and asthma as covariates.

We then focused on participants with silent mucus plugs, by assessing the associations of score categories (0, 1-2 and 3+) and outcomes, using *a priori* multivariable linear and logistic regression models. For multivariable regression models, we considered the no mucus plug group as the reference group. For all multivariable models, we adjusted for age, sex, race, BMI, smoking status, pack year, congestive heart failure and asthma.

Statistical significance was defined as *P* values less than 0.05. All analyses were performed using the statistical software R (version 4.2.1).

Results

Airway mucus plugs and symptoms of cough or phlegm

In total 4,363 participants were assessed for airway mucus plugs on chest CT and symptoms of cough and phlegm. Among these, 1,739 participants (40%) did not report cough or phlegm, with 627 (35.3%) having mucus plugs (i.e., “silent mucus plug”). The median mucus plug scores were 2 (Interquartile range or IQR 1-4) and 2.5 (IQR 1-4.67) in participants with silent (n=627) vs. symptomatic mucus plugs (n=1151), respectively. Notably, silent mucus plugs were also frequently found in participants with mucus plug scores of 3 or above (Figure 2).

Upper and middle lobes were more frequently involved in people with silent mucus plugs, whereas lower lobe involvement was more common in people with symptomatic mucus plugs (e-Table 4). These differences were more pronounced in people with mucus plug scores 1-2 than with scores above 3.

Characteristics of individuals with silent vs. symptomatic mucus plugs

We first compared the characteristics of the 1,778 participants with mucus plugs by mucus-related symptoms status (i.e., silent vs. symptomatic mucus plugs, Table 1). The baseline characteristics of individuals without mucus plugs (n=2,585) have been described previously.[3] Compared to those with symptomatic mucus plugs, those with silent mucus plugs were more likely older, female, and former smokers with fewer pack years. These participants also had higher FEV1% predicted, higher percentage of emphysema and lower airway wall thickness on CT scans, and lower SGRQ scores in all domains. There were no significant differences in the distribution of GOLD grades, 6-minute walk distance, resting SpO2, post-bronchodilator FEV1 in liters, and FEV1/FVC. Results were consistent when silent mucus plugs were defined using the ATS-DLD questions (e-Table 1).

In both male and female participants, former smokers were less likely to have symptoms of cough or phlegm than current smokers (Figure 3). Women were more likely to have silent mucus plugs than men regardless of smoking status. The proportion of participants without cough or phlegm was lower in the mucus plug score 3+ group than in the score 1-2 group in all strata (sex and smoking status). Of note, the proportion of former smokers (who quit smoking by the time of the study participation) was 55.5% among male participants and 58.5% in female participants. This difference did not reach statistical significance (Chi-square test p-value = 0.05).

Risk and protective factors of silent mucus plugs

In the multivariable model (Table 2), the risk factors of silent mucus plugs (vs. symptomatic mucus plugs) were older age, female sex, and Black race, while current smoking status and history of asthma were protective factors (i.e., associated with symptomatic mucus plugs rather than silent mucus plugs). BMI, pack years and history of congestive heart failure were not associated with the odds of silent mucus plugs in the multivariable model. When silent

mucus plugs were defined using the ATS-DLD questions, results were consistent with the same direction of effect in all covariates, although race did not reach statistical significance (e-Table 2).

Risk factors of cough and phlegm in the absence of mucus plugs

We also compared the characteristics of participants without mucus plugs (n=2,585) between those with cough and phlegm (n=1,112) vs. those without those symptoms (n=1,473) (e-Table 5). In a multivariable model, male sex, non-Hispanic White race, higher BMI, current smoking status, more pack years, and history of asthma were significantly associated with increased odds of having cough or phlegm symptoms (e-Table 6).

Characteristics of participants without cough and phlegm by mucus plug score category

We then focused on all participants without cough and phlegm symptoms (n= 1,739) to compare their characteristics by mucus plug score (e-Table 7). Compared to participants without mucus plugs, those with a mucus plug score of 3 or higher were more likely to be older, women, former smokers and have lower BMI. They tend to have severe-to-very severe COPD (GOLD grades 3 and 4). These participants also had a shorter 6-MWD and lower resting SpO2. A history of asthma was more common with higher mucus plug burden. SGRQ scores (symptom, activity, impact and total) were higher among those with higher mucus plug burden.

Associations of silent mucus plugs with measures of disease severity

Among asymptomatic individuals, mucus plug score categories of 1-2 and 3 or higher were associated with shorter 6-MWD, lower resting SpO2 and FEV1, more emphysema on CT imaging, thicker airway walls, higher SGRQ scores (i.e., worse quality of life) and greater odds of severe exacerbations in the past 12 months, compared to those with no mucus plug in

adjusted models (Table 3, e-Figure 1). The effect sizes were larger in the mucus plug score category of 3 or higher than the score category of 1-2 for 6-MWD, SGRQ scores, FEV1/FVC, FEV1% predicted, quantitative emphysema, airway wall thickness and small airway disease. Similarly, the odds of exacerbation in the past 12 months were greater in the 3+ than 1-2 category. The results were consistent when we defined silent mucus plugs using the cough and phlegm questions of the ATS-DLD questionnaire (e-Table 3).

