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"Chronic Obstructive Pulmonary Disease Phenotypes"

Dissertation

Spyridon Fortis

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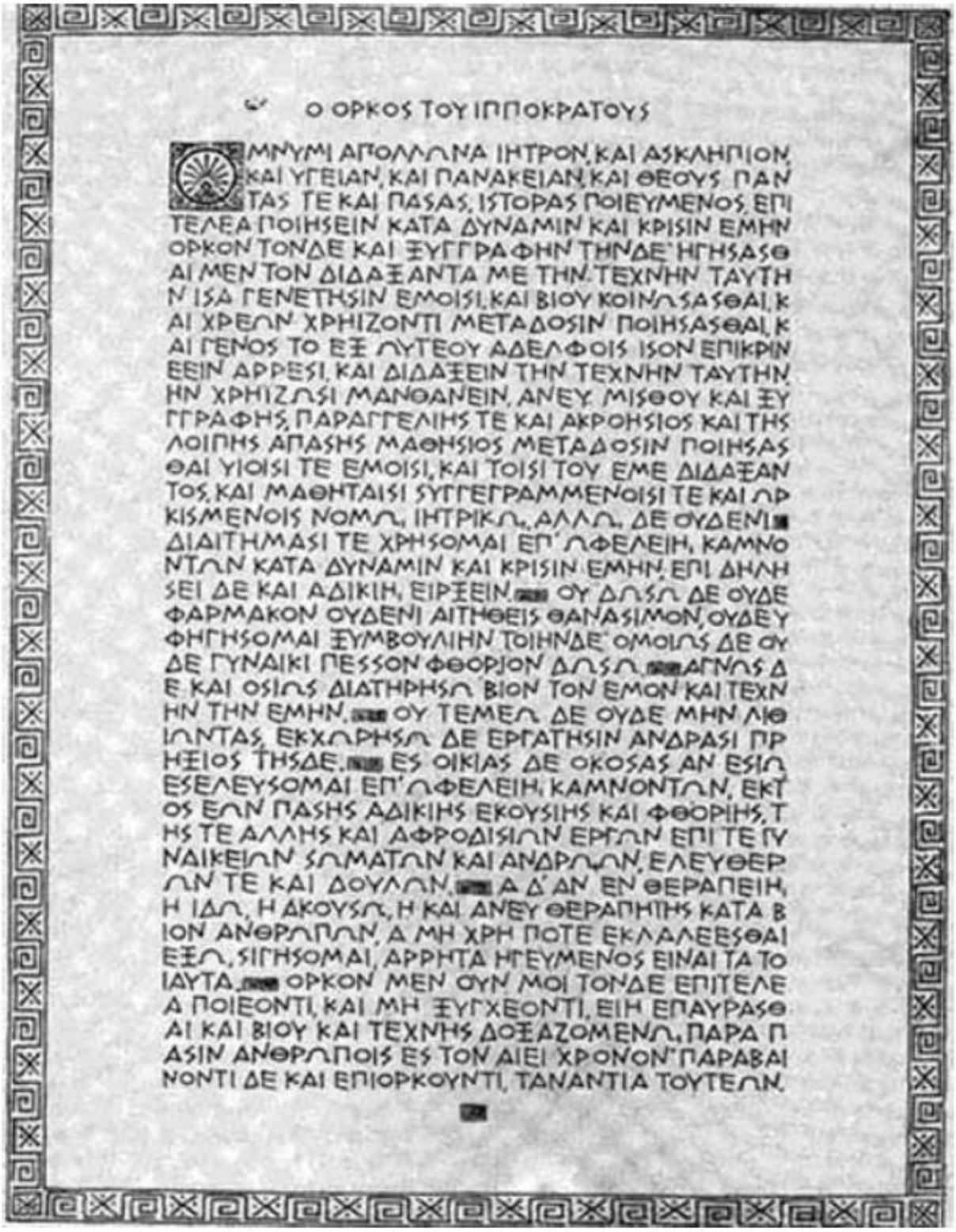

Ο ΟΡΚΟΣ ΤΟΥ ΙΠΠΟΚΡΑΤΟΥΣ

ΟΜΝΥΜΙ ΑΠΟΛΛΩΝΑ ΙΗΤΡΟΝ, ΚΑΙ ΑΣΚΛΗΠΙΟΝ, ΚΑΙ ΥΓΕΙΑΝ, ΚΑΙ ΠΑΝΑΚΕΙΑΝ, ΚΑΙ ΘΕΟΥΣ ΠΑΝΤΑΣ ΤΕ ΚΑΙ ΠΑΣΑΣ, ΙΣΤΟΡΑΣ ΠΟΙΕΥΜΕΝΟΣ, ΕΠΙΤΕΛΕΑ ΠΟΙΗΣΕΙΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ ΟΡΚΟΝ ΤΟΝΔΕ ΚΑΙ ΞΥΓΓΡΑΦΗΝ ΤΗΝΔΕ· ΗΓΗΣΑΣΘΑΙ ΜΕΝ ΤΟΝ ΔΙΔΑΞΑΝΤΑ ΜΕ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ ΙΣΑ ΓΕΝΕΤΗΣΙΝ ΕΜΟΙΣΙ, ΚΑΙ ΒΙΟΥ ΚΟΙΝΩΣΑΣΘΑΙ, ΚΑΙ ΧΡΕΩΝ ΧΡΗΙΖΟΝΤΙ ΜΕΤΑΔΟΣΙΝ ΠΟΙΗΣΑΣΘΑΙ, ΚΑΙ ΓΕΝΟΣ ΤΟ ΕΞ ΩΥΤΕΟΥ ΑΔΕΛΦΟΙΣ ΙΣΟΝ ΕΠΙΚΡΙΝΕΙΝ ΑΡΡΕΣΙ, ΚΑΙ ΔΙΔΑΞΕΙΝ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ, ΗΝ ΧΡΗΙΖΩΣΙ ΜΑΝΘΑΝΕΙΝ, ΑΝΕΥ ΜΙΣΘΟΥ ΚΑΙ ΞΥΓΓΡΑΦΗΣ, ΠΑΡΑΓΓΕΛΙΗΣ ΤΕ ΚΑΙ ΑΚΡΟΗΣΙΟΣ ΚΑΙ ΤΗΣ ΛΟΙΠΗΣ ΑΠΑΣΗΣ ΜΑΘΗΣΙΟΣ ΜΕΤΑΔΟΣΙΝ ΠΟΙΗΣΑΣΘΑΙ ΥΙΟΙΣΙ ΤΕ ΕΜΟΙΣΙ, ΚΑΙ ΤΟΙΣΙ ΤΟΥ ΕΜΕ ΔΙΔΑΞΑΝΤΟΣ, ΚΑΙ ΜΑΘΗΤΑΙΣΙ ΣΥΓΓΕΓΡΑΜΜΕΝΟΙΣΙ ΤΕ ΚΑΙ ΩΡΚΙΣΜΕΝΟΙΣ ΝΟΜΩ, ΙΗΤΡΙΚΩ, ΑΛΛΩ, ΔΕ ΟΥΔΕΝΙ ΔΙΔΑΙΤΗΜΑΣΙ ΤΕ ΧΡΗΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ, ΚΑΜΝΟΝΤΩΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ, ΕΠΙ ΔΗΛΗΣΕΙ ΔΕ ΚΑΙ ΑΔΙΚΙΗ, ΕΙΡΞΕΙΝ. ΟΥ ΔΩΣΩ ΔΕ ΟΥΔΕ ΦΑΡΜΑΚΟΝ ΟΥΔΕΝΙ ΑΙΤΗΘΕΙΣ ΘΑΝΑΣΙΜΟΝ, ΟΥΔΕ ΥΦΗΓΗΣΟΜΑΙ ΞΥΜΒΟΥΛΙΗΝ ΤΟΙΗΝΔΕ· ΟΜΟΙΩΣ ΔΕ ΟΥΔΕ ΓΥΝΑΙΚΙ ΠΕΣΣΟΝ ΦΘΟΡΙΟΝ ΔΩΣΩ. ΑΓΝΩΣ ΔΕ ΚΑΙ ΟΣΙΩΣ ΔΙΑΤΗΡΗΣΩ ΒΙΟΝ ΤΟΝ ΕΜΟΝ ΚΑΙ ΤΕΧΝΗΝ ΤΗΝ ΕΜΗΝ. ΟΥ ΤΕΜΕΩ ΔΕ ΟΥΔΕ ΜΗΝ ΛΙΘΙΩΝΤΑΣ, ΕΚΧΩΡΗΣΩ ΔΕ ΕΡΓΑΤΗΣΙΝ ΑΝΔΡΑΣΙ ΠΡΗΞΙΟΣ ΤΗΣΔΕ. ΕΣ ΟΙΚΙΑΣ ΔΕ ΟΚΟΣΑΣ ΑΝ ΕΣΙΩ ΕΣΕΛΕΥΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ, ΚΑΜΝΟΝΤΩΝ, ΕΚΤΟΣ ΕΩΝ ΠΑΣΗΣ ΑΔΙΚΙΗΣ ΕΚΟΥΣΙΗΣ ΚΑΙ ΦΘΟΡΙΗΣ, ΤΗΣ ΤΕ ΑΛΛΗΣ ΚΑΙ ΑΦΡΟΔΙΣΙΩΝ ΕΡΓΩΝ ΕΠΙ ΤΕ ΓΥΝΑΙΚΕΙΩΝ ΣΩΜΑΤΩΝ ΚΑΙ ΑΝΔΡΩΩΝ, ΕΛΕΥΘΕΡΩΝ ΤΕ ΚΑΙ ΔΟΥΛΩΝ. Α Δ' ΑΝ ΕΝ ΘΕΡΑΠΕΙΗ, Η ΙΔΩ, Η ΑΚΟΥΣΩ, Η ΚΑΙ ΑΝΕΥ ΘΕΡΑΠΗΙΗΣ ΚΑΤΑ ΒΙΟΝ ΑΝΘΡΩΠΩΝ, Α ΜΗ ΧΡΗ ΠΟΤΕ ΕΚΛΑΛΕΕΣΘΑΙ ΕΞΩ, ΣΙΓΗΣΟΜΑΙ, ΑΡΡΗΤΑ ΗΓΕΥΜΕΝΟΣ ΕΙΝΑΙ ΤΑ ΤΟΙΑΥΤΑ. ΟΡΚΟΝ ΜΕΝ ΟΥΝ ΜΟΙ ΤΟΝΔΕ ΕΠΙΤΕΛΕΑ ΠΟΙΕΟΝΤΙ, ΚΑΙ ΜΗ ΞΥΓΧΕΟΝΤΙ, ΕΙΗ ΕΠΑΥΡΑΣΘΑΙ ΚΑΙ ΒΙΟΥ ΚΑΙ ΤΕΧΝΗΣ ΔΟΞΑΖΟΜΕΝΩ, ΠΑΡΑ ΠΑΣΙΝ ΑΝΘΡΩΠΟΙΣ ΕΣ ΤΟΝ ΑΙΕΙ ΧΡΟΝΟΝ· ΠΑΡΑΒΑΙΝΟΝΤΙ ΔΕ ΚΑΙ ΕΠΙΟΡΚΟΥΝΤΙ, ΤΑΝΑΝΤΙΑ ΤΟΥΤΕΩΝ.

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Dedications

I dedicate my dissertation work to my wife, Theoni, and my children, Chrysa and Haris.

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I would like to acknowledge and thank the members of my Dissertation Committee: Dr Dimitrios Georgopoulos, Professor of Pulmonary and Critical Care Medicine at University of Crete, Dr Alejandro Comellas, Professor of Pulmonary and Critical Care Medicine at University of Iowa, and Dr Nikolaos Tzanakis, Professor of Pulmonary Medicine and Epidemiology at University of Crete who made this work possible.

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Περίληψη

Η Χρόνια Αποφρακτική Πνευμονοπάθεια (ΧΑΠ) ορίζεται ως επίμονα αναπνευστικά συμπτώματα και περιορισμός της ροής του αέρα στους αεραγωγούς λόγω ανωμαλιών των αεραγωγών και/ή των κυψελιδών του πνεύμονα που προκαλούνται συνήθως από επιβλαβή σωματίδια ή αέρια και επηρεάζονται από παράγοντες ξενιστή. Ιστορικά, δύο φαινότυποι έχουν περιγραφεί για τον περαιτέρω χαρακτηρισμό της νόσου: η χρόνια βρογχίτιδα που σχετίζεται με φλεγμονή των αεραγωγών και το κύριο χαρακτηριστικό της είναι ο χρόνιος παραγωγικός βήχας και το εμφύσημα που σχετίζεται με καταστροφή των των κυψελιδών του πνεύμονα και παρουσιάζεται με δύσπνοια. Αν και, αυτοί οι φαινότυποι μπορεί να παρέχουν κάποιο πρόσθετο χαρακτηρισμό της παθοφυσιολογίας της νόσου, δεν είναι αρκετά εκτενείς για τη ΧΑΠ που είναι μια ετερογενής νόσο και δεν παρέχουν φαινοτυπική κατηγοριοποίηση που υποδεικνύει ειδική θεραπεία. Επιπλέον, ο τρέχων ορισμός της ΧΑΠ δεν περιλαμβάνει ασθενείς με σημαντικά αναπνευστικά συμπτώματα, ένα ποσοστό των οποίων έχει υψηλή θνησιμότητα, οι οποίοι δεν έχουν αποφρακτική φυσιολογία. Σε αυτή τη μελετη περιγράφουμε φαινότυπους της ΧΑΠ που είναι κλινικά χρήσιμοι και παρέχουν πρόσθετη πρόγνωστικη αξία και ενδεχομένως μπορεί να υποδηλώνουν ανταπόκριση σε ορισμένες θεραπείες ή αναφέρονται σε ασθενείς που δυνητικά έχουν ασθένεια με πιθανές θεραπευτικές επιλογές.

Σε αυτή τη διατριβή, δείξαμε ότι ορισμένα χαρακτηριστικά της ανταπόκρισης στα βρογχοδιασταλτικά (συνδυασμένη ανταπόκριση σε FEV1 και FVC) μπορούν να βοηθήσουν στον εντοπισμό ασθενών με ΧΑΠ των οποίων η νόσος μιμειται το άσθμα (Asthma-COPD overlap). Οι ασθενείς με ΧΑΠ που έχουν ανταπόκριση στα βρογχοδιασταλτικά σε κάθε σπιρομέτρηση σε πολλαπλές μετρήσεις φαίνεται να έχουν περισσότερα «ασθματικά» χαρακτηριστικά, μεγαλύτερη επιδείνωση της πνευμονικής λειτουργίας με το πέρασμα του χρόνου, και σοβάροτερη νόσο των μικρών αεραγωγών σε σχέση με εκείνους τους ασθενείς που δεν έχουν ανταπόκριση στα βρογχοδιασταλτικά σε κάθε σπιρομέτρηση. Αυτοί οι ασθενείς μπορεί να έχουν δραματική ανταπόκριση στη βιολογική θεραπεία π.χ. anti-IL5 παρόμοια με την ανταπόκριση που έχουν οι ασθενείς με άσθμα.

Επιπλέον, δείξαμε ότι τα άτομα με φυσιολογική σπιρομέτρηση που έχουν συχνές αναπνευστικές παροξύνσεις έχουν αυξημένη θνησιμότητα και διατρέχουν υψηλό κίνδυνο για επιδείνωση της πνευμονικής λειτουργίας και εξέλιξης σε ΧΑΠ. Απαιτείται περαιτέρω έρευνα για να αξιολογηθεί εάν η θεραπεία αυτών των ατόμων που έχουν φυσιολογική σπιρομέτρηση μπορεί να βελτιώσει μακροπρόθεσμα την υγεία τους, συμπεριλαμβανομένης της πρόληψης της εξέλιξης σε ΧΑΠ. Σε άτομα με παθολογική σπιρομέτρηση που δεν είναι αποφρακτική (Preserved Ratio Impaired Spirometry or PRISm), η παγίδευση αέρα είναι παρούσα σε άτομα με συχνές αναπνευστικές

παροξύνσεις, αυξημένη θνησιμότητα, και συνδέεται μα υψηλότερο κίνδυνο εξέλιξης σε ΧΑΠ. Απαιτείται περαιτέρω έρευνα για να αξιολογηθεί εάν τα άτομα με PRISm επωφελούνται από την φαρμακευτικές αγώγες που χρησιμοποιούνται στη ΧΑΠ.

Αυτή η περαιτέρω κατηγοριοποιήση της ΧΑΠ σε επιμέρους φαινότυπους που είναι κλινικά χρήσιμοι μπορεί να βοηθήσει στον εντοπισμό ασθενών που ανταποκρίνονται καλά σε υπάρχουσες θεραπείες. Απαιτείται περαιτέρω έρευνα σε εκείνα τα άτομα με αναπνευστικό σύμπτωμα ή με υψηλό κίνδυνο για εξέλιξη σε ΧΑΠ, π.χ. άτομα με βεβαρυμένο ιστορικό καπνίσματος, που δεν έχουν ακόμη αποφρακτική σπιρομέτρηση (κανονική σπιρομέτρηση ή PRISm) για να αξιολογηθεί σε κλινικές δοκιμές αν η θεραπεία αυτών των ατόμων μπορεί να βελτιώσει την υγεία τους, συμπεριλαμβανομένης της πρόληψης της εξέλιξης σε ΧΑΠ.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality worldwide and is associated with high morbidity and resource utilization. COPD is a heterogeneous disease with variability in the disease characteristics between patients. In this study, we described clinically relevant phenotypes of COPD and we examined methods to identify these phenotypes.

The study was designed and conducted as PhD thesis of Dr Spyridon Fortis under the supervision of Dr Dimitrios Georgopoulos, Professor of Pulmonary and Critical Care Medicine at University of Crete, Dr Alejandro Comellas, Professor of Pulmonary and Critical Care Medicine at University of Iowa, and Dr Nikolaos Tzanakis, Professor of Pulmonary Medicine and Epidemiology at University of Crete. The Study was conducted at University of Iowa using data from two multicenter prospective ongoing studies: COPDGene and Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS).

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1. Literature Review

Chronic Obstructive Pulmonary Disease (COPD) is defined as persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by noxious particles or gases and influenced by host factors.(1) COPD diagnosis requires not only a consistent history but also the presence of airflow limitation in the spirometry. Historically, two phenotypes have been described to further characterize the disease: chronic bronchitis which is associated with airway inflammation and its main characteristic is chronic productive cough, and emphysema which is associated with alveolar destruction and presents with dyspnea. Although, these phenotypes may provide some additional characterization of the pathophysiology of the disease, they are not extensive enough for COPD, which is heterogenous disease, and do not provide phenotypic categorization that indicate specific treatment.(2) Moreover, the current definition of COPD and phenotypes do not include patients with significant respiratory symptoms, a proportion of which have high mortality, who do not have airflow limitation.(3-5) Below we describe clinically relevant COPD phenotypes that provide prognostication and/or indicate specific treatment and COPD-like phenotypes that do not necessary meet the current diagnostic criteria for COPD but provide additional prognostication and potentially can indicate response to certain treatments.

1.1. Asthma-COPD overlap

Asthma-COPD overlap is a relatively new term that describes the coexistence of asthma and COPD.(6) Definitions have been proposed by scientific groups including Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA) but does not provide any clinically relevant information.(7) Because bronchodilator responsiveness (BDR) is one of the several criteria to confirm lung function variability,(8) BDR presence has been often and erroneously considered equivalent to asthma diagnosis. Although, BDR is more common and greater in patients with asthma than those with COPD, BDR cannot distinguish asthma and

COPD.(9-11)Nevertheless, the association of BDR with clinical outcomes has been extensively studied with conflicting findings.(12, 13) Early studies showed that BDR cannot predict response to treatment.(12-14) . Some reports have showed that BDR is associated with worse respiratory symptoms(15), reduced exercise capacity(16), greater frequency of respiratory exacerbations(17), lesser amount of emphysema(12, 13, 18) and FEV_1 decline(19) whereas others have found no association of BDR with COPD symptoms and outcomes(12, 14, 20). The only outcome which is consistently associated with BDR is FEV_1 decline over time.(19, 21) The inconsistent findings regarding the association of BDR and clinical outcomes may be related to the fact that various BDR definitions and protocols have been tested. BDR has also been defined either as an increase in FEV1 alone, or an increase in FEV1 and/or FVC after bronchodilator administration with various cut-offs(3). BDR according to ATS-ERS guidelines (ATS-BDR) is a composite of a positive response in FEV1 and/or FVC. As ATS-BDR is defined by bronchodilator response in either FEV1 and/or FVC, subjects with ATS-BDR may represent a heterogeneous population. BDR in FEV1 may indicate different disease processes associated with COPD than BDR in FVC. BDR in FVC is more common in small airway disease (19) while BDR in FEV1 is associated with both large and small airway disease (20). **We hypothesized that BDR components would be differentially associated with important COPD outcomes.**

Another drawback of BDR is it instability over time.(14) Nevertheless, the hallmark of asthma is lung variability, and it is not surprising that BDR is not stable over time. Given that BDR variability over time may be differentially associated with different clinical features of obstructive lung disease feature, **we hypothesized that in a population at high-risk for COPD (people with history of heavy smoking), consistent BDR over time is differentially associated with obstructive lung disease features relative to inconsistent or absent BDR.**

1.2. COPD with Hyperinflation

Hyperinflation often occurs in COPD as the disease progresses and is well known to be associated with poor prognosis.(22-25) The landmark study by Casanova and colleagues showed that static hyperinflation defined as an increased inspiratory capacity to total lung capacity ration is associated with increased mortality.(23) More recently studies confirm those findings using other definitions of hyperinflation.(24, 25) Several definitions exist which refer to whether measurements of hyperinflation occur during rest (resting) or exercise (dynamic) and the measurement themselves e.g. functional residual capacity, residual volume.(26)

Lung-volume-reduction surgery can alleviate hyperinflation and improve outcomes including mortality.(27) Patients with upper-predominant emphysema, low post-rehabilitation exercise capacity who underwent Lung-volume-reduction surgery had improved long-term survival. Nevertheless, lung-volume-reduction surgery is associated with high perioperative mortality limiting the enthusiasm for the procedure.(28) Less invasive bronchoscopic procedures using endobronchial valves to reduce hyperinflation have been developed showing improvement in lung function, exercise capacity, quality of life, and possible improvement in mortality.(22, 29, 30) Insertion of endobronchial valves via bronchoscopy are associated with 25-30% risk for pneumothorax and for that reason require inpatient observation for 3 days.(29) Apart from the complications, insertion of endobronchial valves via bronchoscopy is a relatively safe procedure.