Discussion

Recent studies showed associations between mucus plugs identified on CT scans and impaired lung function, worse quality of life, and higher all-cause mortality in patients with COPD.[1-3] In this study we analyzed data from over 4,300 former and current smokers with COPD whose baseline CT scans were assessed for mucus plugs, focusing on participants without cough and phlegm symptoms. We found that older age, female sex, and Black race were risk factors of silent mucus plugs, whereas a history of asthma and current smoking were associated with reduced odds of silent mucus plugging. We also showed that silent mucus plugs were prevalent even in participants with a higher burden of mucus plugs and associated with significant functional, structural, and clinical impairments. Participants with silent mucus plugs had lower exercise capacity, resting SpO2, FEV1, FEV/FVC, worse health-related quality of life, greater emphysema, and thicker airway walls as well as higher odds of having had severe exacerbations in the past 12 months compared to those without mucus plugs.

Chronic cough and phlegm are defining features of chronic bronchitis and are thought to be symptomatic manifestations of mucus dysfunction.[17,18] In recent years, advances in lung

imaging have allowed for more detailed characterization of this airway pathology in COPD. In this study, we used volumetric CT scans to assess mucus plugs in middle-to-large sized airways and found that a large proportion of individuals with airway mucus plugs on CT do not have accompanying symptoms of cough and phlegm. The prevalence of silent mucus plugs observed in our study is in line with data from the SPIROMICS cohort,[2] and in a prior study of patients with asthma.[19] More importantly, in participants with COPD without cough or phlegm, a higher burden of mucus plugs in the lungs was associated with functional and structural impairment. The associations between silent mucus plugs and function and structural impairments held after adjusting for age, sex, race, BMI, smoking status, pack-years and history of congestive heart failure and asthma. The associations between a higher burden of mucus plugs and airflow limitation, lower exercise capacity, and greater CT measures of emphysema and airway wall thickness are consistent with prior studies using COPDGene and SPIROMICS data.[1,2] The present and prior studies further support the use of lung CT to characterize people with COPD, as suggested in recent guidelines.[17,20] Also, the findings suggest mucus plugs may be a potential therapeutic target or can serve as additional selection criteria for clinical trials, although more studies are needed to further delineate these possibilities. Of note, using mucus plugs as a treatment target is under investigation in patients with asthma.[21]

It is unclear why certain individuals with airway mucus plugs present with cough and phlegm and some do not. Notably, even among those with extensive mucus plugs (more than 3 lung segments with mucus plugs) nearly 30% reported no cough or phlegm. We identified several risk factors associated with silent mucus plugs, which were older age, female sex, and Black race. The sensitivity of peripheral cough receptors, which may be influenced by age, could play a role in silent mucus plugs (i.e., an older person might be less sensitive to the same amount of mucus than a younger individual and cough less as a result).[5,22,23] The reasons for

sex difference are unclear but could be related to differences in airway physiology or mucus characteristics that lead to a decreased ability to move mucus proximally.[24] These possibilities could be explored in future studies, for example, of airway physiology or transcriptomic and proteomic data of sputum and epithelial cells. We also found that Black race was associated with increased odds of silent mucus plugs. It is possible that social behavioral (e.g., differences in reporting cough) or environmental factors (e.g., differences in exposure to ambient air pollution and green areas) play a role in racial differences in silent mucus plugs. Additionally, our findings show that current smokers are less likely to have silent mucus plugs compared to former smokers, and more likely to have symptomatic mucus plugs. It is unclear from our results whether current smokers manifest symptoms of cough and phlegm through direct irritation of airways by compounds of cigarettes regardless of the presence of mucus plugs, or whether the characteristics of mucus plugs in smokers are different from those of former smokers. Recent studies showed that expression of specific genes relate to smoking status (e.g., *MUC5AC*) may contribute to the development and progression of COPD.[25] Further studies are needed to explore whether proteomic, transcriptomic, or genomic pathways differ in the formation of silent vs. symptomatic mucus plugs in smokers vs. non-smokers. Finally, we found that a history of asthma was also associated with reduced odds of silent mucus plugs. This is consistent with results from the SARP study, which showed a dissociation between mucus plugs on CT and symptoms in people with severe asthma.[19]

Our study found that participants with silent mucus plugs tend to have more emphysema. The ability to generate a high expiratory flow is important to expectorate mucus in the airways. Emphysema causes reduction in the expiratory airflow due to loss of elastic recoil and increased airway collapsibility.[26] Collapsed airways decrease or block expiratory airflow, and in turn may facilitate mucus retention in the distal airways. As a result, mucus plugs may not be moved proximally enough to cause cough (due to lack of cough receptors in the distal

363 airways), which is compounded by inability to perceive the increased phlegm production.
364 However, we were not able to determine the validity of this hypothesis with our limited
365 observational data.
366
367 It is important to note that, while the perceived disease severity levels measured by
368 SGRQ scores (activity and impact domains) were significantly worse among those with
369 symptomatic mucus plugs, there were no significant differences in spirometry measures, resting
370 SpO2 or 6-minute walk distances between individuals with silent vs. symptomatic mucus plugs.
371 Our results suggest that in individuals who present with impaired spirometry measures and
372 functionality that are disproportionately severe despite the absence of cough and phlegm
373 symptoms, silent airway mucus plugs should be suspected.
374
375 Interestingly, the demographic characteristics of people with silent mucus plugs are the
376 opposite of the typically known demographics of patients with chronic bronchitis, i.e., males,
377 younger age, higher BMI, and greater pack-years of smoking.[17] Also, there were several notable
378 differences in structural changes between silent vs. symptomatic mucus plugs. Those with silent
379 mucus plugs had a higher percentage emphysema on CT. The presence and extent of silent
380 mucus plugs were associated with more small airway disease in people without cough and
381 phlegm. Furthermore, about a quarter of individuals without emphysema nor chronic bronchitis
382 symptoms were found to have mucus plugs on CT. Taken together, these findings suggest that
383 airway mucus plugging may be a distinct phenotype of COPD that shares features of both
384 chronic bronchitis and emphysema, rather than a radiological manifestation of chronic
385 bronchitis.
386
387 Our study has several limitations. First, our study is an observational study and causal
388 statements cannot be made. Second, we defined symptoms of cough and phlegm based on