1.3. COPD with Chronic Hypoxemic Respiratory failure

In the advanced staged of COPD, hypoxemia defined as oxygen saturation below 89% may develop. Oxygen supplementation in patients with COPD and with chronic hypoxemic respiratory failure at rest has shown remarkable long-term mortality benefit with more than 50% increase in survival.(31, 32) However, the benefit of oxygen supplementation in those patients with isolated hypoxemia on exertion (absence of hypoxemia at rest) is either minimal or absent.(33-35) Emtner and colleagues showed oxygen supplementation increased exercise

capacity in patients undergoing exercise training.(34) Patients who received oxygen supplementation while exercising were able to train 4 minutes longer than those who did not receive oxygen. Nonoyama et al. showed the oxygen supplementation improved 5-min walk test by just 15 steps relative to air supplementation. (33) Supplemental oxygen in those with moderate hypoxemia is also not beneficial.(35, 36) Oxygen supplementation in those with isolated nocturnal hypoxemia has no benefit despite that these patient may have less than 90% oxygen saturation more than half of the duration of their sleep.(37, 38)

1.4. COPD with Chronic Hypercapnic Respiratory Failure

Chronic hypercapnic respiratory failure is another consequence of COPD that occurs in advanced stages of the disease and is also associated with increased mortality. Early studies of home non-invasive ventilation (NIV) in those patients showed no benefit(39, 40) but recent randomized control trials (RCTs) showed remarkable outcomes including one-year mortality benefit of 64%.(41, 42) Recent metanalyses found an improvement in mortality, hospitalizations, dyspnea, exercise capacity and health-related quality of life relative to standard treatment.(43, 44) It seems that the benefit is related with a particular ventilator strategy, known as high intensity, that includes large inspiratory to expiratory airway pressure difference, great minute ventilation, and targeting reducing the baseline CO2 levels, as well as with selection of patients with severe disease.(41, 42, 45) RCTs with favorable outcomes recruited patients with severe lung function impairment and hypercapnia who had a recent COPD-related hospitalization or chronic hypoxemic respiratory failure.(41, 42, 46) A recent metanalysis showed that both the baseline arterial CO_2 levels and the magnitude of the CO_2 reduction from the mechanical ventilation are associated with favorable outcomes.(43) Despite the significant benefits from home NIV, it is underutilized among with COPD-related hospitalization and chronic hypercapnic respiratory failure with less of 10% of those using home NIV.(47)

1.5. COPD with Frequent Respiratory Exacerbations

This phenotype of COPD patients has attracted a lot of attention despite that it refers to a small proportion of the total COPD population because consume the largest proportion of the health resources with worse prognosis.(48, 49) Beeh and colleagues in a sample of patients with moderate or severe COPD showed that 13.6% of the patients accounted for 56.6% of the total COPD-related hospitalizations.(48) Although a formal definition for this phenotype does not exist, more than 2 exacerbations a year or one hospitalization has been used as a cut off to identify COPD patients that require escalation of treatment according to GOLD guidelines.(1) Patients with frequent exacerbations may benefit from addition of ICS on bronchodilator therapy, azithromycin, and roflumilast.

This phenotype is heterogenous and probable include patients with chronic bronchitis, asthma-COPD overlap, and chronic hypercapnic respiratory failure. Thus, patients with frequent exacerbations and asthma-COPD overlap may benefit besides addition of ICS and biological therapy.(1, 50) Patients with frequent exacerbations and chronic hypercapnic respiratory failure may see a reduction in hospitalizations with home NIV use.(51) This phenotype should also be considered for other concurrent diagnosis that may increase respiratory exacerbations like antibody deficiency syndrome. A retrospective study of patients with COPD and antibody deficiency syndrome with frequent exacerbations showed that appropriate treatment of these patients reduced the respiratory exacerbations from median of 4 to 1 every year.(52) Further investigation is needed to describe whether this phenotype occur in patients with severe lung disease e.g. severe lung function impairment or in patients with other characteristics. It is also unknown whether frequent exacerbations occur in patients with COPD and mild lung function impairment and whether they are associated with increased burden e.g. increased mortality. **We hypothesized that the burden of disease in COPD with mild-to-moderate lung impairment, and smokers with preserved spirometry, with frequent exacerbations is high.**

1.6. Symptomatic Preserved Spirometry

Recently, this phenotype has been the focus of several investigations because it may reflect a state or conditions that precedes COPD. Woodruff et al. showed that among individuals with at least 20-pack year of current or former smoking exposure, CAT score>10 (highly symptomatic) was with increased respiratory exacerbations and hospitalizations.(4) Balte et al. pooling individual data of 5 prospective cohorts, showed that non-obstructive chronic bronchitis (chronic bronchitis with normal spirometry) was associated with respiratory related hospitalizations and mortality.(53) A metanalysis confirmed that non-obstructive chronic bronchitis was associated increased all-cause mortality in individuals with current or former smoking exposure but not in people without history of smoking exposure.(5) Air trapping in individuals with current or former smoking exposure is associated with increased medication usage, respiratory hospitalizations, progression to COPD, and mortality.(5, 54) Reagan and all showed that among people with at least 10 pack-years current or former smoking exposure , 42.3% have features consistent with obstructive lung disease in the chest CT.(55) COPDGene investigators have led an effort to expand the definition of COPD to include individuals without spirometric obstruction that are at risk for lung function decline or death.(3)

The impact of respiratory exacerbation on COPD is well established but respiratory exacerbations are not well studied in those with preserved lung function. Whether respiratory exacerbations in people with normal lung function result in death without progression to COPD is also unclear. **We hypothesized that respiratory exacerbations in individuals with normal lung function but at risk for COPD, smoked-tobacco exposure, result in lung function decline and progression to COPD.**

1.7. Preserved Ratio Impaired Spirometry (PRISm)

PRISm, also known as restrictive or unclassified spirometry, is a common spirometric pattern which occurs in 10-20% of spirometries.(56-59) PRISm is usually defined as reduced FEV1 with a normal FEV1/FVC(56) but other definitions has applied that refer to a non-obstructive abnormal spirometry.(57) General population studies have shown that it is associated with increased all-cause mortality.(57, 60) Studies in individuals with current or former smoking exposure have shown that PRISm is a heterogenous group with significant symptoms and reduced exercise capacity that include patients with an FEV_1% predict that can range from 44 to 79%, a body mass index (BMI) between 17.2 and 53.8 kg/m^2, and radiographic emphysema in the chest CT that can range from less than 1% to up to 11.43%.(56)

In PRISm, total lung capacity (TLC) may help distinguish a restrictive from an obstructive ventilatory defect, according to the American Thoracic Society-European Respiratory Society (ATS- ERS) 2005 guidelines(61). However, a true “restrictive disease” is very unlikely in high-risk for obstruction lung disease individuals with no interstitial lung disease and unremarkable body mass index (BMI). In COPDGene, the prevalence of PRISm is 12% despite the fact that participants with interstitial lung disease were excluded and body mass index (BMI) in PRISm individuals was slightly higher than the BMI in smokers with normal lung function(56, 62). In addition, a single center study showed that among individuals with PRISm and TLC above the lower limit of normal (LLN), only 26% had a clinical diagnosis of obstructive lung disease(63). Moreover, only 15% of those with PRISm and TLC>LLN develop obstructive spirometry over a median follow-up time of 3 years(64). Currently, there is no available diagnostic test in clinical practice to identify which patients with PRISm may have features classically associated with obstructive lung disease.

In obstructive lung diseases, residual volume (RV) may increase at the expense of FVC with total lung capacity (TLC) remaining normal(65). Conversely, RV may increase with a preserved FVC resulting in an increased TLC. Both processes result in reduced FVC/TLC ratio which may

antedate the development of obstruction diagnosed using standard FEV_1/FVC criteria. A disproportionate decrease of FVC relative to TLC may occur in patients with a restrictive ventilatory defect that coexists with obstructive lung disease(66). Thus, FVC/TLC represents a composite measure that may be able to identify an occult obstructive ventilatory defect. FVC can be readily obtained from spirometry, while TLC, typically assessed by plethysmography, can also be quantified using an inspiratory chest CT (TLC_{CT}), with prior studies demonstrating strong correlations with the plethysmography results(67, 68).

We hypothesized that reduced FVC/TLC ratio in PRISm is associated with clinical, functional and radiographic features of obstructive lung disease, acute respiratory events and increased mortality, and progression to COPD.

More granular phenotyping of COPD (asthma-COPD overlap, Hyperinflation, CHRF, Frequent Respiratory Exacerbations) can help to identify patients that respond well to existing treatment e.g., ICS, home NIV. Identifying individuals with respiratory symptoms or at risk for COPD who do not have obstructive spirometry yet (normal spirometry or PRISm) is critical in order to assess whether existing treatment of those individuals can improve outcomes including preventing from progression to COPD.

2. Aims of the study

The study aimed to identify phenotypes and COPD-like phenotypes using common diagnostic test and procedures. Because there are no “gold standards” for those phenotypes, we examined the association of common spirometry tests like BDR, clinical features like respiratory exacerbations with clinically relevant outcomes like Chest CT findings, lung function decline over time, mortality etc as outlined below in details.

Before we proceeded with the assessment of phenotypes, we examined whether post-bronchodilator spirometry is superior to pre-bronchodilator spirometry to defined spirometric

patterns like obstructive spirometric patterns and we found that post-bronchodilator spirometry is superior.(69) Post-bronchodilator spirometry was used to define the spirometric patterns for the entire thesis.

Specific Aims

Aim 1: To assess the association of BDR components with chronic bronchitis, dyspnea, exercise capacity and structural lung disease, FEV_1 decline over time, respiratory exacerbations, and mortality in patients with COPD.

Aim 2: To assess the association of BDR category: i) consistent BDR (BDR at every visit), ii) inconsistent BDR (BDR at some but not at every visit), and iii) no BDR at any visit (BDR in none of the visits) with clinical asthma diagnosis, blood eosinophil counts, radiological characteristics of airway inflammation, small airway disease and emphysema, and change in post-bronchodilator FEV_1 over time in smoked tobacco-exposed participants with or without COPD,.

Aim 3: To assess the burden of disease associated with frequent exacerbations, including mortality, and identify factors associated with frequent exacerbations in individuals with current or smoking exposure that have mild-to-moderate lung function impairment and individuals with normal spirometry**.**

Aim 4: To assess the association of respiratory exacerbations with lung function decline and progression to COPD in individuals with current or smoking exposure that have normal spirometry.

Aim 5: To assess the association of FVC/TLC with clinical, functional and radiographic features of obstructive lung disease, respiratory exacerbations, and increased mortality, and progression to COPD in individuals with PRISm.

3. Methods

3.1. Aim 1 Methods

We retrospectively analyzed data from the COPDGene study which is an ongoing cohort study that enrolled subjects at 21 clinical centers throughout the United States (http://www.copdgene.org/). The institutional review boards at each participating center approved the study protocol. Details of the study protocol have been published previously(70). Briefly, all subjects provided informed consent before participation in the study. Subjects were self-identified non-Hispanic whites or African Americans between the ages of 45 and 80 years. They completed a modified ATS Respiratory Epidemiology questionnaire and 6-minute walk test (6-MWT) at the enrollment visit. Dyspnea was assessed using the modified Medical Research Council (mMRC) scale(70). Subjects performed pre- and post-bronchodilator spirometry according to ATS-ERS guidelines(71). Subjects were instructed to withhold only short-acting bronchodilators prior to their visits. After pre-bronchodilator spirometric maneuvers, two puffs of albuterol metered-dose inhaler were administered using a spacer. Post-bronchodilator maneuvers were performed between 15 and 40 minutes after two puffs of albuterol dose inhaler were administered using a spacer. We used the National Health and Nutrition Examination Survey (NHANES) III spirometric reference values to calculate % predicted values (72). We included subjects with COPD (post-bronchodilator $FEV_1/FVC<0.70$), and excluded subjects who had undergone lung transplantation or lung volume reduction surgery and subjects with incomplete pre- and post-bronchodilator spirometry data at enrolment. Subjects performed inspiratory and expiratory chest computed tomography (CT) scans using multidetector CT scanners per protocol(70). Total lung capacity or TLC was measured at maximal inspiration. Functional residual capacity or FRC was measured at end expiration. FRC and TLC %predicted were calculated based on the predicted values(73). Emphysema and gas trapping were

quantitated using 3D Slicer software (www.airwayinspector.org), and airway dimensions were measured using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, IA)(70).

Approximately 5 years after the enrolment visit, a proportion of subjects had a repeat spirometry at a follow-up visit. Subjects were contacted every 6 months and completed a validated questionnaire regarding respiratory exacerbations. Vital status was also ascertained on follow-up. For the primary analysis, we excluded subjects with self-reported history of asthma at enrollment. We performed secondary sensitivity analyses by repeating all models including those with asthma.

3.1.1. Definitions and Outcomes

BDR was defined as an increase in pre-bronchodilator FEV_1 *and/or* FVC ≥12% and ≥200ml after bronchodilator administration (ATS-BDR). We categorized BDR into the following categories: (i) *No-BDR*: no BDR by any criteria, (ii) *FEV_1-BDR*: BDR in FEV_1 but no BDR in FVC, (iii) *FVC-BDR*: BDR in FVC but no BDR in FEV_1, and (iv) *Combined-BDR*: BDR in both FEV_1 and FVC. All BDR categories had to meet both 12% and 200 ml volume criteria. In separate analyses, we also examined BDR as i) an increase in FEV_1 and/or FVC ≥12% (relative percent change), and ii) an increase in FEV_1 and/or FVC ≥ 200ml (volume change).

Chronic bronchitis was defined as productive cough for at least 3 consecutive months in the last two years (56). Emphysema was defined by the percentage of lung volume at maximal inspiration with attenuation less than -950 Hounsfield units (HU). Gas trapping was quantified as the percentage of lung volume at end expiration with attenuation less than -856 HU(74). The square root of wall area for a hypothetical airway with an internal perimeter of 10 mm (Pi10) was derived(75). Respiratory exacerbation was defined as an episode of increased cough, phlegm, or shortness of breath that lasted >48 h and required treatment with antibiotics, systemic steroids, or both. Severe exacerbations required an emergency room visit or hospitalization.

FEV_1 change was calculated as the change in ml/year between enrolment and follow-up and visits.

3.1.2. Statistical Analysis

We categorized subjects at enrolment into 4 groups based on BDR category: No-BDR, FEV_1-BDR, FVC-BDR, and Combined-BDR. We compared characteristics of subjects at enrollment. We used Student's t-test or Wilcoxon rank sum test for normal and non-normal continuous variables respectively, and Fischer's exact or Chi-squared test for categorical variables. We performed multivariable logistic and generalized linear regression models as appropriate for associations between BDR categories and chronic bronchitis, mMRC, CT emphysema and gas trapping, 6-MWT distance, and FEV_1 change. For exacerbation analysis, we created zero-inflated negative binomial models as exacerbations followed a Poisson distribution and data were over-dispersed. Follow-up time was included in the models as an offset. All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI) and post-bronchodilator FEV_1 %predicted. We performed Cox proportional hazards regression analysis to examine the association of BDR categories with mortality, with adjustment for age, sex, race, smoking status, smoking pack-years, BMI, post-bronchodilator FEV_1% predicted. We tested additional models by including subjects with self-reported history of asthma diagnosis (Supplement). Finally, we tested similar associations for BDR defined as relative percent change and relative volume change in separate models (Supplement). We used R software package (http://www.r-project.org/) for all statistical analysis. Statistical significance was set at a two-sided alpha of 0.05.

3.2. Aim 2 Methods

We retrospectively analyzed data from SPIROMICS, a prospective observational study conducted at multiple clinical centers in the United States (https://www.spiromics.org/spiromics/). The study

protocol has been approved by the institutional review boards at each participating center (**Supplement**). All participants gave written informed consent. SPIROMICS ernolled participants with ≥20 pack-year smoking exposure and: a post-bronchodilator $FEV_1/FVC<0.7$ or a post-bronchodilator $FEV_1/FVC\geq 0.7$ with an FVC ≥ lower limit of normal (LLN). Details of the study protocol have been published previously.(76)

We used data of individuals with history of ≥20 pack-years of smoking exposure who participated in SPIROMICS. Briefly, participants in SPIROMICS were individuals 40-80 years of age from the general population. Individuals with Body Mass Index (BMI) >40 kg/m^2, unstable cardiovascular disease, and lung disease other than asthma and COPD were excluded. Participants had up to five in-person visits over up to 10 years. At the first visit, they answered questionnaires which included demographics, smoking exposure, medical history, and medication usage, had a complete blood count, and had high-resolution chest CT scans. At each visit, participants had pre- and post-bronchodilator spirometry performed according to American Thoracic Society/European Respiratory Society guidelines,(71) and centralized quality assurance for acceptability and repeatability. Participants were instructed to withhold/refrain from vigorous exercise (0.5 hours), smoking (1 hour), eating a large meal (2 hours), alcohol (4 hours), caffeine (6 hours), inhaled albuterol (6 hours), inhaled ipratropium (8 hours), and any other bronchodilators for 24 hours before spirometry. Post-bronchodilator spirometry was performed between 15 and 30 min after four inhalations each of albuterol 90 µg/inhalation and ipratropium 18 µg/inhalation.

Of 2,770 smoked tobacco-exposed participants with or without COPD, we included 2,270 individuals that had both a pre- and post-bronchodilator spirometry in at least two visits but not necessarily at all five visits. After excluding one participant that had a decrease in FVC of more than 50% after bronchodilator administration (post- minus pre-bronchodilator FEV_1 or FVC < -50%), 2,269 individuals were included in the analysis (**e-Figure 1**). We excluded that participant on the basis that such reduction in FVC were more likely due to technical error.

3.2.1. Definitions and Outcomes

For the main analysis, BDR was defined as an increase in FEV_1 and/or FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration (BDR in flow and/or volume) according to the ATS-ERS guidelines (ATS-BDR). However, ATS-BDR definition is a composite of both BDR in FEV_1 and/or FVC and may have limited value to predict outcomes and identify pathology.(77, 78) For that reason, we assessed additional BDR definitions (**e-Figure 2**). FEV_1-BDR was defined as an increase in FEV_1 greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration. FVC-BDR was defined as an increase in FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration. History of asthma was self-reported (**e-Table 1**). Decline of FEV_1 (ml/year) was derived from the slope of a linear regression model that was fitted to values for post-bronchodilator FEV_1 as a function of the number of days since the first visit.

At the first visit participants had high resolution chest CT scans at maximum inspiration (total lung capacity) and maximal expiration (residual volume). Quantitative image analysis was performed using VIDA software (Coralville, IA). Percent emphysema was defined as the percentage of voxels at maximum inspiration with attenuation less than -950 Hounsfield units (HU), and gas trapping was quantified as the percentage of voxels at maximum expiration with attenuation values less than -856 HU(79). Parametric Response Mapping (PRM) was performed using the Imbio Lung Density Analysis (LDA) software application (Imbio, LLC, Minneapolis, MN) to distinguish regions of emphysema from regions of non-emphysematous gas trapping, also called functional small airways disease (PRM^{fSAD}) (80, 81). Pi10 (a measure of airway wall thickness) was defined as the square root of the airway wall area for a hypothetical airway with an internal perimeter of 10 mm.(82)

3.2.2. Statistical Analysis

We categorized participants based on BDR variability into three groups : Consistent BDR when it is present at every visit, ii) Inconsistent BDR when it is present at some but not at every visit, and ii) Never BDR when it is not present at any visit.

We compared the characteristics of participants at baseline (first) visit between groups using ANOVA or the Kruskal–Wallis test for continuous variables and the chi square test or Fisher's exact test for categorical variables. Then we examined the association of BDR groups (exposure) with history of asthma and history of childhood asthma (outcome is a binary variable) using multivariable logistic regression models.

Between BDR groups, we compared Pi10, % PRM^{fSAD}, % emphysema, % gas trapping, blood eosinophil counts, and FEV_1 decline using multivariable linear regression models. Least square means (LSM) were used for pairwise comparisons with adjustment for multiple comparisons using Tukey's method. In addition, we conducted a sensitivity analysis including only participants with normal spirometry defined as post-bronchodilator $FEV_1/FVC \geq 0.7$. We also examined the association of BDR groups (exposure) with progression to COPD at visit 5 (4 years from baseline).

In all the analyses, we adjusted for age, sex, race, smoking status and pack-years smoked, post-bronchodilator FEV_1% predicted at baseline, **and number of visits that the participant completed** because participants may have variable number of visits (2 to 5 visits). All statistical analyses were conducted using R statistical software (R Foundation for Statistical Computing).

3.3. Aim 3 Methods

We analyzed data from COPDGene, an ongoing study conducted at multiple clinical centers throughout the United States (http://www.copdgene.org/). Subjects were current and former smokers with ≥10 pack-years of smoking who self-identified as non-Hispanic whites (NHW) or African Americans (AA) and were between the ages of 45-80 years at enrollment. The

institutional review boards at each participating center approved the study protocol, and written informed consent was obtained from all participants. Details of the study protocol have been published previously.(70) Briefly, participants completed a modified American Thoracic Society Respiratory Epidemiology questionnaire. Dyspnea was assessed using the modified Medical Research Council (mMRC) scale. Subjects performed pre- and post-bronchodilator spirometry according to American Thoracic Society–European Respiratory Society (ATS-ERS) guidelines (71) and a six-minute walk test (6-MWT) at the enrollment visit. Volumetric chest CT scans were obtained at total lung volume (TLV) (maximal inspiration) and at functional residual capacity (FRC) (end-tidal expiration).(70) Percent emphysema and gas trapping were quantified using 3D Slicer software (www.airwayinspector.org).(70)

We included COPD participants with post-bronchodilator FEV1% predicted≥ 50% and participants with normal spirometry. Individuals with lung transplant or lung volume reduction surgery, and those with less than 3 years follow-up data were excluded. Respiratory exacerbation data were collected prospectively after enrollment. Subjects were contacted every 6 months after enrollment and completed a standardized questionnaire regarding respiratory exacerbations through the Longitudinal Follow-Up program. Vital status was also ascertained using information from the social security death index and the Longitudinal Follow-up program.

3.3.1. Definitions and Outcomes

COPD was defined as post-bronchodilator FEV_1/FVC <0.7. Preserved spirometry was defined as post-bronchodilator FEV_1/FVC ≥0.7 and FEV1% predicted ≥80%. Exacerbations were defined as episodes of worsening respiratory symptoms requiring use of antibiotics and/or systemic steroids. Severe exacerbations were defined as those requiring hospitalizations or emergency room visits. Other variable definitions have been previously described(70). We defined frequent exacerbators as those at the top 5% in the average exacerbation frequency.

Since the frequent exacerbator phenotype has not been investigated in COPD patients with mild-to-moderate lung function impairment and smokers with preserved spirometry, we did not use the typical 2 exacerbations/year definition (83). In a sensitivity analysis, we defined frequent exacerbators as those with ≥2 exacerbations per year.

History of acute bronchitis or pneumonia was defined as self-reported history of bronchitis or pneumonia at study enrollment. Similarly, history of asthma was also self-reported. History of cancer was defined as self-reported history of lung, breast, prostate, colon, and/or bladder cancer. Bronchodilator response was defined as an increase in prebronchodilator FEV1 and/or FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration(61).TLV was measured from volumetric inspiratory chest CT scans and is a surrogate of plethysmographic total lung capacity. TLV% predicted was calculated based on MESA predicted values(84). Percent emphysema and gas trapping was calculated as previously(70).

3.3.2. Statistical Analysis

We stratified COPD participants into 3 groups based on their annual rate of respiratory exacerbations: i) No-exacerbation, ii) exacerbators (>0 but less than frequent exacerbators), and iii) frequent exacerbators (top 5% in the rate of respiratory exacerbations). We compared the characteristics of participants between groups using ANOVA for continuous variables and chi-squared or fisher exact test for categorical variables.

In a univariate analysis, we identified variables associated with the frequent exacerbator group (frequent exacerbator vs the rest). Variables associated with the frequent exacerbator group with univariate p value <0.10 were considered for a multivariable logistic regression model. Medication use and current smoking status were not considered for the model as participants with frequent exacerbations used more medications and were less likely to be current smokers

(confounding by indication). Variables were selected for the final model using a stepwise backward variable elimination process to minimize the Akaike information criterion (AIC).(85) We assessed for variable multicollinearity using correlation matrices and variance inflation factors.(86) We repeated the multivariable analysis after multiple imputations(5 datasets) by chained equations (MICE) to account for missing variables.(87) .

We used Cox proportional hazard regression models to examine the association between the groups with all-cause mortality. We also used Cox proportional hazard regression models to examine the association between exacerbations and all-cause mortality. Models included the following covariates: age, gender, race, current smoking status, smoking pack-years, BMI, and post-bronchodilator FEV1% predicted at enrollment. In a sensitivity analysis, we defined frequent exacerbators as those with 2 or more exacerbations per year, and we assessed the association of frequent exacerbations with mortality.

Similarly, we stratified current or former smokers with normal spirometry based on their annual rate of respiratory exacerbations, and we performed the same analysis as above. All statistical analyses were conducted using R statistical software (http://www.r-project.org/) using the following R software packages: 'car', 'dunn.test', 'ggplot2', 'survminer', 'tableone', 'mice', 'pscl', 'MASS', 'AER', 'survival', and 'DescTools'.

3.4. Aim 4 Methods

We analyzed data of participants in COPDGene with at least 10 pack-years smoked-tobacco exposure. COPDGene (http://www.copdgene.org/) is a multicenter study conducted in the US that enrolled participants with ≥10 pack-years of current or former smoked-tobacco exposure were between the ages of 45–80 years at enrollment and self-identified as non-Hispanic whites or African Americans. Details of COPDGene protocol has previously published.(70) The study

protocol has been approved by the institutional review boards at each participating center. Written informed consent was obtained from all participants. Participants underwent an enrollment visit (visit 1), a visit 2 (occurred approximately 5 years after visit 1), and visit 3 (occurred approximately 10 years after visit 1). At each visit, they completed a modified American Thoracic Society Respiratory Epidemiology questionnaire and performed pre- and post-bronchodilator spirometry according to 2005 American Thoracic Society–European Respiratory Society (ATS-ERS).(88) Acute respiratory exacerbation data were collected prospectively after visit 1. Participants were contacted every 6 months after visit 1 and completed a standardized questionnaire regarding acute respiratory exacerbations through the Longitudinal Follow-Up program. Vital status was ascertained using information from the Longitudinal Follow-up program and the social security death index.

We included participants ≥10 pack-years of current or former smoked-tobacco exposure that had available spirometric data both at visit 1 and visit 2. Of those, we excluded participants with abnormal spirometry at visit 1 defined as post-bronchodilator FEV_1/FVC<0.7 and/or FEV_1%predicted<80%.

3.4.1. Definition and Outcomes

We defined respiratory exacerbations as episodes of worsening respiratory symptoms requiring use of antibiotics and/or systemic steroids and those require emergency room visit and hospitalizations as severe exacerbations. COPD was defined as post-bronchodilator FEV1/FVC <0.7. Because of some participants may have developed preserved ratio impaired spirometry (PRISm), abnormal spirometry was considered as outcome, and it was defined as post-bronchodilator FEV_1%predicted<80% and/or FEV1/FVC <0.7. Asthma was defined when a participant answered “Yes” to the following question; “Have you ever had asthma?” Post-bronchodilator FEV_1 % predicted was calculated using the third National Health and Nutrition Examination Survey predicted values.(72)

3.4.2. Statistical Analysis

We categorized participants into 3 groups based on the average exacerbation rate (exacerbation/year) between visit 1 and visit 2 into 3 groups: i) No exacerbation, ii) > 0 exacerbations but ≤ 1 exacerbation/year, and iii) > 1 exacerbation/year. We compared characteristics between groups using chi-square or Fisher's exact test for categorical variables and using ANOVA or Kruskal – Wallis test for continuous variables.

We created generalized linear models with a logit link to assess the association of exacerbation rate with progression to COPD or abnormal spirometry (COPD or PRISm) at visit 2. The main dependent variable (exposure) in the model was the average exacerbation (exacerbation/year) between visit 1 and visit 2. Age, sex, race, smoking-pack years, current smoking status (current or former), body mass index, post-bronchodilator FEV_1 % predicted, and history of self-reported asthma at visit 1 were included as co-variates. We created generalized linear models to assess the association of exacerbation rate between visit 1 and visit 2 with FEV_1 decline (ml/year) between visit 1 and visit 2. We used the same covariates as above. In addition, to assess the association of prior exacerbations with future lung function decline, we created generalized lineal models with exacerbation rate between visit 1 and visit 2 as the main dependent variable (exposure) and progression to COPD and abnormal spirometry at visit 3, and FEV_1 decline (ml/year) between visit 2 and visit 3 as the dependent variables (outcome) among individuals with normal spirometry at visit 2. For those models, we included age, sex, race, smoking-pack years, current smoking status (current or former), body mass index, post-bronchodilator FEV_1 % predicted, and history of self-reported asthma at visit 2 as co-variates. Moreover, we employed Cox proportional hazard regression models to examine the association of exacerbation rate with all-cause mortality. For this analysis, the cohort entry was visit 2 and the main independent variable was the average exacerbation per year between visit 1 and visit 2. We included the following co-variates: Age, sex, race, smoking-pack years, current smoking status (current or

former), body mass index, and post-bronchodilator FEV_1 % predicted at the cohort entry (visit 2). We also assessed the following interactions: exacerbations and COPD abnormal spirometry at visit 2, and exacerbations and abnormal spirometry at visit 2. We conducted all statistical analyses using R statistical software (http://www.r-project.org/) and the following R software packages: 'ggplot2', 'survminer', 'tableone', 'pscl', 'MASS', 'AER', 'survival', and 'DescTools'.

3.5. Aim 5 Methods

We analyzed data from participants in the COPDGene study, an ongoing study conducted at multiple clinical centers through the United States (http://www.copdgene.org/). Participants were current and former smokers with ≥10 pack-years of smoking who self-identified as non-Hispanic whites (NHW) or African Americans (AA) and were between the ages of 45-80 years at enrollment. The institutional review boards at each participating center approved the study protocol and written informed consent was obtained from all participants. Details of the study protocol have been published previously(70). Briefly, participants completed a modified American Thoracic Society Respiratory Epidemiology questionnaire, St. George's Respiratory Questionnaire (SGRQ), and 6-minute walk test (6-MWT) at the enrollment visit. Dyspnea was assessed using the modified Medical Research Council (mMRC) scale. Participants performed pre- and post-bronchodilator spirometry. The complete study protocols were performed in accordance with the relevant guidelines and regulations of American Thoracic Society–European Respiratory Society (ATS-ERS)(71). Volumetric chest CT scans were obtained at TLC_{CT} (maximal inspiration) and at functional residual capacity (FRC_{CT}) (end-tidal expiration) using multidetector CT scanners(70). FRC and TLC% predicted were calculated based on the predicted values (73). Percent emphysema and gas trapping were quantified using 3D Slicer software (www.airwayinspector.org)(70).

We included participants with PRISm at enrollment. We excluded individuals with significant interstitial lung disease or bronchiectasis on chest CT, those with missing post-bronchodilator spirometry or TLC_{CT} measurements at baseline, and participants with post-bronchodilator FVC>TLC_{CT} at enrollment. Approximately 5 years after the enrollment visit, participants were invited for a follow-up visit that included a repeat spirometry and chest CT. Respiratory exacerbation data were collected prospectively after enrollment. Participants were contacted every 6 months after enrollment and completed a standardized questionnaire regarding respiratory exacerbations through the Longitudinal Follow Up program. Vital status was also ascertained using information from the social security death index and the Longitudinal Follow Up program.

3.5.1. Definitions and Outcomes

PRISm was defined as post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC ≥ 0.7. COPD was defined as post-bronchodilator FEV_1/FVC <0.7. The FVC/TLC_{CT} ratio at enrollment was calculated using post-bronchodilator FVC (in liters) from spirometry, while TLC_{CT} was measured from volumetric inspiratory chest CT scans.

Co-morbidities and medication usage were self-reported. Percent emphysema was defined by using the percentage of lung volume at TLC_{CT} with attenuation less than -950 Hounsfield units (HU)(70). Gas trapping was quantified as the percentage of lung volume at FRC with attenuation values less than -856 HU(70). Parametric response mapping analysis was performed on paired registered inspiratory and expiratory images to distinguish functional small airways disease (PRM^{fSAD}) from emphysema by Imbio LLC (Minneapolis, MN) using lung density analysis software(80). As previous described(81), we defined PRM^{fSAD} as the percentage of lung with evidence of gas trapping *not* due to emphysema (i.e. areas of lung with attenuation < -856 HU on expiration minus area of lung with attenuation < -950 HU on inspiration).

Change in FEV_1 between enrollment and 5-year follow up visit was calculated using post-bronchodilator spirometry. Exacerbations were defined as episodes of worsening respiratory symptoms requiring use of antibiotics and/or systemic steroids. Severe exacerbations were defined as those requiring hospitalizations or emergency room visits. Other variable definitions have been previously described(70).

3.5.2. Statistical Analysis

We stratified PRISm participants at the enrollment visit into quartiles by FVC/TLC_{CT}: very high, high, low, and very low. We compared the characteristics of PRISm individuals at the enrollment visit, rates of progression to COPD at the 5-year follow-up visit, and exacerbations over the time between the FVC/TLC_{CT} quartiles. We used Spearman's rank correlation to examine changes in continuous variables with increasing FVC/TLC_{CT}. We used the Cochran Armitage trend test to examine proportion changes with increasing FVC/TLC_{CT} quartile.

We created multivariable logistic and linear regression models with chronic bronchitis, mMRC and SGRQ scores, radiographic measures and 6-MWT distance at the enrollment visit as the dependent variable (outcome) and post-bronchodilator FVC/TLC_{CT} quartile at the enrollment as the independent variable (predictor). All models included the following covariates: age and current smoking status at enrollment, gender, race, pack-years smoked, body mass index (BMI), history of asthma and congestive heart failure. There were no missing values in any of the covariates. We also performed a multivariable linear and logistic regression analysis with change in FEV_1, 6-MWT distance, radiographic measurements, and progression to COPD at the follow-up visit as the dependent variable (outcome) and post-bronchodilator FVC/TLC_{CT} quartile at enrollment as the independent variable (predictor). We included the following covariates in these models: age and current smoking status at enrollment, gender, race, pack-years smoked, body mass index (BMI), history of asthma and congestive heart failure, and change of BMI between enrollment and follow-up visit.

For the exacerbation analysis, we created zero-inflated negative binomial models which included adjustment for age and current smoking status at enrollment, gender, race, pack-years smoked, BMI, chronic bronchitis, history of asthma and congestive heart failure. There were no missing values in any of the covariates. Follow-up time was included as an offset in the models as previously described(89).

We used Cox proportional hazard regression models to examine the association between post-bronchodilator FVC/TLC_{CT} quartile with all-cause mortality. Models included the following covariates: age, gender, race, smoking status, smoking pack-years, BMI, diabetes, history of asthma and congestive heart failure. There were no missing values in any of the covariates.

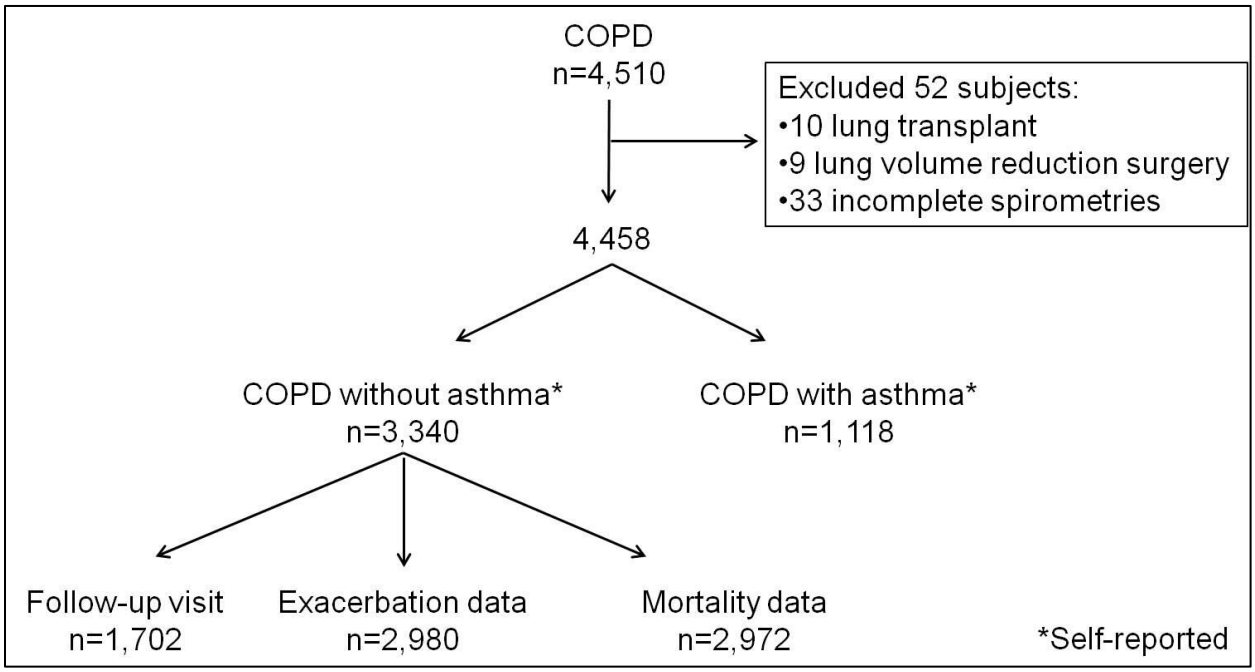
In sensitivity analyses, we repeated selected analyses using PRISm defined as post-bronchodilator FEV1<LLN with a post-bronchodilator FEV1/FVC≥LLN and COPD defined as post-bronchodilator FEV1/FVC<LLN using the NHANES III reference values(72). All statistical analyses were conducted using R statistical software (http://www.r-project.org/) using the following R software packages: ‘dunn.test’, ‘FSA’, ‘pscl’, ‘MASS’, ‘AER’, ‘survival’, and ‘DescTools’.

4. Results

4.1. Aim 1 Results

The cohort included 4,458 subjects with COPD (**Supplement Figure E1 for Consort Diagram**). After excluding 1,118 subjects with self-reported history of asthma diagnosis, 3,340 subjects were included in the analysis. Follow-up data for exacerbations and vital status were available in 2,980 and 2,972 subjects, respectively.

Figure 1. Participants' Flow chart



Baseline Characteristics at enrollment (n = 3,340)

Of all 3,340 subjects in the cohort, 1,083 subjects (32.43%) had ATS-BDR. Compared with No-BDR, subjects with ATS-BDR had higher mMRC and lower post-bronchodilator FEV_1% predicted (**Table 1**). In ATS-BDR subjects, there were more GOLD 3 and 4 subjects than in No-BDR group. ATS-BDR subjects had more radiographic %gas trapping and functional small airway disease, and greater Pi10 than No-BDR.

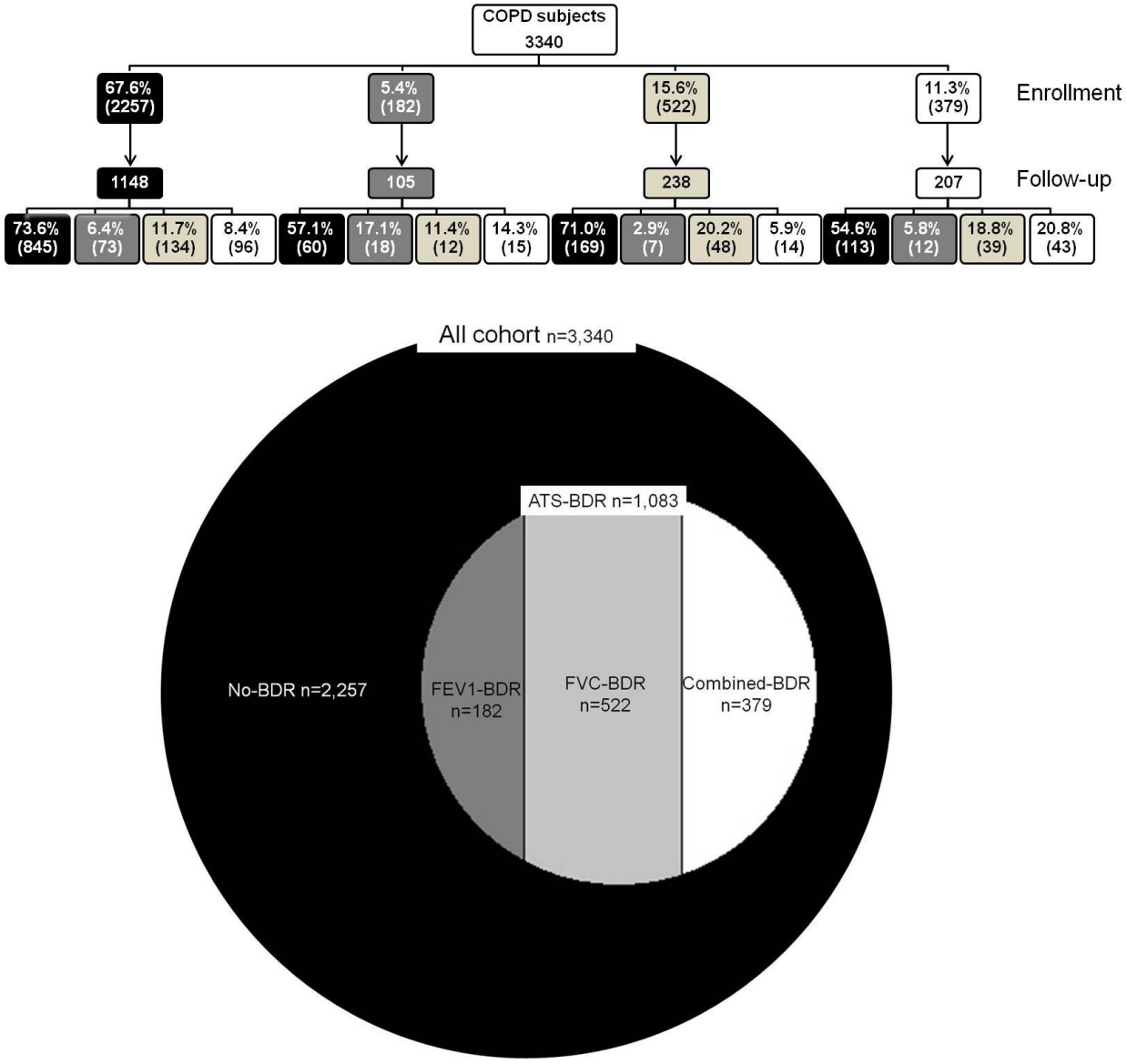
Table 1. Characteristics of COPD subjects at enrollment by bronchodilator response groups (n=3,340).