participants' responses to the study questionnaires. There may be inconsistency between true symptoms and responses to questionnaires due to recall bias or understanding and interpretation of the questions. For example, the differences in statistical significance of results when using ATS-DLD questions may be because the interpretation of the wording of questions differs by participants. Furthermore, our data did not contain information on the generation or the size of the airway at which mucus plugs were identified. While mucus plugs in middle-to-large sized airways may be associated with more symptoms because cough receptors might be less or even absent in small peripheral airways,[5,22,23] we could not prove or disprove this hypothesis in our study. Finally, we defined silent vs. symptomatic mucus plugs solely based on cough and phlegm, but not other symptoms such as shortness of breath, wheezing or chest infection, because our primary question was whether mucus plugs and chronic bronchitis were separable phenotypes of COPD. The term silent mucus plugs should not be interpreted as symptom-free mucus plugs as mucus plugs can present with a broad spectrum of symptoms other than cough and phlegm.

Interpretation

Silent mucus plugs are common in current and former smokers with COPD. Risk factors for silent mucus plugs were older age, female sex, and Black race. Silent mucus plugs are associated with worse quality of life, lung functional and structural measures. Airway mucus plugging may be a distinct phenotype of COPD and could be an imaging biomarker.

Take-Home Points

- **Study question:** Are silent mucus plugs (mucus plugs identified on CT scans in people without cough or phlegm symptoms) clinically significant, and who are more likely to have silent mucus plugs?

- **Results:** Older age, female sex and Black race are risk factors for silent mucus plugs and silent mucus plugs are associated with worse functional, structural, and clinical measures of COPD.

- **Interpretation:** CT assessment of mucus plugs can complement the evaluation of patients with COPD who do not have cough and phlegm symptoms.

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Table 1. Characteristics of participants with silent vs. symptomatic mucus plugs.

Characteristics	Silent mucus plugs (n=627)	Symptomatic mucus plugs (n=1151)	*P* value
Age, years	65.7 (8.3)	63.2 (8.8)	<0.001
Female, n (%)	337 (53.7%)	511 (44.4%)	<0.001
Race, n (%)			0.072
Non-Hispanic White	492 (78.5%)	945 (82.1%)	
Non-Hispanic Black	135 (21.5%)	206 (17.9%)	
BMI, kg/m2	26.8 (5.9)	27.1 (5.8)	0.398
Pack-years, years	51.1 (27.8)	54.0 (28.3)	0.038
Smoking status, n (%)			<0.001
Former smoker	468 (74.6%)	580 (50.4%)	
Current smoker	159 (25.4%)	571 (49.6%)	
GOLD stage, n (%)			0.115
1	82 (13.1%)	87 (7.6%)	
2	214 (34.1%)	423 (36.8%)	
3	196 (31.3%)	408 (35.4%)	
4	135 (21.5%)	233 (20.2%)	
Post-bronchodilator FEV1, liters	1.36 (0.69)	1.39 (0.67)	0.513
Post-bronchodilator FEV1/FVC	0.48 (0.14)	0.48 (0.13)	0.97
Post-bronchodilator FEV1 % predicted	50.9 (22.95)	48.6 (20.36)	0.034
Post-bronchodilator FEF25-75%	54 (41)	55 (38)	0.874
Six-minute walk distance, meters	360 (121)	349 (121)	0.077
Resting SpO2, %	94.7 (3.7)	94.5 (3.6)	0.218
History of congestive heart failure, %	5	4	0.476
History of asthma, %	28	33	0.037
SGRQ Symptom score	27.54 (18.65)	59.06 (20.21)	<0.001
SGRQ Activity score	49.8 (29.4)	62 (25.2)	<0.001
SGRQ Impact score	22.5 (19.6)	35.7 (21.5)	<0.001
SGRQ Total score	31.7 (20.7)	47.4 (20.6)	<0.001
Had COPD exacerbation requiring hospitalizations in the past 12 months, %	12	16	0.017
Presence of emphysema*, %	62	59	0.187
Quantitative emphysema** on CT, % lung volume	15.7 (15.0)	13.2 (13.3)	0.001
Airway wall thickness (Pi10), mm	2.68 (0.59)	2.88 (0.62)	<0.001
Small airway disease, % lung volume	28.6 (12.0)	29.4 (12.7)	0.224

Mean (SD), proportion or count. *Presence of emphysema was defined as affected lung volume greater than 5% on CT. **Estimates include all participants (i.e., averaged including those whose lung volume affected was less than 5%).

Table 2. Risk factors for silent mucus plugs vs. symptomatic mucus plugs.