	ATS-BDR‡ (n=1,083)	No-BDR (n=2,257)
Age, y	63.71 ± 8.84	63.50 ± 8.41
Female, n(%)	452 (41.74%)	920 (40.76%)
African American, n(%)	198 (18.28%)	443 (19.63%)
Body mass index, Kg/m^2	27.63 ± 5.72	27.62 ± 5.95
Pack-years smoking	52.90 ± 27.00	52.66 ± 27.04
Active Smokers, n (%)	475 (43.86%)	998 (44.22%)
Chronic Bronchitis	284 (26.22%)	534 (23.66%)
MMRC	1.83 ± 1.47*	1.72 ± 1.45
ICS, n(%)§	401 (37.40%)	854 (38.40%)
LABA, n(%)§	360 (33.68%)*	852 (38.31%)
LAMA, n(%)§	305 (28.67%)*	760 (34.32%)
Post-FEV1% predicted	56.79 ± 21.92*	59.94 ± 23.34
Post-FVC% predicted	84.14 ± 19.76	82.55 ± 20.46
GOLD stage		
GOLD I: Mild	167 (15.42%)	497 (22.02%)
GOLD II: Moderate	484 (44.69%)	958 (42.45%)
GOLD III: Severe	295 (27.24%)	532 (23.57%)
GOLD IV: Very severe	137 (12.65%)	270 (11.96%)
p-value †	<0.001	ref
FEV1 change after BD, L	0.23 ± 0.15*	0.04 ± 0.13
FVC change after BD, L	0.51 ± 0.30*	0.041 ± 0.21
FEV1/FVC change after BD	-0.013 ± 0.067*	0.005 ± 0.042
% emphysema	12.33 ± 12.50	12.08 ± 12.45
% gas trapping	37.49 ± 20.80*	34.42 ± 20.48
PRM^{fSAD}, %	27.43 ± 12.7*	24.5 ± 12.4
Pi10, mm	3.71 ± 0.13*	3.68 ± 0.13
FRC% predicted	125.20 ± 31.11	118.40 ± 30.02
TLC% predicted	103.50 ± 15.96	101.60 ± 16.46
6-min walk test distance, feet	1255.00 ± 388.26	1249.00 ± 414.91

ATS-BDR= increase in FEV1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.
FEV1-BDR= increase in FEV1≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% and <200ml after bronchodilator administration.
Continue variables are presented as mean ± standard deviation.
Abbreviations: BD= bronchodilator; FRC= functional residual capacity; ICS=inhaled glucocorticosteroids; LABA=long acting b-agonist, LAMA= Long-acting muscarinic antagonist; MMRC= Modified Medical Research Council; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; PRM^{fSAD}=Parametric response mapping (PRM) functional small airway disease; TLC= total lung capacity.
* P<0.05 vs No-BDR using t-test, Wilcox text, Fischer or Chi-Square when appropriate.
† across all GOLD stages shown (vs No-BDR using Chi-Square).
§ Data were available for a subset of subjects.
‡ ATS-BDR= the sum of FEV1-BDR, FVC-BDR and Combined-BDR.
For % emphysema and TLC% predicted analysis, data were available for 3127 subjects.
For % GT and FRC% analysis, data were available for 2788 subjects.
For Pi10 data analysis, data were available for 3102 subjects.
For 6-MWT data analysis, data were available for 3264 subjects.

Of the 1,083 ATS-BDR subjects, 182 (5.45%) had FEV_1-BDR, 522 (15.63%) had FVC-BDR, and 379 (11.34%) had Combined-BDR (**Figure 2**).

Figure 2. Bronchodilator response rates in COPD subjects at enrollment and follow-up visit.



FEV_1-BDR= increase in FEV_1 ≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV_1 < 12% and 200ml after bronchodilator administration
Combined-BDR= an increase in both FEV_1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV_1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV_1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.

Table 2 shows the characteristics of subjects at enrolment categorized into BDR groups.

Table 2. Characteristics of COPD subjects at enrollment by bronchodilator response groups (n=3340).

	FEV_1-BDR (n=182)	**FVC-BDR (n=522)**	**Combined-BDR (n=379)**	**No-BDR (n=2,257)**
Age, y	61.55 ± 8.77*	64.67 ± 8.70*	63.43 ± 8.90	63.50 ± 8.41
Female, n(%)	62 (34.07%)	256 (49.04%)	134 (35.36%)	920 (40.76%)
African American, n(%)	33 (18.13%)	104 (19.92%)	61 (16.09%)	443 (19.63%)
Body mass index, Kg/m^2	28.84 ± 6.27*	27.07 ± 5.57	27.81 ± 5.54	27.62 ± 5.95
Pack-years smoking	50.23 ± 24.94	52.54 ± 27.46	54.66 ± 27.26	52.66 ± 27.04
Active Smokers, n (%)	87 (47.80%)	208 (39.85%)	180 (47.49%)	998 (44.22%)
Chronic Bronchitis	50 (27.47%)	122 (23.37%)	112 (29.55%)*	534 (23.66%)
MMRC	1.54 ± 1.39	2.05 ± 1.50*	1.67 ± 1.42	1.72 ± 1.45
ICS, n(%)§	55 (30.22%)*	239 (46.31%)*	107 (28.61%)*	854 (38.40%)
LABA, n(%)§	49 (26.92%)*	229 (44.64%)*	82 (21.93%)*	852 (38.31%)
LAMA, n(%)§	38 (21.47%)*	193 (37.62%)	74 (19.79%)*	760 (34.32%)
Post- FEV_1% predicted	68.28 ± 16.10*	51.64 ± 24.39*	58.38 ± 18.12	59.94 ± 23.34
Post-FVC% predicted	88.68 ± 16.36*	82.38 ± 22.40	84.39 ± 16.86	82.55 ± 20.46
GOLD stage				
GOLD I: Mild	34 (18.68%)	80 (15.33%)	53 (13.98%)	497 (22.02%)
GOLD II: Moderate	124 (68.13%)	168 (32.18%)	192 (50.66%)	958 (42.45%)
GOLD III: Severe	23 (12.64%)	153 (29.31%)	119 (31.40%)	532 (23.57%)
GOLD IV: Very severe	1 (0.55%)	121 (23.18%)	15 (3.96%)	270 (11.96%)
p-value †	<0.001	<0.001	<0.001	ref
FEV_1 change after BD, L	0.32 ± 0.11*	0.11 ± 0.10*	0.34 ± 0.12*	0.04 ± 0.13
FVC change after BD, L	0.21 ± 0.16*	0.50 ± 0.24*	0.65 ± 0.32*	0.041 ± 0.21
FEV_1/FVC change after BD	0.057 ± 0.040*	-0.046 ± 0.052*	-0.002 ± 0.067	0.005 ± 0.042
% emphysema	8.15 ± 8.71*	14.94 ± 14.08*	10.66 ± 10.77	12.08 ± 12.45
% gas trapping	27.67 ± 15.49*	41.77 ± 22.46*	36.11 ± 18.80	34.42 ± 20.48
PRM^{fSAD}, %	21.6± 10.7*	28.6 ± 13.3*	28.1 ± 12.0*	24.5 ± 12.4
Pi10, mm	3.67 ± 0.15	3.71 ± 0.12*	3.72 ± 0.14*	3.68 ± 0.13
FRC% predicted	112.40 ± 23.31*	130.10 ± 34.72*	124.20 ± 27.04*	118.40 ± 30.02
TLC% predicted	100.10 ± 15.14*	104.60 ± 17.07*	103.40 ± 14.48*	101.60 ± 16.46
6-min walk test distance, feet	1363.00 ± 370.07*	1175.00 ± 407.35	1312.00 ± 347.35	1249.00 ± 414.91

FEV_1-BDR= increase in FEV_1≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV_1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both $FEV_1$and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both $FEV_1$and FVC<12% and <200ml after bronchodilator administration.
Continue variables are presented as mean ± standard deviation.

Abbreviations: BD= bronchodilator; FRC= functional residual capacity; ICS=inhaled glucocorticosteroids; LABA=long acting b-agonist, LAMA= Long-acting muscarinic antagonist; MMRC= Modified Medical Research Council; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; PRM^{fSAD}=Parametric response mapping (PRM) functional small airway disease; TLC= total lung capacity.
* P<0.05 vs No-BDR using t-test, Wilcox text, Fischer or Chi-Square when appropriate.
† across all GOLD stages shown (vs No-BDR using Chi-Square).
§ Data were available for a subset of subjects.
For % emphysema and TLC% predicted analysis, data were available for 3127 subjects.
For % GT and FRC% analysis, data were available for 2788 subjects.
For Pi10 data analysis, data were available for 3102 subjects.
For 6-MWT data analysis, data were available for 3264 subjects.

Compared with No-BDR subjects, FEV_1-BDR subjects were younger and had higher BMI and post-bronchodilator FEV_1 %predicted and FVC %predicted, had less advanced COPD stage, less CT emphysema and CT gas trapping, and less functional small airways disease, lower FRC %predicted and TLC %predicted by CT, and covered greater 6-MWT distance. Compared to No-BDR, FVC-BDR subjects were older, and had greater dyspnea, lower post-bronchodilator FEV_1 %predicted, greater %emphysema and gas trapping, greater functional small airway disease, higher FRC %predicted and TLC %predicted by CT, and shorter 6-MWT distance. Subjects in this category were more likely to have more advanced COPD stage than No-BDR subjects.Compared to No-BDR, Combined-BDR subjects reported a higher frequency of chronic bronchitis, had no difference in CT emphysema and gas trapping, but they had more functional small airway disease and greater Pi10, FRC% predicted, and greater 6-MWT distance.

On multivariable analysis, FEV_1-BDR was not associated with any of the outcomes, but FVC-BDR was associated with greater % gas trapping, FRC% and TLC% predicted (**Table 3**).

Table 3. Associations of bronchodilator response categories with clinical, functional and radiographic features at enrollment in subjects with COPD (n=3,340).

	Chronic Bronchitis		**MMRC**		**6-MWT(feet)**		**Pi10(mm)**	
	OR(95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value
No-BDR	ref		ref		ref		ref	
FEV_1-BDR	1.30 (0.91, 1.85)	0.15	0.09 (-0.09, 0.27)	0.31	30.6(-19.6,80.7)	0.23	0.01(-0.01,0.03)	0.34
FVC-BDR	0.94 (0.73, 1.18)	0.58	0.05 (-0.07, 0.16)	0.41	6.1(-25.88,38.1)	0.71	0.01(-0.003,0.02)	0.16
Combined-BDR	1.24 (0.96, 1.59)	0.09	-0.09 (-0.22, 0.04)	0.17	70.8(35.09,106.4)	<0.001	0.04(0.02,0.05)	<0.001
ATS-BDR*	1.10 (0.92 ,1.31)	0.28	0.01 (-0.08, 0.09)	0.87	33.5 (9.5, 57.5)	0.01	0.02 (0.01, 0.03)	<0.001
	% emphysema		**% gas trapping**		**FRC% predicted**		**TLC% predicted**	
	Coef (95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value
No-BDR	ref		ref		Ref		ref	
FEV_1-BDR	-0.76 (-2.19, 0.67)	0.30	-0.16 (-2.27, 1.96)	0.88	1.41 (-2.52, 5.35)	0.48	0.26(-2.18,2.70)	0.84
FVC-BDR	0.13 (-0.76, 1.02)	0.77	1.47 (0.15, 2.78)	0.03	4.37 (1.91, 6.82)	<0.001	1.53(0.003, 3.05)	0.0496
Combined-BDR	-1.67 (-2.68, -0.65)	0.001	1.41 (-0.08, 2.89)	0.06	5.10 (2.33, 7.87)	<0.001	1.78(0.05,3.51)	0.043
ATS-BDR*	-0.65 (-1.32, 0.03)	0.059	1.18 (0.18, 2.17)	0.02	4.14 (2.28, 5.99)	<0.001	1.40 (0.25, 2.55)	0.02

FEV_1 -BDR= increase in FEV_1 ≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV_1 < 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV_1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV_1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV_1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.

Abbreviations: Coef= Coefficient; FRC= functional residual capacity; MMRC= Modified Medical Research Council; OR= odds ratio; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLC= total lung capacity; 6-MWT= 6-min walk test; 95%CI= 95% confidence interval.

For % emphysema and TLC% predicted analysis, data were available for 3127 subjects
For % GT and FRC% analysis, data were available for 2788 subjects.
For 6-MWT data analysis, data were available for 3264 subjects.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI) and post-bronchodilator FEV_1 % predicted.

Combined-BDR was associated with lower %emphysema, greater functional small airway disease (**Table 4**) and Pi10, FRC and TLC %predicted and longer 6-MWT distance. ATS-BDR was associated with higher % gas trapping, greater functional small airway disease and Pi10, FRC and TLC %predicted and longer 6-MWT distance.

Table 4. Association of bronchodilator response categories with functional small airway disease (n=1,872).

	PRM^{fSAD}	
	Coef (95%CI)	P value
No-BDR	ref	
FEV1-BDR	0.38(-1.71, 2.46)	0.72
FVC-BDR	0.79 (-0.42, 2.0)	0.20
Combined-BDR	3.06 (1.70, 4.4)	<0.001
ATS-BDR	1.56 (0.63, 2.49)	<0.001

FEV1-BDR= increase in FEV1≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.

PRM^{fSAD}=Parametric response mapping (PRM) functional small airway disease

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI) and post-bronchodilator FEV1% predicted.

Change in FEV1 between enrollment and 5-year follow-up visit (n = 1,702)

The mean FEV_1 decline for the cohort was -40.39 $\pm$ 54.52 ml/year. In adjusted analysis, FEV_1-BDR (adjusted beta regression coefficient(Coef)= -18.34, 95%CI= -28.78 to -7.90, p<0.001), FVC-BDR (Coef= -8.11, 95%CI= -15.49 to -0.73, p=0.03), and Combined-BDR (Coef= -21.86, 95%CI= (-29.60 to -14.11 , p<0.001) were all associated with FEV_1 decline over time (**Table 5**). ATS-BDR was also associated with FEV_1 decline (Coef= -15.32, 95%CI= -20.66 to -9.98, p<0.001). Based on the coefficients, Combined-BDR was associated with greater FEV_1 decline.

Table 5. Association of bronchodilator response categories at enrollment with drop in FEV1 between baseline and follow-up visit and respiratory exacerbations in subjects with COPD.

	Change in FEV_1 (ml/year)		**Exacerbations**		**Severe exacerbations**	
Subjects	1,702		2,980		2,980	
	Coef (95%CI)	P value	IRR (95%CI)	P value	IRR (95%CI)	P value
No-BDR	ref		ref		Ref	
FEV_1-BDR	-18.34 (-28.78, -7.90)	<0.001	1.18 (0.90, 1.55)	0.26	0.97 (0.68, 1.40)	0.88
FVC-BDR	-8.11 (-15.49, -0.73)	0.03	1.10 (0.93, 1.30)	0.29	1.09 (0.88, 1.35)	0.42
Combined-BDR	-21.86 (-29.60, -14.11)	<0.001	1.25 (1.03, 1.50)	0.02	1.34 (1.05, 1.71)	0.02
ATS-BDR*	-15.32 (-20.66, -9.98)	<0.001	1.16 (1.02, 1.32)	0.02	1.16 (0.98, 1.37)	0.08

FEV_1-BDR= increase in FEV_1 ≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV_1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV_1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV_1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV_1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.
Abbreviations: Coef= Coefficient; IRR= incidence rate ratio; 95%CI= 95% confidence interval.

*Multivariable logistic regression models with ATS-BDR binary variable= BDR according to ATS guidelines; Yes or NO) as the independent variable.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI) and post-bronchodilator FEV_1% predicted.

Respiratory Exacerbations (n = 2,980*)*

FEV_1-BDR and FVC-BDR were not associated with respiratory exacerbations (**Table 5**). In contrast, Combined-BDR was associated with respiratory exacerbations (Incident rate ratio, IRR =1.25; 95%CI=1.03-1.50, p=0.02) and severe respiratory exacerbations (IRR=1.34, 95%CI=1.05-1.71, p=0.02) (**Table 5**).ATS-BDR was associated with respiratory exacerbations (IRR=1.16, 95%CI=1.02-1.32, p=0.02) but it was not associated with severe respiratory exacerbations (IRR=1.16, 95%CI=0.98-1.37, p=0.08).

Mortality (n = 2,972*)*

Overall, 650 (21.87%) died over a median duration of 2371 (IQR = 2073 - 2652) days follow-up. Mortality was 21.87% (437 of 1,998) in the No-BDR group. Mortality was 21.87% (213 of 974) in

the ATS-BDR group, 12.80% (21 of 164) in the FEV_1-BDR group, 28.54% (133 of 466) in the FVC-BDR group and 17.15% (59 of 344) in the Combined-BDR group. After adjusting for demographics, smoking status, and post-bronchodilator FEV_1 %predicted, FEV_1-BDR (adjusted Hazards Ratio (HR) = 0.87 ;95%CI=0.56-1.35, p=0.53), FVC-BDR (HR =1.00;95%CI=0.83-1.22, p=0.97), and ATS-BDR (HR =0.91;95%CI=0.77-1.07, p=0.25) were not associated with mortality, whereas Combined-BDR was associated with lower mortality (HR =0.76;95%CI=0.58-0.99, p=0.046) (**Table 6**).

Table 6. Association of bronchodilator response categories at enrollment with mortality in subjects with COPD(n=2,972).

	Mortality	
	Adjusted HR (95%CI)	**P value**
No-BDR	ref	
FEV_1-BDR	0.87 (0.56, 1.35)	0.53
FVC-BDR	1.00 (0.83, 1.22)	0.97
Combined-BDR	0.76 (0.58, 0.99)	0.046
ATS-BDR*	0.91 (0.77, 1.07)	0.25

FEV_1-BDR= increase in FEV_1 ≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV_1 < 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV_1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV_1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.
Abbreviations: HR=Hazard ratio; 95%CI= 95% confidence interval.

Cox Hazard regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI) and post-bronchodilator FEV_1 % predicted.

Bronchodilator response at follow-up visit

1,702 subjects completed a spirometry at follow-up visit. Of all subjects with pre- and post-bronchodilator spirometry at follow-up visit (n=1,698), 69.9% had No-BDR and 30.1% had ATS-BDR: 6.5% had FEV_1-BDR, 13.7% had FVC-BDR, and 9.9% had Combined-BDR. Of the No-BDR subjects at enrolment, 73.6% had No-BDR at the follow-up visit. Of FEV_1-BDR subjects, 17.1% had FEV1-BDR at follow-up visit (**Figure 2**). Of FVC-BDR subjects at enrollment, 20.2% had FVC-BDR at follow-up. Of Combined-BDR subjects at enrolment, 20.8% had Combined-BDR at follow-up visit.

Sensitivity Analyses

We repeated the analyses in COPD subjects with and without history of asthma with similar findings **(Table 7-9).** When subjects with GOLD 1 were excluded from the analyses, Combined-BDR remained associated with less emphysema, higher frequency of exacerbations and lower mortality (**Table 7-9**).

Table 7. Association of bronchodilator response categories with clinical, functional and radiographic features at enrollment in COPD subjects with or without history of asthma(n=4,458).

	Chronic Bronchitis		**MMRC**		**6-MWT**		**Pi10(mm)**	
	OR(95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value
No-BDR	ref		ref		ref		ref	
FEV1-BDR	1.26 (0.93, 1.69)	0.13	0.12 (-0.04, 0.27)	0.13	7.80 (-34.40, 50.01)	0.72	0.01 (-0.01, 0.03)	0.20
FVC-BDR	1.03 (0.84, 1.25)	0.80	0.07 (-0.03, 0.17)	0.18	-0.76 (-28.55, 27.04)	0.96	0.02 (0.01, 0.03)	0.004
Combined-BDR	1.32 (1.07, 1.62)	0.01	-0.04 (-0.15, 0.07)	0.46	59.18 (28.53, 89.82)	<0.001	0.05 (0.04, 0.06)	<0.001
	% emphysema		**% gas trapping**		**FRC% predicted**		**TLC% predicted**	
	Coef (95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value	Coef (95%CI)	P value
No-BDR	ref		ref		ref		ref	
FEV1-BDR	-1.12 (-2.31, 0.07)	0.07	-0.02 (-1.80, 1.75)	0.98	1.83 (-1.51, 5.16)	0.28	0.38 (-1.67, 2.42)	0.72
FVC-BDR	-0.30 (-1.07, 0.47)	0.44	0.94 (-0.20 ,2.09)	0.11	3.29 (1.14, 5.44)	0.003	0.94 (-0.38, 2.26)	0.16
Combined-BDR	-1.80 (-2.66, -0.94)	<0.001	1.52 (0.24, 2.79)	0.020	5.47 (3.07, 7.86)	<0.001	1.61 (0.14, 3.09)	0.03

FEV1-BDR= increase in FEV1≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.

Abbreviations: Coef= Coefficient; FRC= functional residual capacity; MMRC= Modified Medical Research Council; OR= odds ratio; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLC= total lung capacity; 6-MWT= 6-min walk test; 95%CI= 95% confidence interval.

For 6-MWT data analysis, data were available for 4,356 subjects.
For Pi10 data analysis, data were available for 4,119 subjects.
For % emphysema and TLC% predicted analysis, data were available for 4,157 subjects
For % GT and FRC% analysis, data were available for 3,669 subjects.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI) and post-bronchodilator FEV1% predicted.

Table 8. Association of bronchodilator response composites at enrollment with drop in FEV1 between baseline and follow-up visit and respiratory exacerbations in COPD subjects with or without history of asthma.

	Change in FEV1 (ml/year)		**Exacerbations**		**Severe exacerbations**	
Subjects	2,268		3,947		3,947	
	Coef (95%CI)	P value	IRR (95%CI)	P value	IRR (95%CI)	P value
No-BDR	ref		ref		ref	
FEV1-BDR	-15.56 (-24.19, -6.93)	<0.001	1.20 (0.97, 1.40)	0.09	1.05 (0.78, 1.41)	0.74
FVC-BDR	-6.02 (-12.35 ,0.32)	0.063	1.06 (0.92, 1.11)	0.41	1.10 (0.91, 1.32)	0.32
Combined-BDR	-18.19 (-24.61, -11.77)	<0.001	1.33 (1.14, 1.57)	<0.001	1.60 (1.31, 1.97)	<0.001

FEV1-BDR= increase in FEV1≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.
Abbreviations: Coef= Coefficient; IRR= incidence rate ratio; 95%CI= 95% confidence interval.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI) and post-bronchodilator FEV1% predicted.

Table 9. Adjusted Mortality analysis in COPD subjects with or without history of asthma (n= 3,931).

	Adjusted Mortality	
	HR (95%CI)	P value
No-BDR	ref	
FEV1-BDR	0.85 (0.62, 1.29)	0.54
FVC-BDR	1.01 (0.85, 1.20)	0.90
Combined-BDR	0.75 (0.59, 0.95)	0.017

FEV1-BDR= increase in FEV1≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV1< 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.
Abbreviations: HR=Hazard ratio; 95%CI= 95% confidence interval.

Cox Hazard regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI) and post-bronchodilator FEV1% predicted.

Then we defined BDR as an increase ≥12% (without the requirement of 200 ml change) in FEV_1 and/or FVC (relative change), we found that combined-percent-BDR was associated with respiratory exacerbations (**Table 10)** but not with mortality (**Table 11**).

Table 10. Association of bronchodilator response categories at enrollment with drop in FEV1 between baseline and follow-up visit and respiratory exacerbations when bronchodilator response was defined as a change of FEV_1 and/or FVC≥12%.

	Change in FEV1 (ml/year)		**Exacerbations**		**Severe exacerbations**	
	1,702		2,980		2,980	
	Coef (95%CI)	P value	IRR (95%CI)	P value	P value	P value
No-BDR	ref		ref		ref	
FEV1-BDR	-15.93 (-24.30, -7.55)	<0.001	1.27 (1.04, 1.55)	0.018	1.33 (1.03, 1.72)	0.028
FVC-BDR	-7.79 (-16.29, 0.71)	0.072	1.02 (0.83, 1.27)	0.82	1.07 (0.81, 1.40)	0.64
Combined-BDR	-20.09 (-27.11, -13.06)	<0.001	1.26 (1.07, 1.48)	0.005	1.33 (1.08, 1.62)	0.007

FEV1-BDR= increase in FEV1≥12% but a change in FVC< 12% after bronchodilator administration.
FVC-BDR= increase in FVC≥12% but a change in FEV1< 12% after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥12% after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% after bronchodilator administration.

Abbreviations: Coef= Coefficient; IRR= incidence rate ratio; 95%CI= 95% confidence interval.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI) and post-bronchodilator FEV1% predicted.

Table 11. Association of bronchodilator response categories at enrollment with mortality in subjects with COPD when bronchodilator response was defined as a change of FEV_1 and/or FVC≥12% (n=2,972).

	Adjusted Mortality	
	HR (95%CI)	P value
No-BDR	ref	
FEV1-BDR	0.99 (0.76, 1.28)	0.93
FVC-BDR	0.91 (0.69, 1.20)	0.50
Combined-BDR	0.94 (0.78, 1.15)	0.55

FEV1-BDR= increase in FEV1≥12% but a change in FVC< 12% after bronchodilator administration
FVC-BDR= increase in FVC≥12% but a change in FEV1< 12% after bronchodilator administration
Combined-BDR= an increase in both FEV1 and FVC≥12% after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<12% after bronchodilator administration.

Abbreviations: HR=Hazard ratio; 95%CI= 95% confidence interval.

Cox Hazard regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, congestive heart failure, coronary artery disease, diabetes, hypertension, sleep apnea and stroke.
When we defined BDR as an increase ≥200ml (without the requirement of a 12% change) in $FEV_1$and/or FVC (absolute change), we observed that combined-volume-BDR was associated with mortality (**Table 12**) but not with respiratory exacerbations **(Table 13).**

Table 12. Association of bronchodilator response categories at enrollment with drop in FEV1 between baseline and follow-up visit and respiratory exacerbations when bronchodilator response was defined as a change of FEV_1 and/or FVC≥ 200ml.

	Change in FEV1 (ml/year)		**Exacerbations**		**Severe exacerbations**	
Subjects	1,702		2,980		2,980	
	Coef (95%CI)	P value	IRR (95%CI)	P value	P value	P value
No-BDR	ref		ref		ref	
FEV1-BDR	-20.08 (-32.77, -7.40)	0.002	1.32 (0.94, 1.84)	0.11	1.42 (0.91, 2.25)	0.13
FVC-BDR	-6.41 (-12.47, -0.35)	0.038	1.06 (0.92, 1.22)	0.45	1.09 (0.90, 1.31)	0.38
Combined-BDR	-19.94 (-26.52, -13.36)	<0.001	1.10 (0.93, 1.30)	0.25	1.16 (0.93, 1.44)	0.20

FEV1-BDR= increase in FEV1≥200ml but a change in FVC< 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥200ml but a change in FEV1< 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<200ml after bronchodilator administration.

Abbreviations: Coef= Coefficient; IRR= incidence rate ratio; 95%CI= 95% confidence interval.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI) and post-bronchodilator FEV1% predicted.

Table 13. Association of bronchodilator response categories at enrollment with mortality in subjects with COPD when bronchodilator response was defined as a change of FEV_1 and/or FVC≥ 200ml (n=2,972).

	Adjusted Mortality	
	HR (95%CI)	P value
No-BDR	ref	
FEV1-BDR	0.88 (0.48, 1.62)	0.68
FVC-BDR	0.93 (0.78, 1.11)	0.44
Combined-BDR	0.75 (0.59, 0.96)	0.025

FEV1-BDR= increase in FEV1≥200ml but a change in FVC< 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥200ml but a change in FEV1< 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV1 and FVC≥200ml after bronchodilator administration.
No-BDR= a change in both FEV1 and FVC<200ml after bronchodilator administration.

Abbreviations: HR=Hazard ratio; 95%CI= 95% confidence interval.

Cox Hazard regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, congestive heart failure, coronary artery disease, diabetes, hypertension, sleep apnea and stroke.

In additional models adjusted for long-acting inhaled medication use, we found again that Combined-BDR was associated with increased exacerbations whereas FEV_1-BDR and FVC-BDR were not associated with exacerbations (**Table 14**).

Table 14. Association of bronchodilator response categories at enrollment with respiratory exacerbations in subjects with COPD.

	Exacerbations		**Severe exacerbations**	
Subjects	2,980		2,980	
	IRR (95%CI)	P value	IRR (95%CI)	P value
No-BDR	ref		Ref	
FEV_1-BDR	1.36 (1.04, 1.77)	0.02	1.17 (0.81, 1.69)	0.40
FVC-BDR	1.17 (0.99, 1.39)	0.064	1.16 (0.94, 1.45)	0.17
Combined-BDR	1.52 (1.26, 1.84)	<0.001	1.66 (1.29, 2.12)	<0.001
ATS-BDR*	1.32 (1.16, 1.50)	<0.001	1.32 (1.12, 1.57)	<0.001

FEV_1-BDR= increase in FEV_1 ≥12% and ≥200ml but a change in FVC< 12% and 200ml after bronchodilator administration.
FVC-BDR= increase in FVC≥12% and ≥200ml but a change in FEV_1 < 12% and 200ml after bronchodilator administration.
Combined-BDR= an increase in both FEV_1 and FVC≥12% and ≥200ml after bronchodilator administration.
No-BDR= a change in both FEV_1 and FVC<12% and <200ml after bronchodilator administration.
ATS-BDR= increase in pre-bronchodilator FEV_1 and/or FVC ≥12% and ≥200ml after bronchodilator administration.
Abbreviations: Coef= Coefficient; IRR= incidence rate ratio; 95%CI= 95% confidence interval.

*Multivariable logistic regression models with with ATS-BDR binary variable= BDR according to ATS guidelines; Yes or NO) as the independent variable.

All models included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV_1% predicted, and medication usage.

4.2. Aim 2 Results

Of 2,269 participants included in the analysis, 813 never had ATS-BDR, 991 had inconsistent ATS-BDR, and 325 had consistent ATS-BDR. **Table 1** shows the number of visits categorized by BDR category. Never and consistent ATS-BDR groups had more participants that had only 2 visits relative to the inconsistent group. We observed similar distributions using the FEV_1-BDR and FVC-BDR definitions.

Table 1. Number of visits by bronchodilator responsiveness group.

ATS-BDR			
	Never ATS-BDR (n=813)	**Inconsistent ATS-BDR (n=991)**	**Consistent ATS-BDR (n=325)**
Visits, n (%)			
2	244 (30%)	133 (13.4%)	127 (39.1%)
3	235 (28.9%)	274 (27.6%)	86 (26.5%)
4	200 (24.6%)	328 (33.1%)	75 (23.1%)
5	134 (16.5%)	256 (25.8%)	37 (11.4%)
FEV_1-BDR			
	Never FEV_1-BDR (n=1014)	**Inconsistent FEV_1-BDR (n=906)**	**Consistent FEV_1-BDR (n=209)**
Visits, n (%)			
2	299 (29.5%)	119 (13.1%)	86 (41.1%)
3	301 (29.7%)	238 (26.3%)	56 (26.8%)
4	252 (24.9%)	305 (33.7%)	46 (22.0%)
5	162 (16.0%)	244 (26.9%)	21 (10.0%)
FVC-BDR			
	Never FVC-BDR (n=1144)	**Inconsistent FVC-BDR (n=797)**	**Consistent FVC-BDR (n=188)**
Visits, n (%)			
2	313 (27.4%)	112 (14.1%)	79 (42.0%)
3	333 (29.1%)	209 (26.2%)	53 (28.2%)
4	302 (26.4%)	266 (33.4%)	35 (18.6%)
5	196 (17.1%)	210 (26.3%)	21 (11.2%)

Abbreviation: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Abbreviation: FEV_1-BDR = increase in forced expiratory volume in one second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Abbreviation: FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Table 2 shows the characteristics of ATS-BDR groups. Participants with consistent ATS-BDR were older and more frequently white, had lower body mass index (BMI), more accumulated smoking exposure, were more likely to use inhaled bronchodilators and inhaled glucocorticosteroids, and had worse lung function at baseline than the rest of the participants. Changes in FEV_1 and FVC after bronchodilators at baseline were greater in participants with consistent BDR.

Table 2. Baseline characteristics of participants categorized by bronchodilator responsiveness(n=2,269)**.**

Characteristics at Visit 1	Never ATS-BDR	Inconsistent ATS-BDR	Consistent ATS-BDR	P Value*
n	813	991	325	
Age, years ± SD	63.1 ± 9.3	64.5 ± 8.5	64.7 ± 8.0	0.001
Females, n (%)	390 (48.0%)	460 (46.4%)	131 (40.3%)	0.062
Whites, n (%)	618 (76.0%)	776 (78.3%)	276 (84.9%)	0.004
Body mass Index, Kg/m^2 ± SD	28.5 ± 5.2	28.0 ± 5.2	27.3 ± 5.2	0.001
Pack-Years ± SD	46.3 ± 26.5	50.7 ± 24.8	52.9 ± 23.7	<0.001
Current Smoker, n (%)	304 (37.8%)	348 (35.7%)	137 (42.5%)	0.090
Asthma, n (%)	109 (13.4%)	223 (22.5%)	82 (25.2%)	<0.001
Childhood Asthma, n(%)	38 (4.7%)	103 (10.4%)	37 (11.4%)	<0.001
Bronchodilator, n (%)	265 (32.9%)	553 (56.5%)	214 (66.0%)	<0.001
Inhaled corticosteroids, n (%)	172 (21.3%)	391 (40.0%)	148 (45.8%)	<0.001
Pre-FEV_1, L ± SD	2.42 ± 0.83	1.71 ± 0.77	1.38 ± 0.58	<0.001
Pre-FEV_1% predicted ± SD	83.9 ± 22.0	60.9 ± 23.9	47.6 ± 17.0	<0.001
Pre-FVC, L ± SD	3.56 ± 1.00	3.07 ± 0.98	2.94 ± 0.90	<0.001
Pre-FVC% predicted ± SD	94.2 ± 16.1	82.7 ± 19.2	76.4 ± 17.8	<0.001
Pre-FEV_1/FVC ± SD	88.0 ± 16.4	71.7 ± 19.5	61.4 ± 15.2	<0.001
Post-FEV_1, L ± SD	2.53 ± 0.87	1.93 ± 0.81	1.73 ± 0.67	<0.001
Post-FEV_1% predicted ± SD	87.7 ± 22.6	68.5 ± 24.5	59.6 ± 19.5	<0.001
Post-FVC, L ± SD	3.60 ± 1.01	3.34 ± 0.99	3.51 ± 0.94	<0.001
Post- FVC% predicted ± SD	95.2 ± 16.0	90.0 ± 18.2	91.4 ± 18.0	<0.001
Post -FEV_1/FVC ± SD	91.1 ± 17.1	74.7 ± 20.0	64.6 ± 16.1	<0.001
ΔFEV_1 after BD , ml ± SD	110 ± 110	220 ± 170	350 ± 180	<0.001
ΔFEV_1 after BD, % ± SD	4.8 ± 4.9	15.1 ± 13.4	27.3 ± 14.3	<0.001
ΔFVC after BD, ml ± SD	40 ± 150	270 ± 270	570 ± 300	<0.001
ΔFVC after BD , % ± SD	1.3 ± 4.4	10.1 ± 11.0	21.2 ± 13.1	<0.001

Continue variables are presented as mean ± SD.

***** ANOVA or Kruskal–Wallis test for continuous and chi square of fisher exact test for categorical variables.

We categorized smoked tobacco-exposed participants with or without COPD based on ATS-BDR intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit.

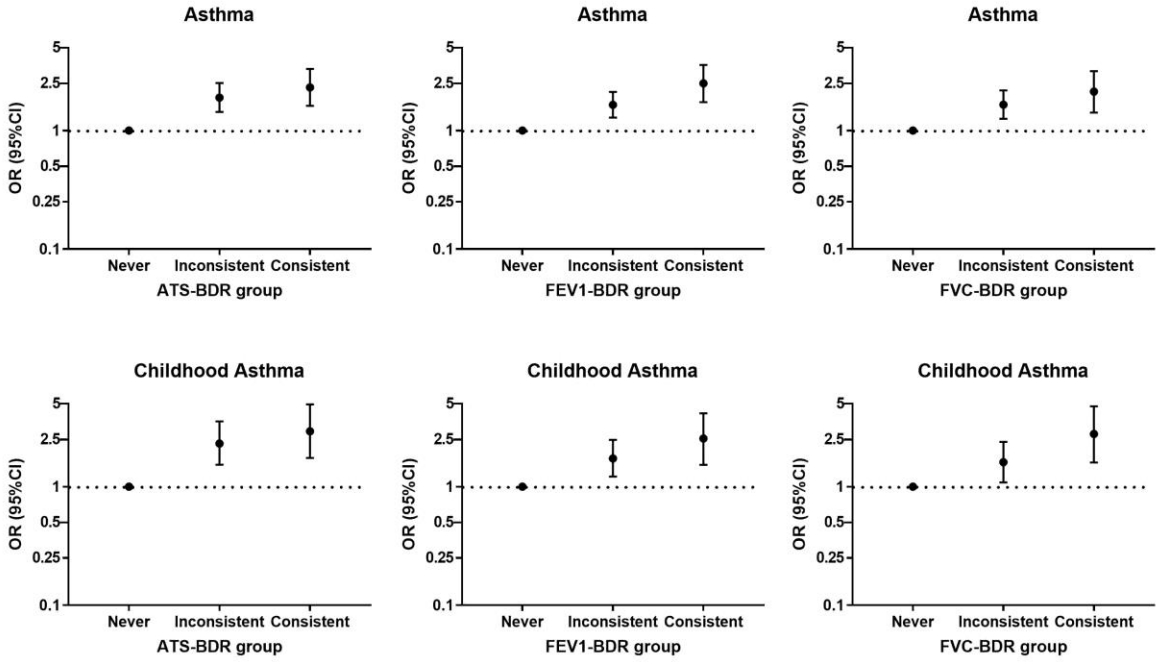
Abbreviations: ΔFEV_1 after BD = change in FEV_1 after bronchodilator administration; ΔFVC after BD = change in FVC after bronchodilator administration; ATS-BDR = an increase in FEV1 and/or FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration according to the ATS-ERS guidelines; BDR = bronchodilator responsiveness; FEV_1 = forced expiratory volume in 1 second ; FVC = forced vital capacity; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; Pre- = pre-bronchodilator; Post- = post-bronchodilator; PRM^{fSAD} = parametric response mapping functional small airway disease.

History of Asthma

After adjusting for demographics, smoking exposure and baseline lung function, using the ATS-BDR definition, we found associations with a history of asthma in both the inconsistent BDR group (OR (odds ratio) = 1.90; 95%CI 1.44 to 2.52; P<0.001) and the consistent BDR group (OR = 2.31; 95%CI 1.62 to 3.31; P<0.001) relative to the never BDR group (**Figure 1**). We observed the same pattern using the FEV_1-BDR and FVC-BDR definitions.

We found similar results regarding the association of BDR variability with a history of childhood asthma (**Figure 1**)

Figure 1. Association of bronchodilator responsiveness group with asthma and childhood asthma.



We categorized smoked tobacco-exposed participants with or without COPD based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit.

Multivariable logistic regression models with BDR group as the independent variable and asthma diagnosis as the dependent variable. All models included the following covariates: age, sex, race, smoking status, pack-years smoked, and post-bronchodilator FEV_1% predicted at first visit, as well as number of visits.

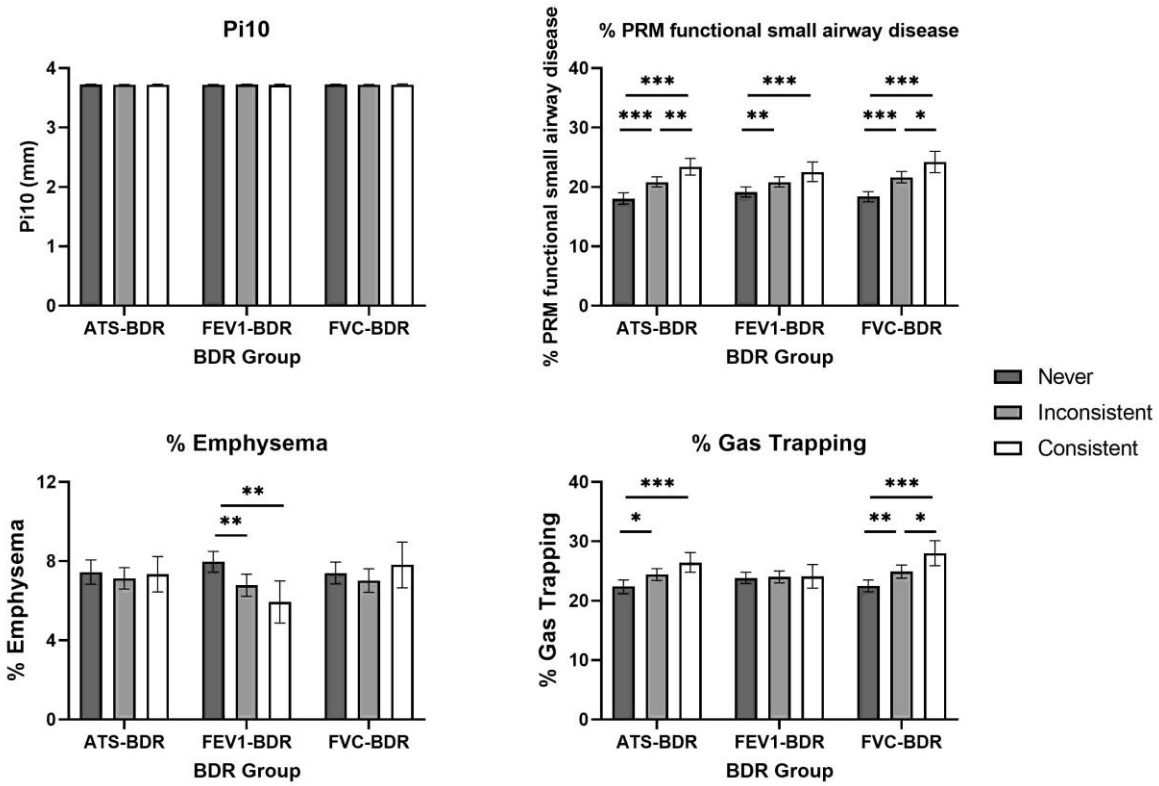
Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; OR = odds ratio; 95%CI = 95% confidence interval.

Radiographic findings

In the adjusted analysis, there was no difference in Pi10 across BDR groups regardless of the BDR definition used (**Figure 2**). Percent PRM^{fSAD} was significantly greater in participants with consistent ATS-BDR (23.4%; 95%CI 22.0 to 24.8%) than % PRM^{fSAD} in participants with

inconsistent (20.8%; 95%CI 20.0 to 21.7%; P<0.001) and never ATS-BDR (18.0%; 95%CI 17.1 to19.0%; P<0.001) (**Figure 2**). Percent PRM^{fSAD} was significantly greater in the inconsistent compared to the never ATS-BDR group (P=0.003). We observed similar findings using the FEV_1-BDR and FVC-BDR definitions. Percent emphysema did not vary between BDR groups using the ATS-BDR and FVC-BDR definitions. When using the FEV_1-BDR definition, % emphysema was greater in the never BDR group with an average of 8.0% (95%CI 7.4 to 8.5%) relative to the inconsistent BDR 6.8% (95%CI 6.2 to 7.3%; P=0.003) and the consistent BDR 5.9% (95%CI 4.9 to 7.0%; P=0.001) (**Figure 2**). Percent gas trapping was greater in participants with consistent BDR relative to participants with never BDR when ATS-BDR and FVC-BDR definitions were applied but it did not vary when FEV_1-BDR was used (**Figure 2**).

Figure 2. Association of bronchodilator responsiveness group with chest CT findings.



* P<0.05, ** P<0.01, *** P<0.001

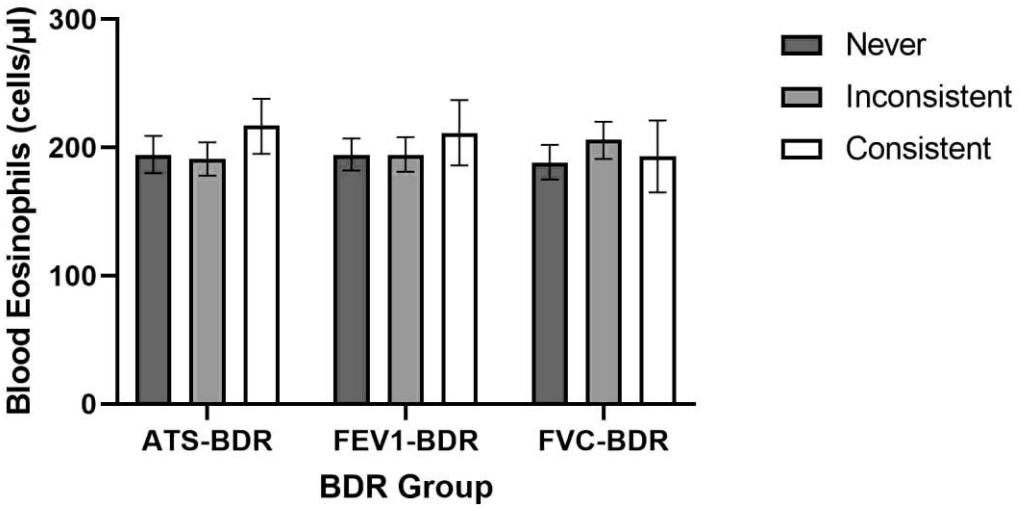
We categorized smoked tobacco-exposed participants with or without COPD based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit. Multivariable linear regression models with bronchodilator responsiveness group as the independent variable and Pi10, PRM^{fSAD}, % emphysema, and % gas trapping as the dependent variable. All models included the following covariates: age, sex, race, smoking status and pack-years smoked, and post-bronchodilator FEV_1% predicted at first visit, as well as number of visits. Based on these models, we calculated least square mean (LSM). Pairwise comparisons using Tukey's method correction for LSM were employed. **Values in the figures are presented as LSM with 95%CI.**

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; PRM^{fSAD} = parametric response mapping functional small airway disease.