Covariate	**Odds ratio (95% CI)**	***P* value**
Age	1.02 (1.01, 1.04)	0.004
Female sex (vs. male)	1.4 (1.12, 1.74)	0.003
Black race (vs. non-Hispanic White)	1.93 (1.44, 2.59)	<0.001
BMI	0.99 (0.97, 1.01)	0.45
Currently smoking (vs. former smoker)	0.35 (0.27, 0.45)	<0.001
Pack Years	0.997 (0.993, 1.001)	0.193
History of congestive heart failure	1.18 (0.7, 1.97)	0.533
History of asthma	0.69 (0.54, 0.88)	0.003

Odds ratios with 95% confidence intervals and p-values from a multivariable logistic regression model are shown.

499 Table 3. Associations of silent mucus plugs with measures of lung function, quality of life, and

500 structural changes on chest imaging in multivariable models.

	Mucus plug score category (Number of lung segments with mucus plugs)			
	1-2 vs. 0		3+ vs. 0	
Linear regression models				
Outcome	**Mean difference (95% CI)**	**p-value**	**Mean difference (95% CI)**	**p-value**
6-min walk distance, meters	-35.88 (-50.17, -21.58)	<0.001	-61.48 (-78.61, -44.35)	<0.001
Resting SpO2, %	-0.88 (-1.25, -0.51)	<0.001	-0.68 (-1.13, -0.23)	0.003
SGRQ Total score	6.48 (4.22, 8.75)	<0.001	10.2 (7.46, 12.93)	<0.001
SGRQ Impact score	5.48 (3.42, 7.53)	<0.001	9.01 (6.53, 11.49)	<0.001
SGRQ Activity score	8.31 (4.94, 11.69)	<0.001	12.51 (8.43, 16.58)	<0.001
Post-bronchodilator FEV1/FVC	-0.05 (-0.07, -0.04)	<0.001	-0.08 (-0.1, -0.07)	<0.001
Post-bronchodilator FEV1 % predicted	-9.79 (-12.38, -7.21)	<0.001	-16.21 (-19.33, -13.09)	<0.001
Emphysema, % lung volume	4.16 (2.66, 5.66)	<0.001	5.34 (3.52, 7.17)	<0.001
Airway wall thickness (Pi10), mm	0.22 (0.15, 0.28)	<0.001	0.39 (0.31, 0.47)	<0.001
Small airway disease, % lung volume	4.16 (2.72, 5.6)	<0.001	6.53 (4.77, 8.29)	<0.001
Logistic regression models				
Outcome	**Odds Ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Had COPD exacerbations requiring hospitalizations in the past 12 months	1.79 (1.14, 2.76)	0.0101	2.26 (1.38, 3.62)	<0.001

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503 *Multivariable models adjusted for age, sex, race, BMI, smoking status, pack year, congestive heart failure and asthma. Coefficients

504 and *P* values are shown.

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507 Figure 1. Inclusion flowchart.

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510 Figure 2. Histograms of mucus plug scores by cough or phlegm symptoms.

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514 Figure 3. Proportion of participants without symptoms by mucus plug score category stratified
515 by sex and smoking status. The absolute number of participants without symptoms belonging to
516 each group is shown on top of each bar (the total number in parenthesis). For example, among
517 463 female current smokers with a mucus plug score of zero, 153 had no cough or phlegm.
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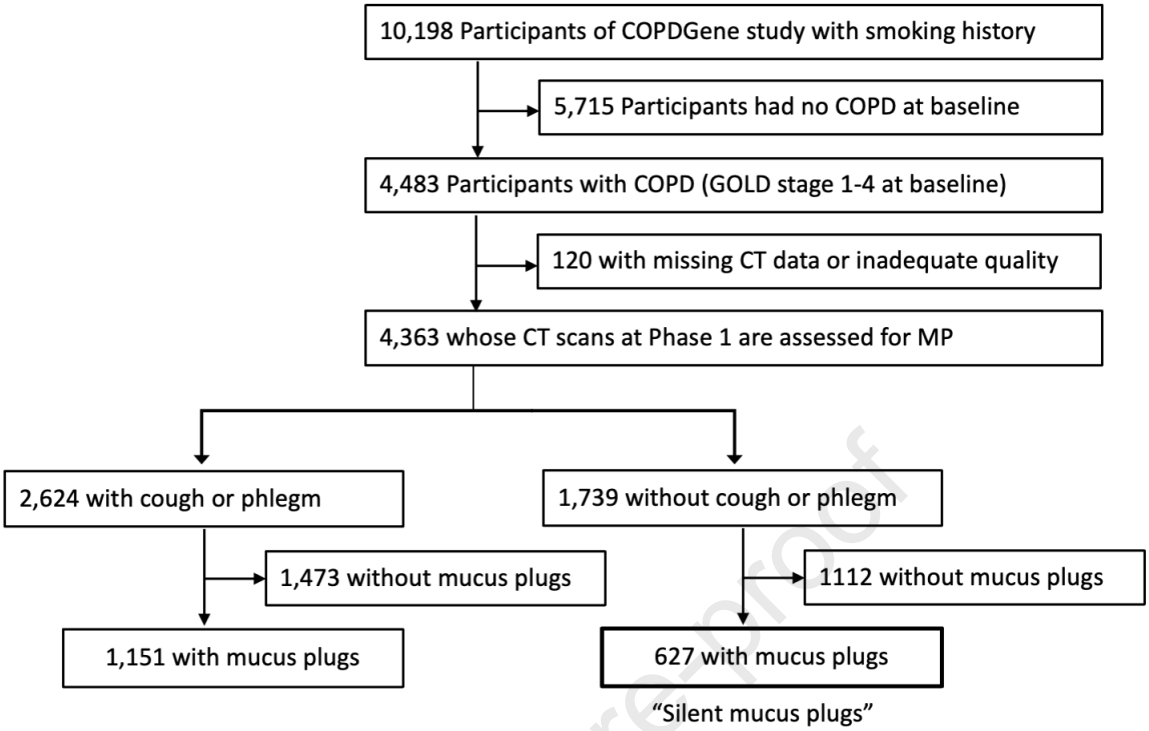