Eosinophil counts

In the adjusted analysis, there was no difference in blood eosinophil counts across BDR groups regardless of the BDR definition used (**Figure 3**).

Figure 3. Association of bronchodilator responsiveness group with blood eosinophil counts at baseline.



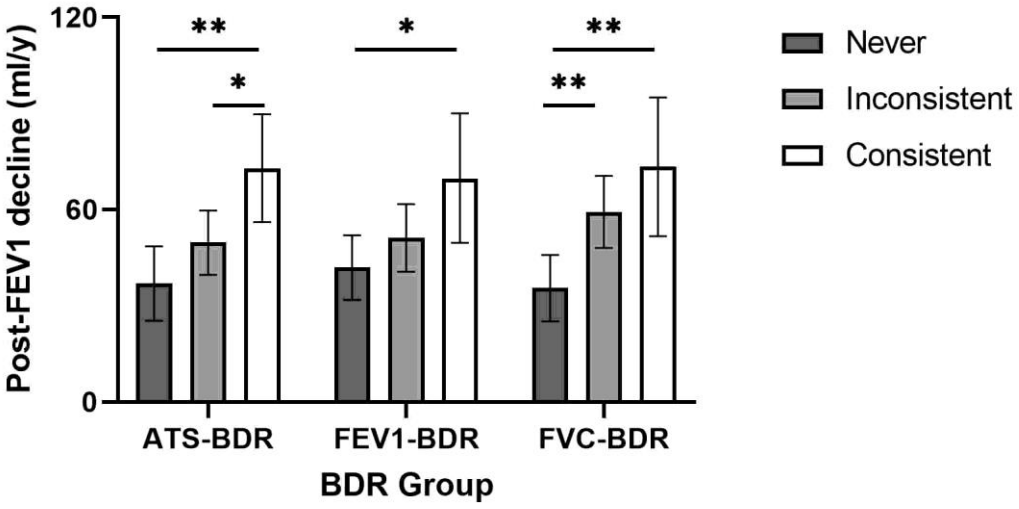
We categorized smoked tobacco-exposed participants with or without COPD based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit. Multivariable linear regression models with bronchodilator responsiveness group as the independent variable and plasma eosinophil levels at baseline as the dependent variable. All models included the following covariates: age, sex, race, smoking status and pack-years smoked, and post-bronchodilator FEV_1% predicted at first visit, as well as number of visits. Based on these models, we calculated least square mean (LSM). Pairwise comparisons using Tukey's method correction LSM were employed. **Values in the figures are presented as LSM with 95%CI.**

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Post-bronchodilator FEV_1 decline

The post-bronchodilator FEV_1 decline was greater in participants with consistent (73 ml/year; 95%CI 56 to 90 ml/year) than the decline in both participants with inconsistent ATS-BDR (50 ml/year; 95%CI 40 to 60 ml/year;P=0.035) and participants with never ATS-BDR (37 ml/year; 95%CI 25 to 49 ml/year;P=0.001) (**Figure 4**). When using FEV_1-BDR and FVC-BDR definitions, the post-bronchodilator FEV_1 decline was greater in participants with consistent compared to never BDR.

Figure 4. Association of bronchodilator responsiveness group with decline in post-bronchodilator forced expiratory volume in one second over time.



* P<0.05, ** P<0.01, *** P<0.001

We categorized smoked tobacco-exposed participants with or without COPD based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit. Multivariable linear regression models with bronchodilator responsiveness group as the independent variable and decline in post-bronchodilator forced expiratory volume in one second % predicted over time as the dependent variable. All models included the following covariates: age, sex, race, smoking status and pack-years smoked, and post-bronchodilator FEV_1% predicted at first visit, as well as number of visits. Based on these models, we calculated least square mean (LSM). Pairwise comparisons using Tukey's method correction for LSM were employed. **Values in the figures are presented as LSM with 95%CI.**

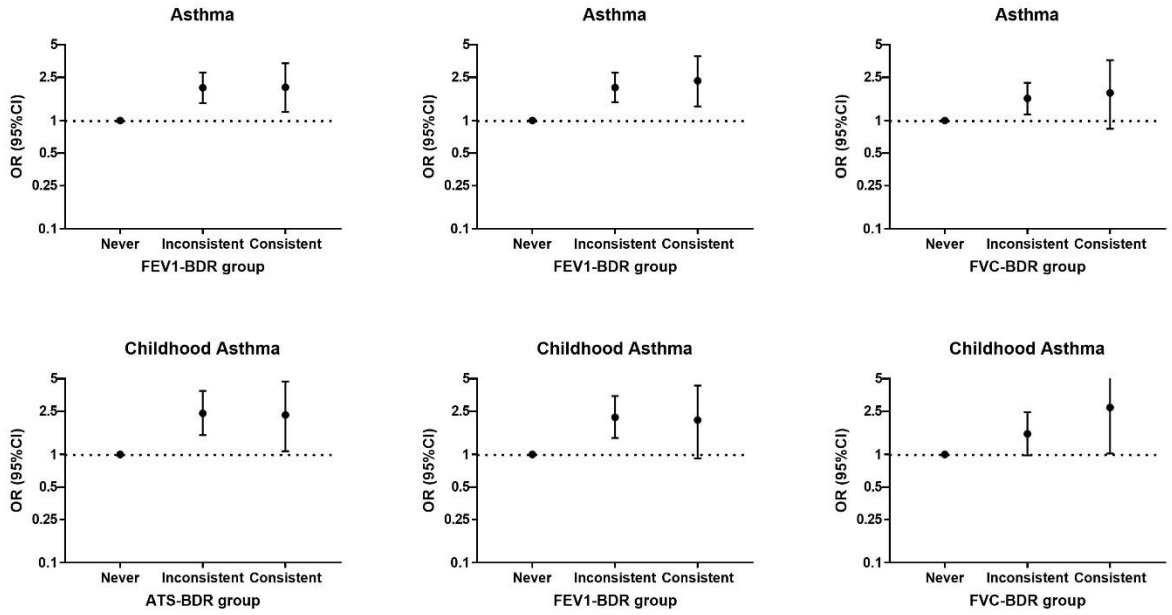
Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Analysis in Participants with normal spirometry (n=1,481)

In the adjusted analysis of those with normal spirometry at baseline, we observed similar findings to those in the main analysis (**Figure 5 to 7**), except that when using the FEV_1-BDR definition, % emphysema was greater in the consistent and inconsistent BDR relative to never BDR group. In 756 participants with available spirometric data at visit 5 (4 years from baseline), we found that 29.9% (100 of 334) in the never ATS-BDR, 66.7% (246 of 369) in the inconsistent ATS-BDR, and

90.6% (48 of 53) in the consistent ATS-BDR group developed COPD at visit 5 (**Figure 8**). In the adjusted analysis, both inconsistent (OR = 3.20; 95%CI 2.21 to 4.66;P<0.001) and consistent ATS-BDR group (OR = 9.48; 95%CI 3.77 to 29.12;P<0.001) were associated with progression to COPD at visit 5 relative to never ATS-BDR group (**Table 3**). We observed the same pattern using the FEV_1-BDR and FVC-BDR definitions.

Figure 5. Association of bronchodilator responsiveness group with asthma and childhood asthma in participants with normal spirometry at baseline.

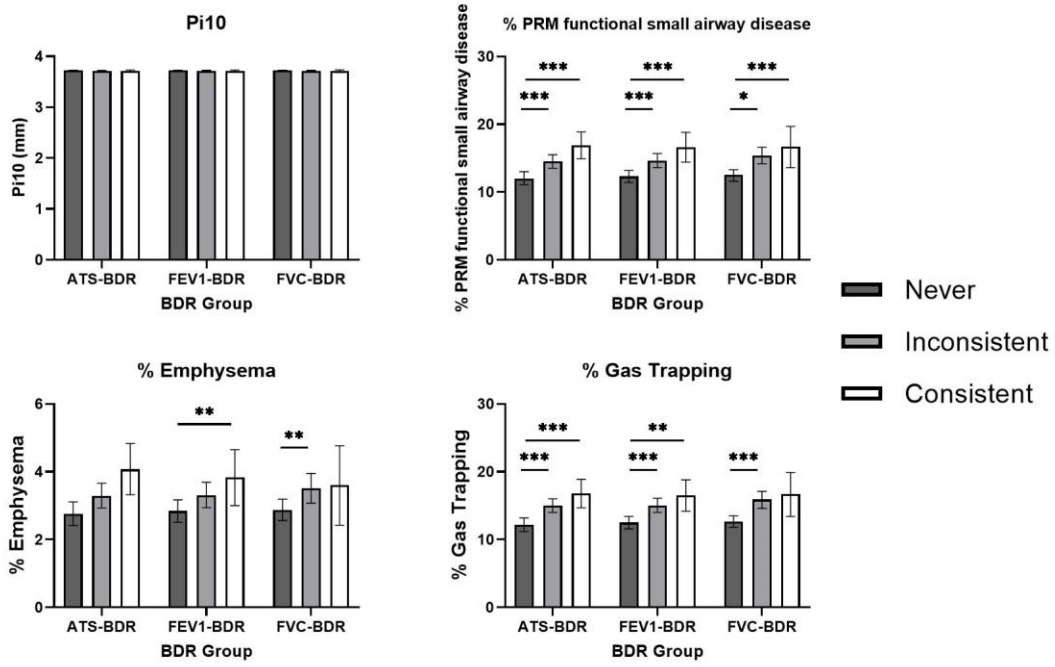


We categorized smoked tobacco-exposed participants without normal spirometry based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit.

Multivariable logistic regression models with BDR group as the independent variable and asthma diagnosis as the dependent variable. All models included the following covariates: age, sex, race, smoking status, pack-years smoked, and post-bronchodilator FEV_1% predicted at first visit, as well as number of visits.

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; OR = odds ratio; 95%CI = 95% confidence interval.

Figure 6. Association of bronchodilator responsiveness group with chest CT findings in participants with normal spirometry at baseline.

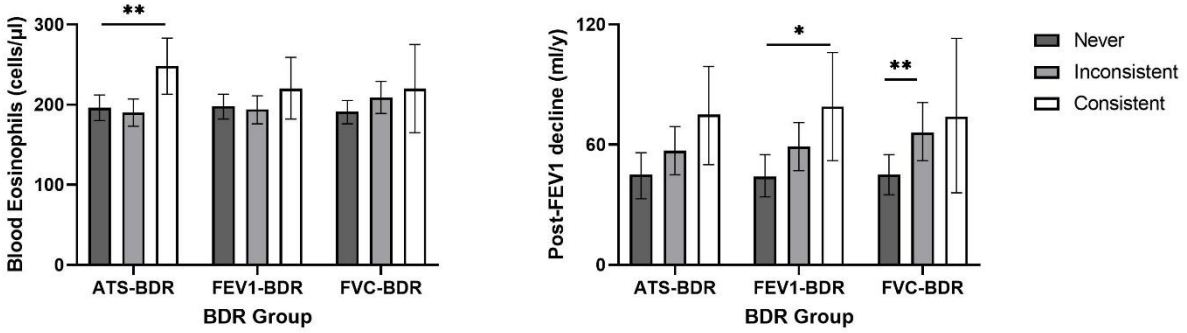


* P<0.05, ** P<0.01, *** P<0.001

We categorized smoked tobacco-exposed participants with normal spirometry based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit. Multivariable linear regression models with bronchodilator responsiveness group as the independent variable and Pi10, PRM^{fSAD}, % emphysema, and % gas trapping as the dependent variable. All models included the following covariates: age, sex, race, smoking status and pack-years smoked, and post-bronchodilator FEV1% predicted at first visit, as well as number of visits. Based on these models, we calculated least square mean (LSM). Pairwise comparisons using Tukey's method correction for LSM were employed. **Values in the figures are presented as LSM with 95%CI.**

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; PRM^{fSAD} = parametric response mapping functional small airway disease.

Figure 7. Association of bronchodilator responsiveness group with blood eosinophil counts at baseline and decline in post-bronchodilator forced expiratory volume in one second over time.

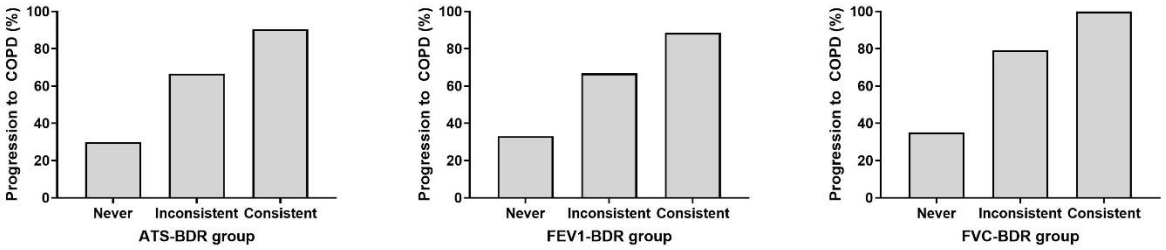


* P<0.05, ** P<0.01, *** P<0.001

We categorized smoked tobacco-exposed participants with or without COPD based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit. Multivariable linear regression models with bronchodilator responsiveness group as the independent variable and plasma eosinophil levels at baseline or decline in post-bronchodilator forced expiratory volume in one second % predicted over time as the dependent variable. All models included the following covariates: age, sex, race, smoking status and pack-years smoked, and post-bronchodilator FEV_1% predicted at first visit, as well as number of visits. Based on these models, we calculated least square mean (LSM). Pairwise comparisons using Tukey's method correction LSM were employed. **Values in the figures are presented as LSM with 95%CI.**

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Figure 8. Bronchodilator responsiveness group and COPD at visit 5 in participants with normal spirometry at baseline.



We categorized smoked tobacco-exposed participants with or without COPD based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit.

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV_1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration.

Table 3. Association of bronchodilator responsiveness group with and progression to COPD in participants with normal spirometry at baseline.

	ATS-BDR		**FEV_1-BDR**	
	OR (95%CI)	P value	OR (95%CI)	P value
Never	ref	ref	ref	ref
Inconsistent	3.20 (2.21, 4.66)	<0.001	3.02 (2.09, 4.37)	<0.001
Consistent	9.48 (3.77, 29.1)	<0.001	6.88 (2.67, 21.5)	<0.001

We categorized smoked tobacco-exposed participants normal spirometry based on BDR variability intro three groups: Consistent BDR when it is present in every visit, ii) Inconsistent BDR when it is present at some but not in every visit, and ii) Never BDR when it is not present at any visit.

Multivariable logistic regression models with BDR group as the independent variable and progression to COPD at visit 5 (4 years from baseline) as the dependent variable. All models included the following covariates: age, sex, race, smoking status, pack-years smoked, and post-bronchodilator FEV1% predicted at first visit, as well as number of visits.

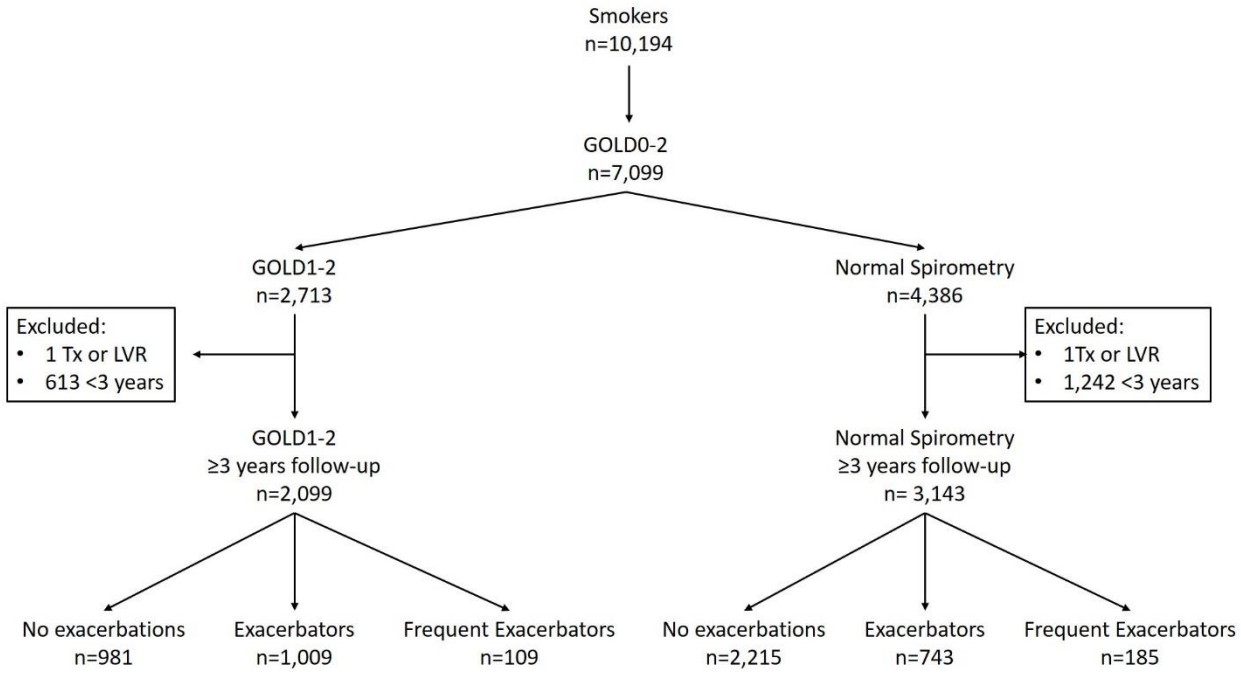
*** We did not perform an analysis using FVC-BDR because there was a complete separation in consistent FVC-BDR (all participants with consistent FVC-BDR progressed to COPD at visit 5).**

Abbreviations: ATS-BDR = increase in forced expiratory volume in one second and/or forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; BDR = bronchodilator responsiveness; FEV1-BDR = increase in forced expiratory volume in 1 second greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; FVC-BDR = increase in forced vital capacity greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration; OR = odds ratio; 95%CI = 95% confidence interval.

4.3. Aim 3 Results

Of 10,194 participants in COPDGene with at least 10 pack-years history of smoking, 2,713 have COPD with post-bronchodilator FEV1%predicted≥50% and 4,368 have normal spirometry (**Figure 1**). Of 2,713 participants with COPD and post-bronchodilator FEV1%predicted≥50%, we excluded 1 that had lung transplant/lung volume reduction and 613 for whom we did not have exacerbation data for at least 3 years. Of 4,386 current or former smokers with preserved spirometry, we excluded one that had lung transplant/lung volume reduction and 1,242 for whom we did not have exacerbation data for at least 3 years. We analyzed data of 2,099 COPD participants with post-bronchodilator FEV1%predicted≥50% and 3,143 current or former smokers with preserved spirometry.

Figure 1. Consort Diagram.



LVR= lung volume reduction; Tx= Lung transplant

*Participants with exacerbation data for < 3 years were excluded.

COPD participants with mild-to-moderate lung function impairment (n=2,099)

In COPD participants with post-bronchodilator FEV1%predicted≥50%, the median duration of follow-up was 8 years (interquartile range = 6.6-8.9). The top 5% in exacerbation frequency (n=109) had 1.8 or more exacerbations per year (frequent exacerbators), 1,009 had >0 exacerbation/year but less than 1.8 exacerbation a year (exacerbators), and 981 had no exacerbations. **Table 1** shows the characteristics of the 3 groups. The count of respiratory exacerbations was 5,913 for all COPD participants, 3,886 (65.7%) for the exacerbators, and 2027 (34.3%) for the frequent exacerbators. The count of severe respiratory exacerbations was

1,919 for all COPD participants, 1,308 (68.2%) for the exacerbators, and 611 (31.8%) for the frequent exacerbators.

In frequent exacerbators during a median follow-up time of 7.4 years (interquartile range = 5.7-8.8), the median count of exacerbations was 18 with a range of 6-36 (interquartile range = 13-22) and median count of severe exacerbations was 4 with a range of 0-28 (interquartile range = 1-8).

Table 1. Characteristics of COPD participants with post-bronchodilator FEV1%predicted≥50% and at least 3 years follow up (n= 2,099).

	No Exacerbation	Exacerbators	Frequent exacerbators	P value*
Exacerbations per year	0	>0 and <1.8	>=1.8	
n	981	1009	109	
Follow-up duration, y (IQR)	7.9(6-8.8)	8.1 (7.1-9)	7.4 (5.7-8.8)	<0.001
Age, y ± SD	63.40 ± 8.47	63.47 ± 8.67	62.32 ± 8.62	0.411
Female, n (%)	399 (40.7%)	544 (53.9%)	56 (51.4%)	<0.001
African American, n (%)	199 (20.3%)	190 (18.8%)	17 (15.6%)	0.43
Active smokers, n (%)	460 (46.9%)	435 (43.1%)	35 (32.1%)	0.007
Pack-years smoking ± SD	48.21 ± 25.70	49.27 ± 25.41	55.58 ± 29.73	0.02
Body mass index, kg/m2 ± SD	27.76 ± 5.23	28.97 ± 6.34	29.02 ± 5.94	<0.001
History of Asthma, n (%)	147 (15.0%)	250 (24.8%)	40 (36.7%)	<0.001
History of acute bronchitis, n (%)	334 (34.0%)	588 (58.3%)	79 (72.5%)	<0.001
History of pneumonia, n (%)	324 (33.0%)	476 (47.2%)	74 (67.9%)	<0.001
Obstructive Sleep Apnea, n (%)	118 (12.0%)	199 (19.7%)	28 (25.7%)	<0.001
Gastroesophageal Reflux, n (%)	230 (23.5%)	354 (35.1%)	48 (44.0%)	<0.001
Diabetes Mellitus, n (%)	104 (10.6%)	117 (11.6%)	12 (11.0%)	0.78
History of Cancer, n (%)	72 (7.3%)	104 (10.3%)	19 (17.4%)	<0.001
Chronic bronchitis, n (%)	163 (16.6%)	258 (25.6%)	42 (38.5%)	<0.001
mMRC>2, n (%)	281 (28.7%)	463 (46.1%)	81 (74.3%)	<0.001
Post-FEV1% predicted ± SD	75.37 ± 14.77	70.63 ± 13.79	64.35 ± 11.65	<0.001
Post-FVC% predicted ± SD	93.58 ± 15.64	90.98 ± 15.93	88.67 ± 15.63	<0.001
Bronchodilator response, n (%)	281 (28.9%)	351 (34.9%)	46 (43.0%)	<0.001
6-min-walk-test distance, ft ± SD	1437.25 ± 357.68	1357.60 ± 352.82	1197.26 ± 339.28	<0.001
ICS/LABA, n (%)	141 (14.4%)	275 (27.3%)	61 (56.0%)	<0.001
LAMA, n (%)	105 (10.7%)	259 (25.7%)	50 (45.9%)	<0.001
ICS, n (%)	44 (4.5%)	84 (8.3%)	15 (13.8%)	<0.001
LABA, n (%)	32 (3.3%)	42 (4.2%)	8 (7.3%)	0.10
Total exacerbations per year ± SD	0.00 ± 0.00	0.50 ± 0.42	2.66 ± 0.80	<0.001
Severe exacerbations per year ± SD	0.00 ± 0.00	0.17 ± 0.24	0.81 ± 0.83	<0.001
Total exacerbations ± SD	0.00 ± 0.00	3.85 ± 3.27	18.60 ± 7.30	<0.001
Severe exacerbations ± SD	0.00 ± 0.00	1.30 ± 1.79	5.61 ± 5.77	<0.001
Emphysema, % ± SD	6.47 ± 6.70	7.37 ± 7.73	11.31 ± 10.23	<0.001
Gas trapping, % ± SD	23.44 ± 14.03	26.61 ± 14.48	33.94 ± 15.75	<0.001
TLV, L ± SD	5.95 ± 1.42	5.74 ± 1.33	5.92 ± 1.46	0.00401
TLV% predicted ± SD	109.14 ± 16.16	110.74 ± 17.08	113.10 ± 18.45	0.0176
Pi10, mm ± SD	3.65 ± 0.13	3.68 ± 0.13	3.69 ± 0.14	<0.001

*ANOVA for continuous and chi square of fisher exact test for categorical variables.

Data regarding gastroesophageal reflex, mMRC, bronchodilator response, 6-min-walk-test distance, TLV, Pi10, gas trapping and emphysema were missing in 1,2,6,11,21,103,119,333, and 103 participants, respectively.

ICS= inhaled glucocorticosteroids; IQR = interquartile range; LABA= long acting beta-agonist; LAMA= long acting muscarinic antagonist; mMRC= modified Medical Research Council scale, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 sec %predicted; post-FVC% predicted = post-bronchodilator forced vital capacity %predicted, Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV= total lung volume at maximum inspiratory volumes measure by chest CT.

Lung function (every 10% increase in FEV1%predicted with an odds ratio (OR)= 0.82;95%CI=0.68-0.99), 6-min walk distance (every 100 ft increase; OR=0.94; 95%CI=0.88-1.00),%emphysema (every 1%; OR=1.05; 95%CI=1.02-1.07), dyspnea (OR=2.35; 95%CI=1.41-4.00), chronic bronchitis (OR=1.85; 95%CI=1.17-2.90), history of asthma (OR=2.13; 95%CI=1.35-3.34), history of acute bronchitis and/or pneumonia (OR=2.04; 95%CI=1.17-3.77), and history of cancer (OR=1.95; 95%CI=1.05-3.45) were associated with the frequent exacerbator group (**Table 2**). Analysis after multiple imputations for missing values showed almost identical findings.

Table 2. Factors associated with the frequent exacerbator phenotype among COPD participants with post-bronchodilator FEV1%predicted≥50% and at least 3 years of follow-up(n= 2,099).

	OR (95%CI)	P value
Post-FEV1% predicted, every 10%	0.82 (0.68, 0.99)	0.044
6-min-walk-test distance, every 100ft	0.94 (0.88, 1.00)	0.046
Emphysema, %	1.05 (1.02, 1.07)	<0.001
mMRC>2	2.35 (1.41, 4.00)	0.001
Chronic bronchitis	1.85 (1.17, 2.90)	0.007
History of Asthma	2.13 (1.35, 3.34)	0.001
History of acute bronchitis and/or Pneumonias	2.04 (1.17, 3.77)	0.016
History of Cancer	1.95 (1.05, 3.45)	0.027

Variables tested but not retained for the final model include: Pack-years smoking, Pi10, TLV% predicted, Gastroesophageal Reflux, Bronchodilator response, and Obstructive Sleep Apnea.

Data regarding 6-min-walk-test distance, Emphysema, and mMRC were missing in 21,103, and 6 participants, respectively. We performed an additional analysis after multiple imputations accounting for missing values showing similar findings. We performed an additional analysis after multiple imputations accounting for missing values with almost identical findings.

Cancer = self-reported history of lung, breast, prostate, colon, and/or bladder cancer, mMRC= modified Medical Research Council scale, OR = odds ratio, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 sec %predicted, Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV= total lung volume at maximum inspiratory volumes measure by chest CT.

In the mortality analysis, there were 102 (10.4%) deaths in the group with no exacerbations, 119 (11.8%) in the exacerbator group, and 24 (22%) in the frequent exacerbator group (**Figure 2**). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, the frequent exacerbator phenotype was associated with increased mortality (hazard ratio (HR)= 1.98;95%CI= 1.25-3.13, p=0.004) (**Table 3**).

Figure 2. Crude survival in COPD participants with post-bronchodilator FEV1% predicted≥50% (n=2,099) stratified by exacerbation group: i) No exacerbations (No exacerbation), ii)Exacerbations/year>0 and <1.8(Exacerbators), and iii) Exacerbation/year≥1.8 (Frequent Exacerbators).

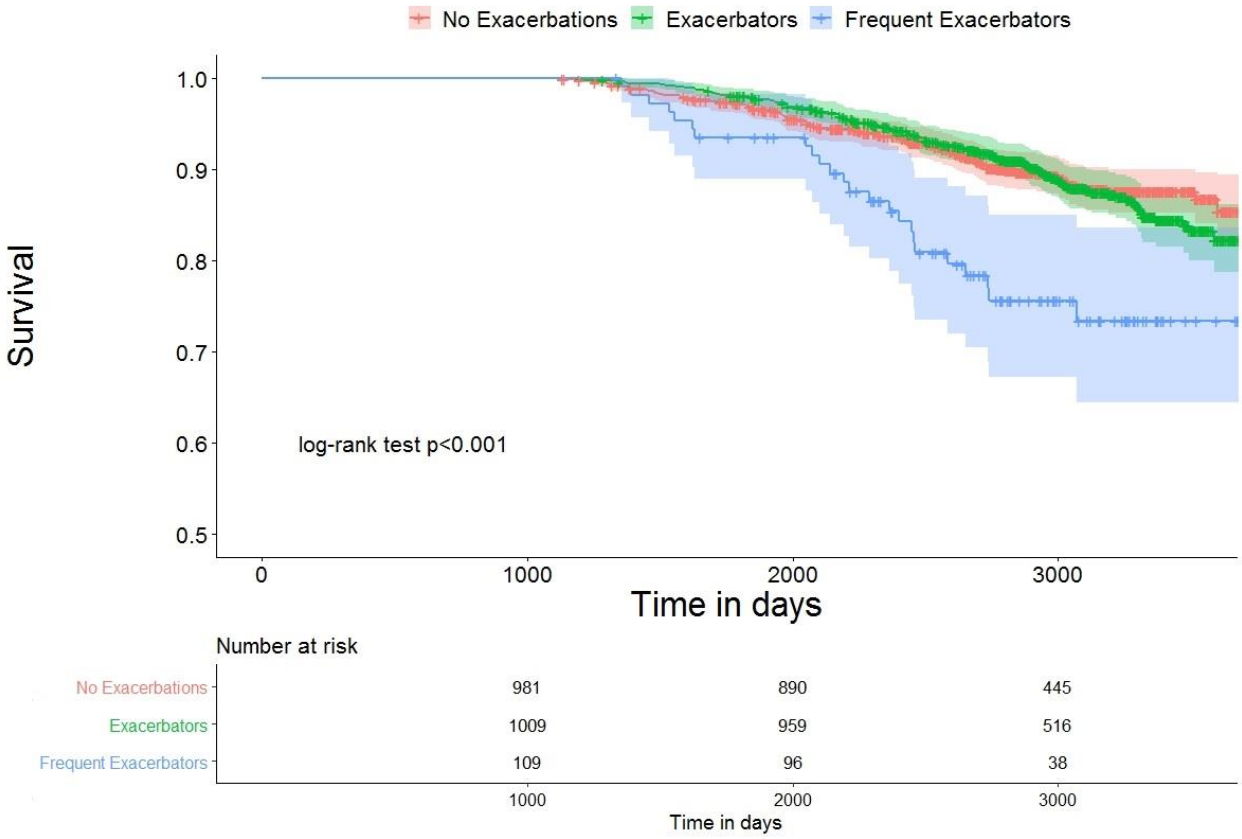


Table 3. Association of exacerbation group with mortality in COPD participants with post-bronchodilator FEV1%predicted≥50% with at least 3 years follow up (n=2,099).

	HR (95%CI)	**P value**
No Exacerbation (n=981)	ref	ref
Exacerbators (n=1,009)	0.91 (0.70, 1.20)	0.52
Frequent exacerbators (n= 109)	1.98 (1.25, 3.13)	0.004

Cox Proportional Hazards regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

HR=hazard ratio.

When we defined frequent exacerbator phenotype as ≥2 exacerbation/years, we observed similar findings (**Table 4**). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, an increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR= 1.40, 95%CI= 1.21-1.62, p<0.001).

Table 4. Association of exacerbation group (frequent exacerbators defined as those with 2 or more per year) with mortality in COPD participants with post-bronchodilator FEV1% predicted≥50% and at least 3 years of follow-up (n= 2,099).

	HR (95%CI)	P value
Participants with No Exacerbation (n=981)	ref	ref
Participants with >0 and <2 exacerbations (n= 1,033)	0.93 (0.71, 1.22)	0.59
Participants with ≥2 exacerbations (n= 85)	2.01 (1.23, 3.29)	0.006

Cox Hazard regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

HR=hazard ratio.

Current or former smokers with normal spirometry (n=3,143)

In current or former smokers with normal spirometry, the median duration of follow-up was 8.1 years (interquartile range = 6.9-8.9). The top 5% in exacerbation frequency (n= 185) had 0.8 or more exacerbations per year (frequent exacerbators), 743 had >0 exacerbations but less than 0.8 exacerbation a year (exacerbators), and 2,215 had no exacerbations. **Table 5** shows the characteristics of the 3 groups. The count of total respiratory exacerbations was 3,548 for all participants with normal spirometry, 1620 (45.7%) for the exacerbators, and 1928 (54.3%) for the frequent exacerbators. The count of severe respiratory exacerbations was 1,086 for all participants with normal spirometry, 519 (44.8%) for the exacerbators, and 567 (55.2%) for the frequent exacerbators.

Table 5. Characteristics of current and former smokers with normal spirometry with at least 3 years follow up (n=3,143).

	No Exacerbation	Exacerbators	Frequent exacerbators	P value*
Exacerbations per year	0	>0 and <0.8	>=0.8	
n	2215	743	185	
Follow-up duration, y (IQR)	8(6.5-8.8)	8.4(7.5-9.1)	8(6.9-8.8)	<0.001
Age, y ± SD	58.07 ± 8.60	58.38 ± 8.60	57.12 ± 8.45	0.2
Female, n (%)	1049 (47.4%)	463 (62.3%)	123 (66.5%)	<0.001
African American, n	699 (31.6%)	212 (28.5%)	67 (36.2%)	0.09
Active smokers, n (%)	1103 (49.8%)	349 (47.0%)	92 (49.7%)	0.41
Pack-years smoking ± SD	36.98 ± 20.57	35.72 ± 18.55	43.78 ± 25.54	<0.001
Body mass index, kg/m2 ± SD	28.70 ± 5.55	30.01 ± 6.09	30.91 ± 6.59	<0.001
History of Asthma, n (%)	179 (8.1%)	123 (16.6%)	73 (39.5%)	<0.001
History of acute bronchitis, n (%)	634 (28.6%)	364 (49.0%)	114 (61.6%)	<0.001
History of pneumonia, n (%)	565 (25.5%)	268 (36.1%)	88 (47.6%)	<0.001
Obstructive Sleep Apnea, n (%)	244 (11.0%)	126 (17.0%)	43 (23.2%)	<0.001
Gastroesophageal Reflux, n (%)	428 (19.3%)	236 (31.8%)	71 (38.4%)	<0.001
Diabetes Mellitus, n (%)	224 (10.1%)	102 (13.7%)	29 (15.7%)	0.004
History of Cancer, n (%)	115 (5.2%)	49 (6.6%)	12 (6.5%)	0.31
Chronic bronchitis, n (%)	197 (8.9%)	118 (15.9%)	42 (22.7%)	<0.001
mMRC>2, n (%)	374 (16.9%)	190 (25.6%)	88 (47.6%)	<0.001
Post-FEV1% predicted ± SD	97.76 ± 11.37	96.72 ± 11.60	94.38 ± 10.66	<0.001
Post-FVC% predicted ± SD	96.56 ± 11.56	95.58 ± 12.06	94.69 ± 10.85	0.026
Bronchodilator response, n (%)	214 (9.8%)	61 (8.4%)	25 (13.5%)	0.11
6-min-walk-test distance, ft ± SD	1534.40 ± 352.08	1484.22 ± 353.94	1366.52 ± 332.02	<0.001
ICS/LABA, n (%)	45 (2.0%)	49 (6.6%)	39 (21.1%)	<0.001
LAMA, n (%)	31 (1.4%)	19 (2.6%)	22 (11.9%)	<0.001
ICS, n (%)	23 (1.0%)	16 (2.2%)	15 (8.1%)	<0.001
LABA, n (%)	2 (0.1%)	5 (0.7%)	4 (2.2%)	<0.001
Total exacerbations per year ± SD	0.00 ± 0.00	0.27 ± 0.19	1.37 ± 0.76	<0.001
Severe exacerbations per year ± SD	0.00 ± 0.00	0.09 ± 0.14	0.41 ± 0.50	<0.001
Moderate-to-severe exacerbations, n (%)	0.00 ± 0.00	2.18 ± 1.50	10.42 ± 6.73	<0.001
Severe exacerbations, n (%)	0.00 ± 0.00	0.70 ± 1.10	3.06 ± 3.70	<0.001
Emphysema, % ± SD	2.36 ± 2.77	2.50 ± 3.13	2.36 ± 2.87	0.56
Gas trapping, % ± SD	10.72 ± 8.67	10.29 ± 8.05	10.58 ± 8.53	0.54
TLV, L ± SD	5.46 ± 1.32	5.20 ± 1.22	5.10 ± 1.18	<0.001
TLV% predicted ± SD	102.95 ± 15.56	103.06 ± 14.94	104.06 ± 14.54	0.66
Pi10, mm ± SD	3.63 ± 0.11	3.65 ± 0.11	3.67 ± 0.12	<0.001

*ANOVA for continuous and chi square of fisher exact test for categorical variables.

Data regarding bronchodilator response, 6-min-walk-test distance, TLV, Pi10, gas trapping and emphysema were missing in 40,10,184,199,582, and 184 participants, respectively.

ICS= inhaled glucocorticosteroids; LABA= long acting beta-agonist; LAMA= long acting muscarinic antagonist; mMRC= modified Medical Research Council scale, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 sec %predicted; post-FVC% predicted = post-bronchodilator forced vital capacity %predicted, Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV= total lung volume at maximum inspiratory volumes measure by chest CT.

In frequent exacerbators during a median follow-up time of 8 years (interquartile range = 6.9-8.8), the median count of exacerbations was 8 with a range of 3-48 (interquartile range = 7-11)

and median count of severe exacerbations was 2 with a range of 0-18 (interquartile range = 0-5).

Pack-years (every 10 with OR=1.13; 95%CI=1.05-1.21), dyspnea (OR=2.10; 95%CI=1.44-3.05), history of asthma (OR=3.63; 95%CI=2.52-5.20), history of acute bronchitis and/or pneumonia (OR=2.16; 95%CI=1.50-3.16), and history of obstructive sleep apnea (OR=1.58; 95%CI=1.04-2.34) were associated with the frequent exacerbator group (**Table 6**). We performed an additional analysis after multiple imputations accounting for missing values with almost identical findings.

Table 6. Factors associated with frequent exacerbators among current and former smokers with normal spirometry and at least 3-years follow-up (n=3,143).

	OR (95%CI)	P value
Pack-years, every 10	1.13 (1.05, 1.21)	<0.001
Post-FEV1% predicted, every 10%	0.88 (0.75, 1.02)	0.01
6-min-walk-test distance, every 100ft	0.96 (0.91, 1.01)	0.076
Female	1.35 (0.95, 1.95)	0.099
mMRC>2	2.10 (1.44, 3.05)	<0.001
Chronic bronchitis	1.42 (0.93, 2.13)	0.0.097
History of Asthma	3.63 (2.52, 5.20)	<0.001
History of acute bronchitis and/or Pneumonia	2.16 (1.50, 3.16)	<0.001
Obstructive sleep apnea	1.58 (1.04, 2.34)	0.03

Variables tested but not retained in the final model include: body mass index, Pi10, Diabetes, Gastroesophageal Reflux, and Bronchodilator response.

Data regarding 6-min-walk-test distance missing in 10 participants.
We performed an additional analysis after multiple imputations accounting for missing values with almost identical findings.

mMRC= modified Medical Research Council scale, OR = odds ratio, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 sec %predicted, Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm.

In the mortality analysis, there were 93 (4.2%) deaths in the group with no exacerbations, 28 (3.8%) in the exacerbator group, and 14 (7.6%) in the frequent exacerbator group. After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, the frequent exacerbator group was associated with increased mortality compared to that with no exacerbations (HR= 2.25;95%CI= 1.26-4.01, p=0.006) (**Table 7**). When we defined frequent exacerbator phenotype as ≥2 exacerbation/years, we observed similar findings (**Table 8**). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, an increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR= 1.66, 95%CI= 1.24-2.22, p<0.001).

Table 7. Association of exacerbation group with mortality in current and former smokers with normal spirometry with at least 3 years of follow-up (n=3,143).

	HR (95%CI)	**P value**
No Exacerbation (n=2,215)	ref	ref
Exacerbators (n=743)	1.02 (0.67, 1.57)	0.92
Frequent Exacerbators (n=185)	2.25 (1.26, 4.01)	0.006

Cox Proportional Hazards regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

95%CI= 95% Confidence interval; HR=hazard ratio.

Table 8. Association of exacerbation group (frequent exacerbators defined as those with 2 or more per year) with mortality in COPD participants with normal spirometry and at least 3 years of follow-up (n= 2,099).

	HR (95%CI)	P value
Participants with No Exacerbation (n= 2,215)	ref	ref
Participants with >0 and <2 exacerbations (n= 899)	1.19 (0.81, 1.74)	0.38
Participants with ≥2 exacerbations (n= 29)	3.73 (1.15, 12.08)	0.028

Cox Hazard regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index(BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

HR=hazard ratio.

4.4. Aim 4 Results

Of 10,194 participants in COPDGene with at least 10 pack-years history of smoking, we included 5,856 with available spirometric data both on visit 1 and visit 2. Of those we excluded 3,228 with abnormal spirometry on visit 1. The remaining 2,628 were included in the analysis (**Figure 1**).

Figure 1. Participants' flow chart.

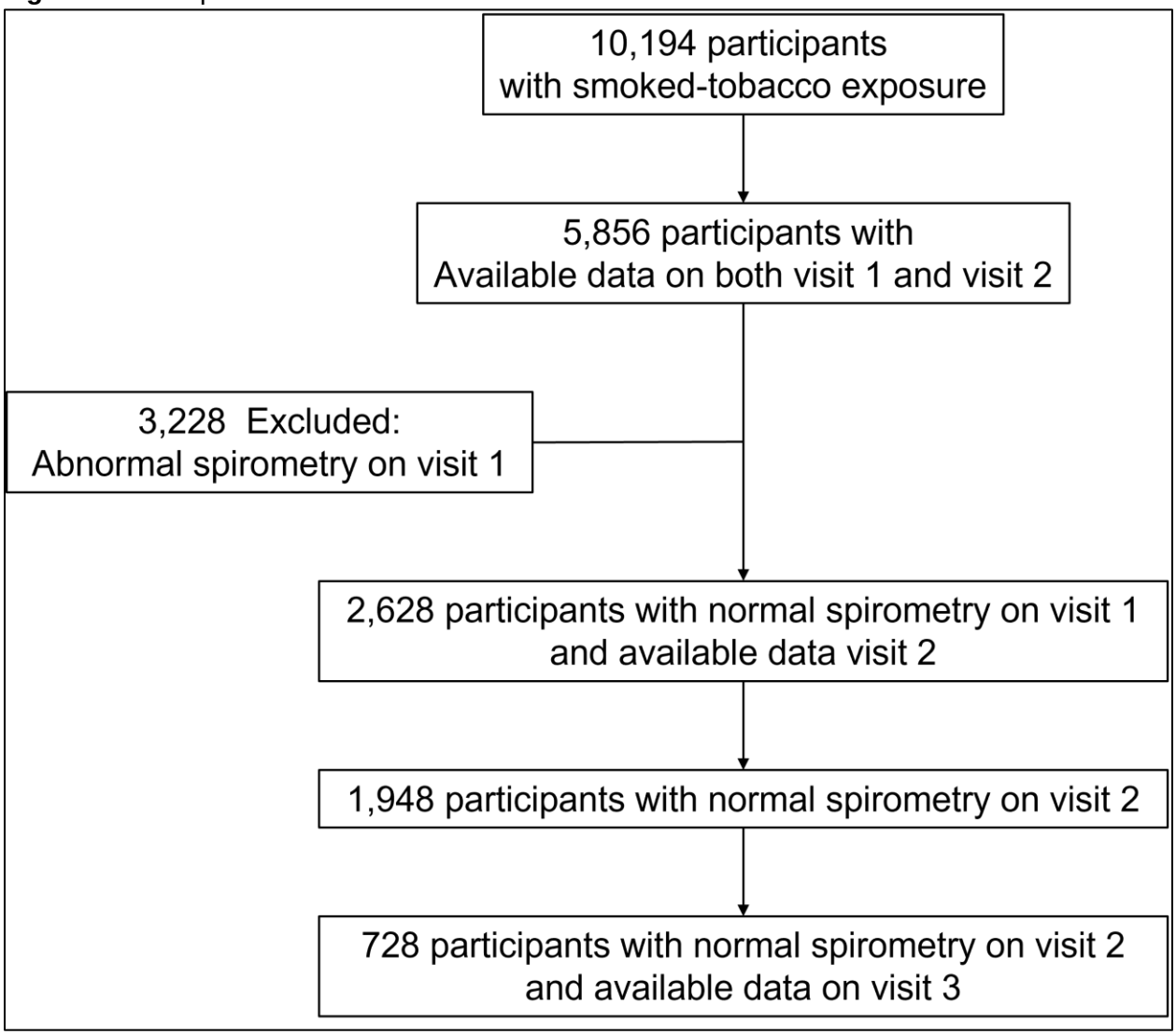


Table 1 shows their characteristics. Briefly, participants with higher exacerbations rates were enriched by more females and had higher body mass index, more accumulating smoking exposure, worse lung function, and suffer more often from chronic bronchitis and asthma relative to those with no exacerbations. In addition, participants with more exacerbations use medications more often.