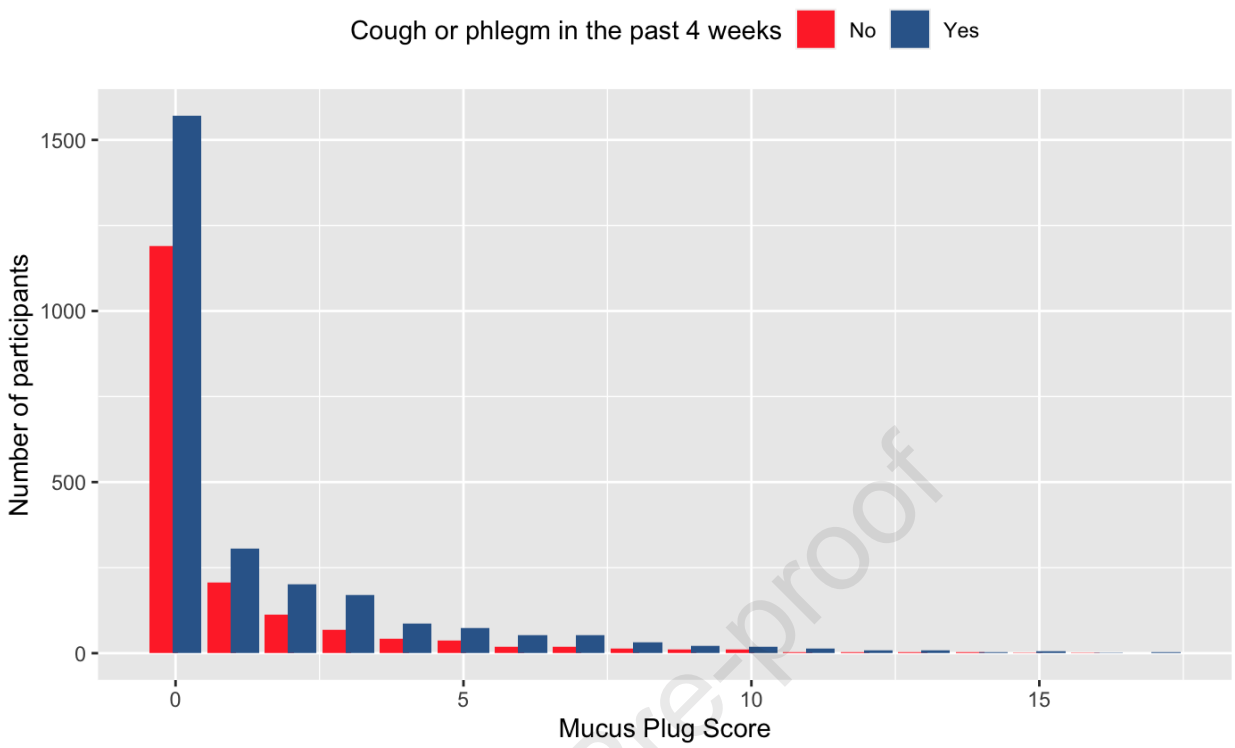

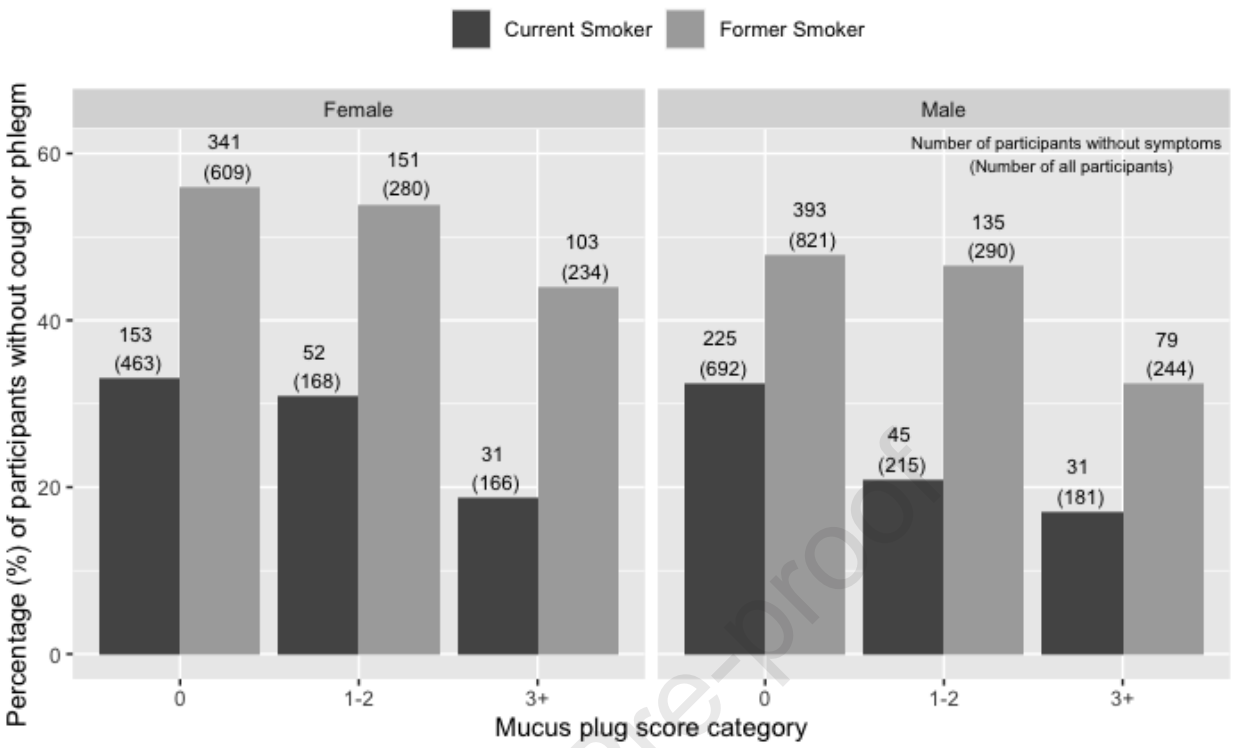

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Dr. Cho reported receiving grants from Bayer. Dr. Diaz reported receiving personal fees from Boehringer Ingelheim and having a patent for Methods and Compositions Relating to Airway Dysfunction pending (701586-190200USPT). Dr. Terry reported that she and/or her husband are general stockholders with no controlling interest in the following: Johnson & Johnson, Kimberly-Clark Corp, Microsoft Corp, Amgen Inc, Bristol Myers Squibb, Cisco Systems Inc, Medtronic, Merck & Co Inc, Procter & Gamble, Crisper Therapeutics, Nvidia, Texas Instruments, Hewlett Packard, United Health, Abbott Labs, Eli Lilly and Co, AbbVie Inc, and LyondellBasell Industries. Mr. Ruben San José Estépar reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study. Dr. Raúl San José Estépar reported being a founder and equity holder of Quantitative Imaging Solutions and receiving grants from Boehringer Ingelheim, contracts to serve as image core from Insmed and Lung Biotechnology; and personal fees from LeukoLab and Chiesi. Dr. Yen is supported by NIH R01HL149861, R01HL164824, and U01HL089897. No other disclosures were reported.

e-Table 1. Characteristics of participants with silent vs. symptomatic mucus plugs using ATS-DLD questions.

	Silent MP (n=666)	Symptomatic MP (n=1112)	p-value
Age, years	66.17 (8.15)	62.85 (8.72)	<0.001
Female, %	52.9	44.6	<0.001
Non-Hispanic Black, %	16.8	20.6	0.046
BMI	27.06 (5.79)	26.95 (5.82)	0.675
Pack Years	50.9 (25.38)	54.28 (29.65)	0.011
Current smoker, %	22	52	<0.001
Congestive heart failure history, %	5	4	0.33
Asthma history, %	27	33	0.005
SGRQ Activity score	50.34 (29.3)	62.11 (25.18)	<0.001
SGRQ Impact score	22.47 (18.99)	36.16 (21.7)	<0.001
SGRQ Total score	32.32 (20.6)	47.61 (20.69)	<0.001
6-minute walk distance, meters	362.29 (121.64)	347.48 (120.39)	0.014
Resting SpO2	94.44 (3.82)	94.67 (3.51)	0.22
Post-bronchodilator FEV1, liters	1.36 (0.71)	1.39 (0.66)	0.486
Post-bronchodilator FEV1 % pred	50.75 (23.21)	48.59 (20.09)	0.046
Post-bronchodilator FEV1/FVC	0.47 (0.14)	0.48 (0.13)	0.601
Airway wall thickness (Pi10), mm	2.68 (0.58)	2.89 (0.62)	<0.001
Small airway disease, % lung volume	29.21 (11.84)	29.08 (12.83)	0.847
Presence of emphysema*, %	64	58	0.011
Quantitative emphysema** on CT, % lung volume	15.83 (14.83)	13.06 (13.37)	<0.001
Had COPD exacerbation requiring hospitalizations in the past 12 months, %	0.18 (0.38)	0.28 (0.45)	<0.001
GOLD grade 1	92	77	
GOLD grade 2	225	412	
GOLD grade 3	200	404	
GOLD grade 4	149	219	

ATS-DLD: American Thoracic Society Division of Lung Disease (ATS-DLD) 1978 Questionnaire. BMI: Body Mass Index. SGRQ: St. George's Respiratory Questionnaire. SpO2: Oxygen saturation on pulse oximetry (%).

e-Table 2. Risk factors for silent mucus plugs vs. symptomatic mucus plugs using the ATS-DLD questions.

	Odds Ratio (95% CI)	p-value
Age	1.02 (1.01, 1.04)	0.001
Female sex (vs. male)	1.36 (1.09, 1.7)	0.006
Black race (vs. non-Hispanic White)	1.06 (0.78, 1.43)	0.702
BMI	1 (0.99, 1.02)	0.664
Currently smoking (vs. former smoker)	0.31 (0.24, 0.4)	<0.001
Pack years	0.994 (0.990, 0.998)	0.007
History of congestive heart failure	1.42 (0.84, 2.38)	0.186
History of asthma	0.67 (0.53, 0.86)	0.002

ATS-DLD: American Thoracic Society Division of Lung Disease (ATS-DLD) 1978 Questionnaire.
BMI: Body Mass Index.

e-Table 3. Associations of silent mucus plugs with clinical, functional, and CT measures of disease, using the ATS-DLD questions.

	Mucus plug score category (Number of lung segments with mucus plugs)			
	1-2 vs. 0		3+ vs. 0	
Linear regression models				
Outcome	**Mean difference (95% CI)**	**p-value**	**Mean difference (95% CI)**	**p-value**
6-min walk distance, meters	-28.83 (-42.59, -15.06)	<0.001	-59.85 (-76.5, -43.21)	<0.001
Resting SpO2, %	-0.81 (-1.21, -0.42)	<0.001	-0.78 (-1.26, -0.3)	0.0016
SGRQ Total score	6.22 (3.96, 8.49)	<0.001	8.47 (5.7, 11.24)	<0.001
SGRQ Impact score	4.89 (2.86, 6.92)	<0.001	7.08 (4.59, 9.56)	<0.001
SGRQ Activity score	8.54 (5.23, 11.85)	<0.001	10.61 (6.56, 14.65)	<0.001
Post-bronchodilator FEV1/FVC	-0.05 (-0.07, -0.04)	<0.001	-0.08 (-0.1, -0.06)	<0.001
Post-bronchodilator FEV1 % predicted	-9.88 (-12.45, -7.3)	<0.001	-15.05 (-18.2, -11.9)	<0.001
Emphysema, % lung volume	4.09 (2.6, 5.58)	<0.001	4.58 (2.76, 6.41)	<0.001
Airway wall thickness (Pi10), mm	0.23 (0.17, 0.29)	<0.001	0.38 (0.3, 0.45)	<0.001
Small airway disease, % lung volume	4.41 (3.01, 5.8)	<0.001	6.99 (5.27, 8.7)	<0.001
Logistic regression models				
Outcome	**Odds Ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Had COPD exacerbations requiring hospitalizations in the past 12 months	1.36 (0.95, 1.94)	0.0899	1.87 (1.25, 2.76)	0.0019

*Multivariable models adjusted for age, sex, race, BMI, smoking status, pack year, congestive heart failure and asthma. Coefficients and *P* values are shown.

ATS-DLD: American Thoracic Society Division of Lung Disease (ATS-DLD) 1978 Questionnaire. BMI: Body Mass Index. SGRQ: St. George's Respiratory Questionnaire. SpO2: Oxygen saturation on pulse oximetry (%).

e-Table 4. Lobar involvement of mucus plugs in silent vs. symptomatic mucus plugs.

	Mucus Plug score 1-2		Mucus Plug score 3+	
	Mucus-related Symptom Status		Mucus-related Symptom Status	
Lobe	Silent N (%)	Symptomatic N (%)	Silent N (%)	Symptomatic N (%)
RUL	122 (31.9%)	140 (24.6%)	150 (61.5%)	346 (59.6%)
RML	66 (17.2%)	81 (14.2%)	128 (52.5%)	291 (50.1%)
RLL	152 (39.7%)	280 (49.1%)	198 (81.1%)	501 (86.2%)
LUL	82 (21.4%)	94 (16.5%)	131 (53.7%)	273 (47%)
LIN	40 (10.4%)	56 (9.8%)	92 (37.7%)	267 (46%)
LLL	123 (32.1%)	217 (38.1%)	185 (75.8%)	458 (78.8%)

Upper and middle lobe involvement appeared to be more common in people with silent mucus plugs, whereas lower lobe involvement was more frequent in people with symptomatic mucus plugs. These differences were more pronounced in people with mucus plug scores 1-2 than with scores above 3.

e-Table 5. Univariable comparisons in participants without mucus plugs by mucus-related symptom status (n=2,585)

Variable	No cough or phlegm (n=1112)	Cough or phlegm (n=1473)
Age	63.11 (8.5)	61.72 (8.48)
Female, %	44	39
Black race, %	25	24
BMI	28.34 (5.83)	28.61 (6.4)
Pack Years	48.32 (25.7)	52.21 (26.59)
Current smokers, %	34	53
History of congestive heart failure, %	3	5
History of asthma	21	29

BMI: Body Mass Index.

e-Table 6. Risk factors of having cough or phlegm among participants without mucus plugs (n=2,585)

Variable	Odds Ratio (95% CI)	*P* value
Age	1 (0.99, 1.01)	0.758
Female sex (vs. male)	0.81 (0.68, 0.96)	0.015
Black race (vs. non-Hispanic White)	0.69 (0.56, 0.86)	<0.001
BMI	1.02 (1, 1.03)	0.041
Pack Years	1.01 (1, 1.01)	<0.001
Currently smoking (vs. former smoker)	2.58 (2.11, 3.17)	<0.001
History of congestive heart failure	1.44 (0.93, 2.26)	0.108
History of asthma	1.79 (1.46, 2.21)	<0.001

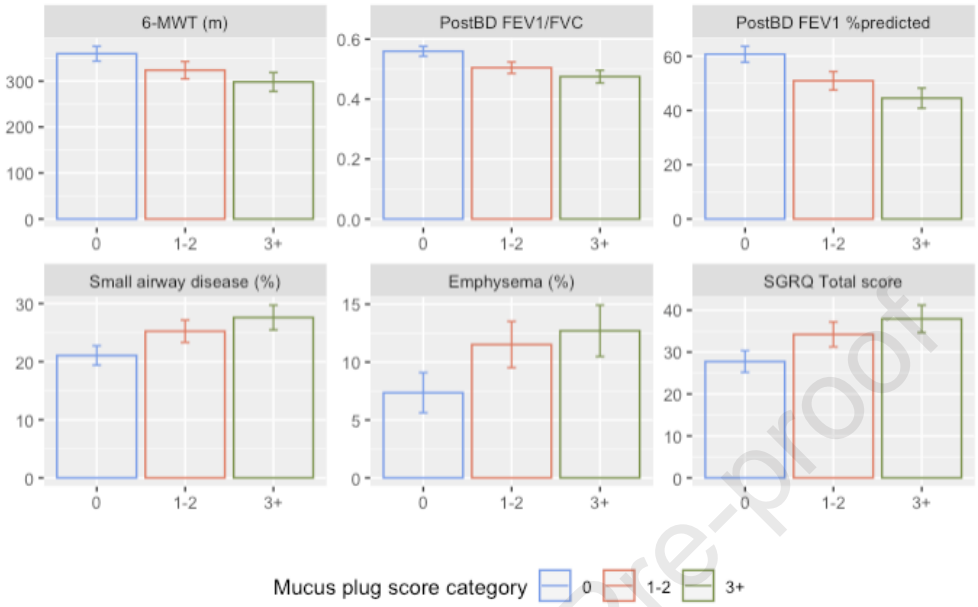
BMI: Body Mass Index. CI: Confidence interval.

e-Table 7. Characteristics of participants without cough or phlegm by mucus plug score category.

Characteristics	Mucus plug score category (Number of lung segments with mucus plugs) 0 (n=1112)	1-2 (n=383)	3+ (n=244)	*P* value
Age, years	63.1 (8.5)	65.8 (7.9)	65.5 (8.8)	<0.001
Female, n (%)	494 (44.4%)	203 (53.0%)	134 (54.9%)	<0.001
Race, n (%)				0.106
Non-Hispanic White	829 (74.6%)	295 (77.0%)	197 (80.7%)	
Non-Hispanic Black	283 (25.4%)	88 (23.0%)	47 (19.3%)	
BMI, kg/m2	28.3 (5.8)	27.4 (5.9)	26.0 (5.8)	<0.001
Pack-years, years	48.3 (25.7)	51.3 (28.8)	50.9 (26.2)	0.059
Smoking status, n (%)				<0.001
Former smoker	734 (66.0%)	286 (74.7%)	182 (74.6%)	
Current smoker	378 (34.0%)	97 (25.3%)	62 (25.4%)	
History of congestive heart failure, %	3	5	5	0.078
History of asthma, %	21	23	34	<0.001
SGRQ Symptom score	19.23 (16.89)	26.21 (18.27)	29.62 (19.07)	<0.001
SGRQ Activity score	37.6 (29.2)	48.1 (29.2)	52.5 (29.5)	<0.001
SGRQ Impact score	14.6 (16.8)	21.1 (19.4)	24.7 (19.7)	<0.001
SGRQ Total score	22.4 (19.2)	30.3 (20.6)	34.0 (20.8)	<0.001
Had COPD exacerbations requiring hospitalizations in the past 12 months, %	7	11	14	<0.001
GOLD stage, n (%)				<0.001
1	313 (28.1%)	56 (14.6%)	26 (10.7%)	
2	525 (47.2%)	147 (38.4%)	67 (27.5%)	
3	189 (17%)	119 (31.1%)	77 (31.6%)	
4	85 (7.6%)	61 (15.9%)	74 (30.3%)	
Post-bronchodilator FEV1, liters	1.91 (0.8)	1.45 (0.71)	1.23 (0.64)	<0.001
Post-bronchodilator FEV1/FVC	0.57 (0.12)	0.49 (0.14)	0.45 (0.15)	<0.001
Post-bronchodilator FEV1 % predicted	66.0 (22)	53.9 (22.6)	46.1 (22.8)	<0.001
Post-bronchodilator FEF 25-75%	85 (51)	58 (43)	48 (36)	<0.001
6-min walk distance, meters	412 (125)	367 (116)	349 (128)	<0.001
Resting SpO2, %	95.8 (2.9)	94.7 (3.8)	94.8 (3.5)	<0.001
Emphysema on CT, %	8.5 (11.4)	14.9 (14.6)	17.1 (15.5)	<0.001
Airway wall thickness (Pi10), mm	2.4 (0.5)	2.6 (0.6)	2.8 (0.6)	<0.001
Small airway disease, %	21.0 (12.5)	27.2 (11.4)	30.9 (12.6)	<0.001

Mean (SD), proportion or count. *P* values are calculated for each characteristic using univariable linear regression models with the mucus plug score category (0, 1-2 and 3+) as an ordinal variable. BMI: Body Mass Index. SGRQ: St. George's Respiratory Questionnaire SpO2: Oxygen saturation on pulse oximetry (%).

e-Figure 1. Functional, clinical, and CT measures of disease in participants without mucus-related symptoms by mucus plug score category.



Adjusted means of the outcomes from multivariable models adjusting for age, sex, race, BMI, smoking status, pack year, congestive heart failure and asthma. The 95% confidence interval of the adjusted mean for each group is shown as an error bar. 6-MWT: 6-minute walk test (in meters). PostBD: Post-bronchodilator.