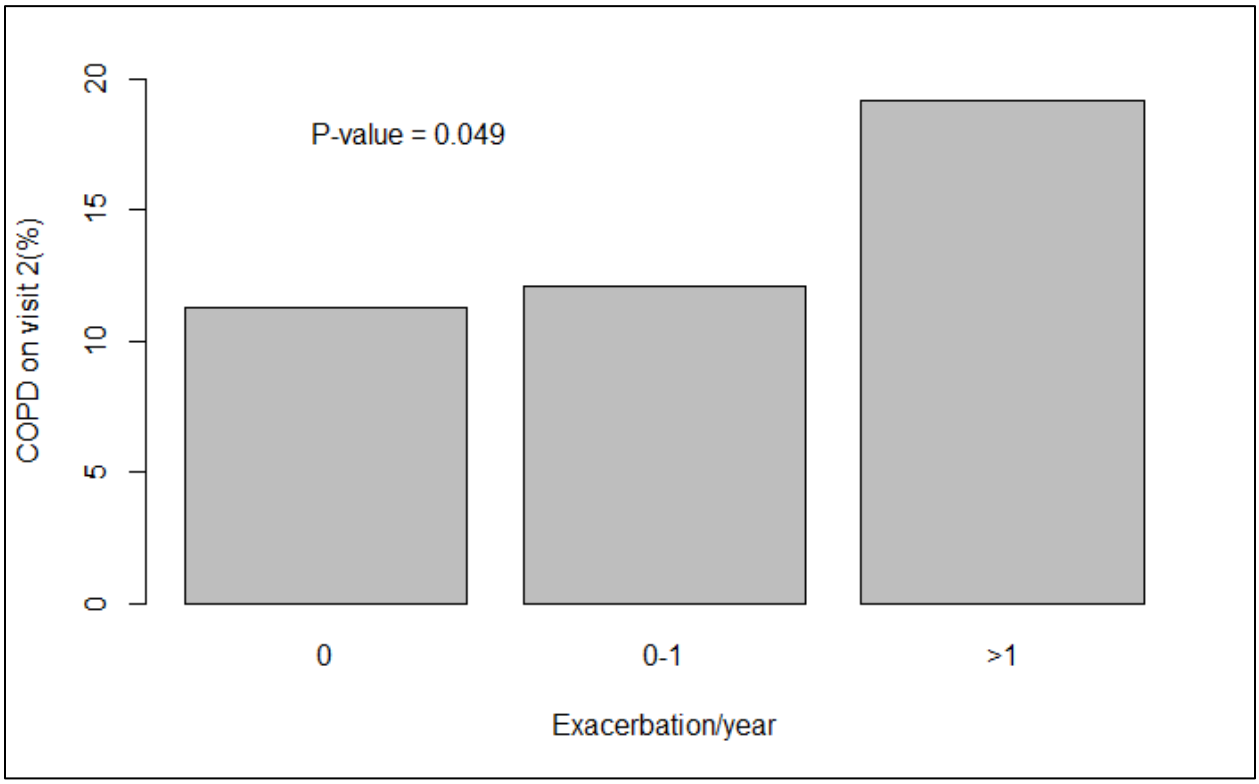
Table 1. Characteristics of participants by exacerbation group.

	0	exacerbator	frequent	P value
n	1901	428	104	
Age_P1 (mean (SD))	58.24 (8.55)	57.91 (7.98)	58.36 (8.78)	0.75
gender = 2 (%)	915 (48.1)	288 (67.3)	72 (69.2)	<0.001
race = 2 (%)	611 (32.1)	128 (29.9)	32 (30.8)	0.654
BMI_P1 (mean (SD))	28.79 (5.57)	30.04 (5.97)	31.50 (6.73)	<0.001
ATS_PackYears_P1 (mean (SD))	36.54 (20.18)	35.27 (18.72)	43.31 (26.35)	0.001
SmokCigNow_P1 = 1 (%)	914 (48.1)	204 (47.7)	45 (43.3)	0.632
Chronic_Bronchitis_P1 = 1 (%)	164 (8.6)	75 (17.5)	19 (18.3)	<0.001
AsthmaYes_P1 = 1 (%)	170 (8.9)	80 (18.7)	42 (40.4)	<0.001
Cortsterinhal_P1 = 1 (%)	19 (1.0)	13 (3.1)	10 (9.8)	<0.001
CombcCSBagon_P1 = 1 (%)	39 (2.1)	33 (7.8)	23 (22.1)	<0.001
tiotrop_P1 = 1 (%)	24 (1.3)	14 (3.3)	15 (14.6)	<0.001
FEV1pp_post_P1 (mean (SD))	97.69 (11.32)	96.80 (12.00)	93.47 (9.15)	0.001
FVCpp_post_P1 (mean (SD))	96.55 (11.52)	95.86 (12.79)	93.50 (9.66)	0.024
FEV1_FVC_post_P1 (mean (SD))	0.78 (0.05)	0.79 (0.05)	0.78 (0.06)	0.279
Average Exacerbations/year	0	0.38 (0.24)	1.67 (0.77)	<0.001
Average Severe Exacerbations/year	0	0.10 (0.17)	0.41 (0.56)	<0.001

Spirometry on visit 2

Of 1,901 participants with no exacerbations between visit 1 and visit 2, 215 (11.3%) developed COPD while 52 of 428 (12.1%) participants with 0-1 exacerbation/year, and 20 of 104 (19.1%) developed COPD at visit 2 (**Figure 2**).

Figure 2. Progression to COPD in individuals with history of current or former smoked-tobacco exposure and normal spirometry.



Of those with no exacerbations between visit 1 and visit 2, 359 (18.9%) developed abnormal spirometry while 93 (21.7%) participants with 0-1 exacerbation/year, and 33 (31.7%) developed abnormal spirometry at visit 2. After adjusting for demographics, smoking exposure, body mass index, lung function, and history of asthma, exacerbation/year was associated (odds ratio [OR] = 1.32 (95%CI 1.00 to 1.74; P=0.045) but severe exacerbation/year was not associated with COPD at visit 2 (OR= 1.67 (95%CI 0.83 to 3.11; P= 0.12). Similarly, exacerbation/year was associated (OR= 1.27 (95%CI 1.00 to 1.62; P=0.048) but severe exacerbation/year was not associated with abnormal spirometry at visit 2 (OR= 1.50 (95%CI 0.84 to 2.64; P= 0.16). **Figure 3** shows the lung function decline between visit 1 and visit 2 as a function of exacerbation rate (average exacerbations/year between visit 1 and visit 2).

Figure 3. Lung function decline between visit 1 and visit 2 as a function of exacerbation rate (average exacerbations/year between visit 1 and visit 2).

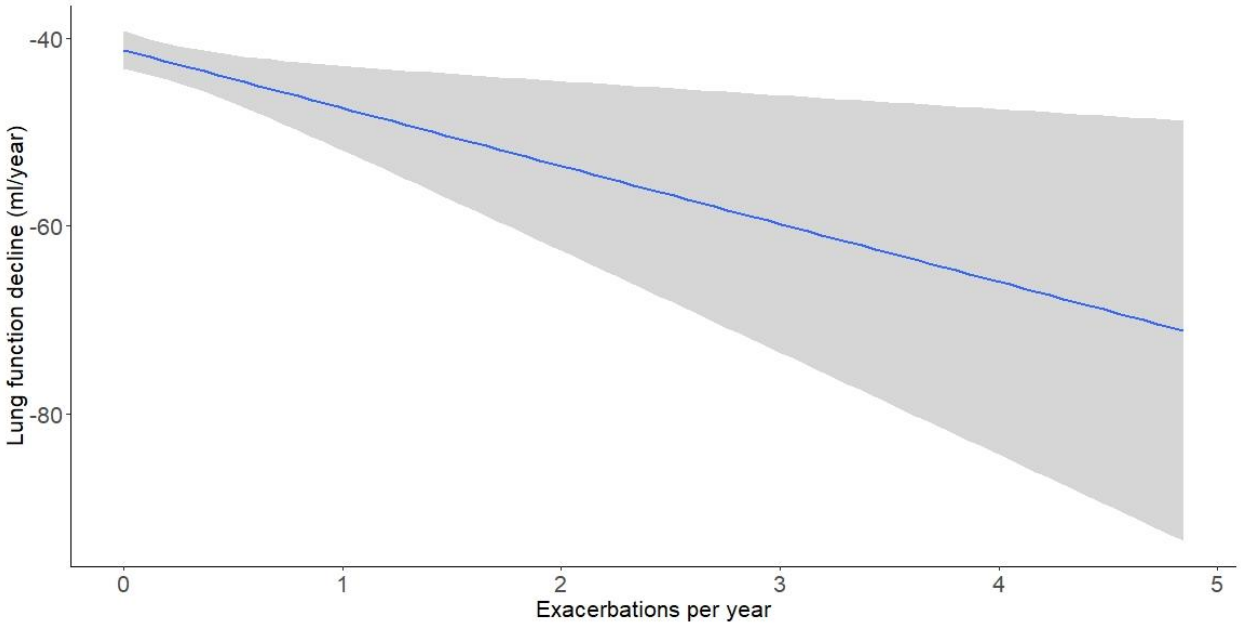
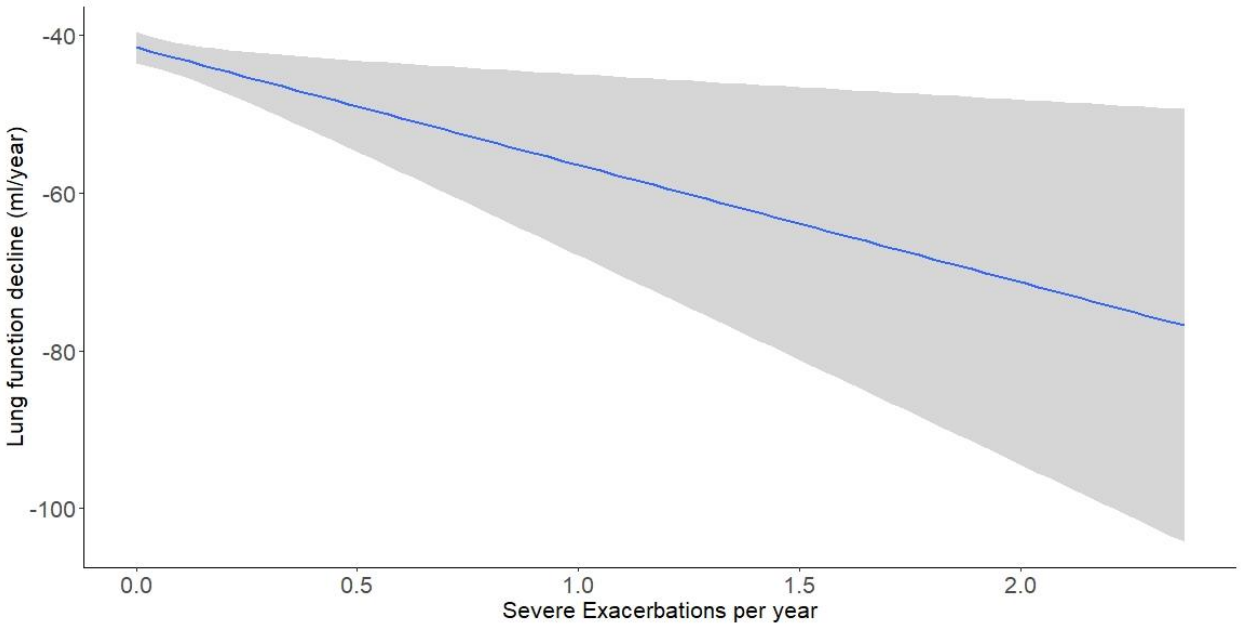


Figure 4 shows the lung function decline between visit 1 and visit 2 as a function of exacerbation rate (severe exacerbations/year between visit 1 and visit 2). After adjusting for demographics, smoked-tobacco exposure, body mass index, lung function, and history of asthma, one exacerbation/year was associated with 8.97 ml/year post-FEV_1 decline (95%CI 4.19 to 13.75; P<0.001) and one severe exacerbation/year was associated with 17.3 ml/year post-FEV_1 decline (95%CI 5,63 to 29.00; P=0.004).

Figure 4. Lung function decline between visit 1 and visit 2 as a function of severe exacerbation rate (average severe exacerbations/year between visit 1 and visit 2).



We also examined the association of prior exacerbations with progression to COPD and abnormal spirometry at visit 3 and future lung function decline between visit 2 and visit 3 among those have normal spirometry at visit 2 (n=728). After adjusting for demographics, smoking exposure, body mass index, lung function, and history of asthma, neither exacerbation/year (OR= 1.69; 95%CI 0.97 to 2.63; P= 0.07) nor severe exacerbations/year between visit 1 and visit 2 were associated with COPD at visit 3 (OR= 3.33; 95%CI 0.58 to 7.40; P= 0.28). Neither exacerbation/year (OR= 1.36; 95%CI 0.86 to 2.17; P= 0.20) nor severe exacerbations/year between visit 1 and visit 2 were associated with abnormal spirometry at visit 3 (OR= 2.32; 95%CI 0.51 to 6.36; P= 0.42). Similarly, neither exacerbation/year (a decline of 4.88 ml/year; 95%CI -4.46 to 14.24 ; P=0.31) nor severe exacerbations/year between visit 1 and visit 2 were

associated lung function decline between visit 2 and visit 3 (a decline of 15.97 ml/year ; 95%CI -9.52 to 41.46 ; P=0.22).

Mortality Analysis

Among 2,333 participants with normal spirometry at visit 1 and were alive at visit 2 (cohort entry), the median follow-up time after visit 2 was 2,424 days (Interquartile Interval [IQI]: 1,927 to 2,746) and there were 215 deaths. Exacerbations/year between visit 1 and visit 2 was associated with mortality (hazard ratio [HR] = 1.51;95%CI 1.24 to 1.84; P<0.001). Neither the interaction between exacerbation/year and COPD at visit 2 (HR= 0.96;95%CI 0.56 to 1.62; P=0.87) nor the interaction between exacerbation/year and abnormal spirometry at visit 2 were associated with mortality (HR= 1.10;95%CI 0.73 to 1.67; P=0.665). Severe exacerbations/year between visit 1 and visit 2 was associated with mortality (HR = 1.94;95%CI 1.41 to 2.69; P<0.001). Neither the interaction between exacerbation/year and COPD at visit 2 (HR= 0.61;95%CI 0.26 to 1.42; P=0.25) nor the interaction between exacerbation/year and abnormal spirometry at visit 2 were associated with mortality (HR= 0.92;95%CI 0.49 to 1.73; P=0.81).

Among those participants with normal spirometry both at visit 1 and 2, exacerbations/year (HR = 1.40;95%CI 1.09 to 1.81; P=0.009) and exacerbations/year between visit 1 and visit 2 were associated with mortality (HR = 1.90;95%CI 1.23 to 2.91; P=0.004).

4.5. Aim 5 Results

Of 10,199 COPDGene participants with at least 10 or more pack-years of smoking and no significant interstitial lung disease or bronchiectasis, 1,260 of them had PRISm at the enrollment visit. After excluding one individual with no available post-bronchodilator spirometry, 121 with no TLC_{CT} measures and 7 individuals with FVC > TLC_{CT}, 1,131 participants were included in the analysis. The median value of FVC/TLC_{CT} was 0.59 (IQR= 0.53-0.66). Of these 1,131 participants, 617 of them had acceptable spirometry measurements at the 5-year follow-up visit, 967 had available data regarding respiratory exacerbations, and 960 had vital status data available.

Baseline Characteristics at the enrollment visit (n = 1,131)

Table 1 shows the characteristics of participants by FVC/TLC_{CT} quartile. Age, BMI, pack-years smoking exposure, mMRC and SGRC scores, % emphysema and gas trapping, and % functional small airways disease increase with decreasing FVC/TLC_{CT}. An increased proportion of females and decreased proportion of African Americans were associated with decreasing FVC/TLC_{CT}. Participants in the lower FVC/TLC_{CT} quartiles a higher prevalence of comorbidities.

Table 1. Baseline characteristics of smokers with preserved ratio impaired spirometry across post-bronchodilator forced vital capacity /total lung capacity ratio (FVC/TLC_{CT}) quartiles (n=1,131).

	High air trapping→Low air trapping				
FVC/TLC Quartile	**Very Low quartile (n=283)**	**Low quartile (n=283)**	**High quartile (n=282)**	**Very High quartile (n=283)**	**P for trend**
FVC/TLC_{CT}	**<0.53**	**0.53 - 0.59**	**0.59-0.66**	**>0.66**	
Age, y ± SD	62.83 ± 8.82	57.68 ± 7.34	55.70 ± 6.96)	52.84 ± 6.27	<0.001
Female, n(%)	186 (65.7%)	169 (59.7%)	143 (50.7%)	115 (40.6%)	<0.001
African American, n(%)	86 (30.4%)	89 (31.4%)	126 (44.7%)	174 (61.5%)	<0.001
BMI, Kg/m^2 ± SD	32.99 ± 7.42	32.84 ± 7.50	30.24 ± 6.88	31.05 ± 6.97	<0.001
Pack-Years ± SD	49.46 ± 28.69	43.51 ± 22.51	39.12 ± 20.08	38.06 ± 22.63	<0.001
Active Smoker, n(%)	154 (54.4%)	162 (57.2%)	180 (63.8%)	213 (75.3%)	<0.001
Chronic Bronchitis, n(%)	53 (18.7%)	54 (19.1%)	52 (18.4%)	42 (14.8%)	0.23
mMRC ± SD	1.70 ± 1.47	1.56 ± 1.44	1.21 ± 1.37	1.44 ± 1.50	<0.001
SGRQ ± SD	32.91 ± 22.69	30.06 ± 23.29	24.50 ± 20.54	29.71 ± 23.78	<0.001
Asthma, n(%)	75 (26.5%)	64 (22.6%)	51 (18.1%)	60 (21.2%)	0.064
CHF, n(%)	21 (7.4%)	17 (6.0%)	5 (1.8%)	8 (2.8%)	0.001
DM, n(%)	75 (26.5%)	75 (26.5%)	44 (15.6%)	42 (14.8%)	<0.001
HTN, n(%)	150 (53.0%)	151 (53.4%)	133 (47.2%)	120 (42.4%)	0.004
CAD, n(%)	25 (8.8%)	32 (11.3%)	12 (4.3%)	10 (3.5%)	<0.001
OSA, n(%)	68 (24.0%)	61 (21.6%)	56 (19.9%)	38 (13.4%)	0.002
CVA, n(%)	15 (5.3%)	10 (3.5%)	7 (2.5%)	7 (2.5%)	0.049
LAMA, n(%)	33 (12.1%)	18 (6.5%)	18 (6.5%)	15 (5.4%)	0.005
ICS, n(%)	19 (7.0%)	19 (6.8%)	12 (4.4%)	13 (4.6%)	0.131
LABA, n(%)	7 (2.6%)	1 (0.4%)	1 (0.4%)	4 (1.4%)	0.2482
ICS/LABA, n(%)	59 (21.6%)	36 (12.9%)	22 (7.9%)	24 (8.6%)	<0.001
Post-FEV1% ± SD	65.74 ± 9.65	71.33 ± 7.32	72.04 ± 6.54	73.02 ± 5.92	<0.001
Post-FVC% ± SD	66.70 ± 10.07	72.47 ± 7.68	73.47 ± 7.58	75.05 ± 7.25	<0.001
BDR, n(%)	40 (14.4%)	41 (14.6%)	30 (10.8%)	47 (16.8%)	0.71
§% Emphysema ± SD	2.02 ± 3.32	1.66 ± 2.92	1.48 ± 2.00	1.07 ± 1.53	<0.001
§% Gas trapping ± SD	12.48 ± 8.64	9.06 ± 7.48	8.19 ± 6.65	7.50 ± 5.82	<0.001
‡PRM^{fSAD}, % ± SD	14.63 ± 9.87	10.60 ± 8.65	10.37 ± 9.24	10.13 ± 8.65	<0.001
§FRC_{CT}% ± SD	97.25 ± 18.17	87.62 ± 14.63	80.89 ± 13.00	75.25 ± 12.36	<0.001
TLC_{CT} % ± SD	90.20 ± 13.58	85.82 ± 9.80	77.77 ± 9.48	68.96 ± 9.02	<0.001
#6-MWT, meters ± SD	366.33 ± 110.24	394.00 ± 104.72	406.56 ± 114.12	396.23 ± 109.78	<0.001

§ For % GT and FRC_{CT}% analysis, data were available for 936 subjects.

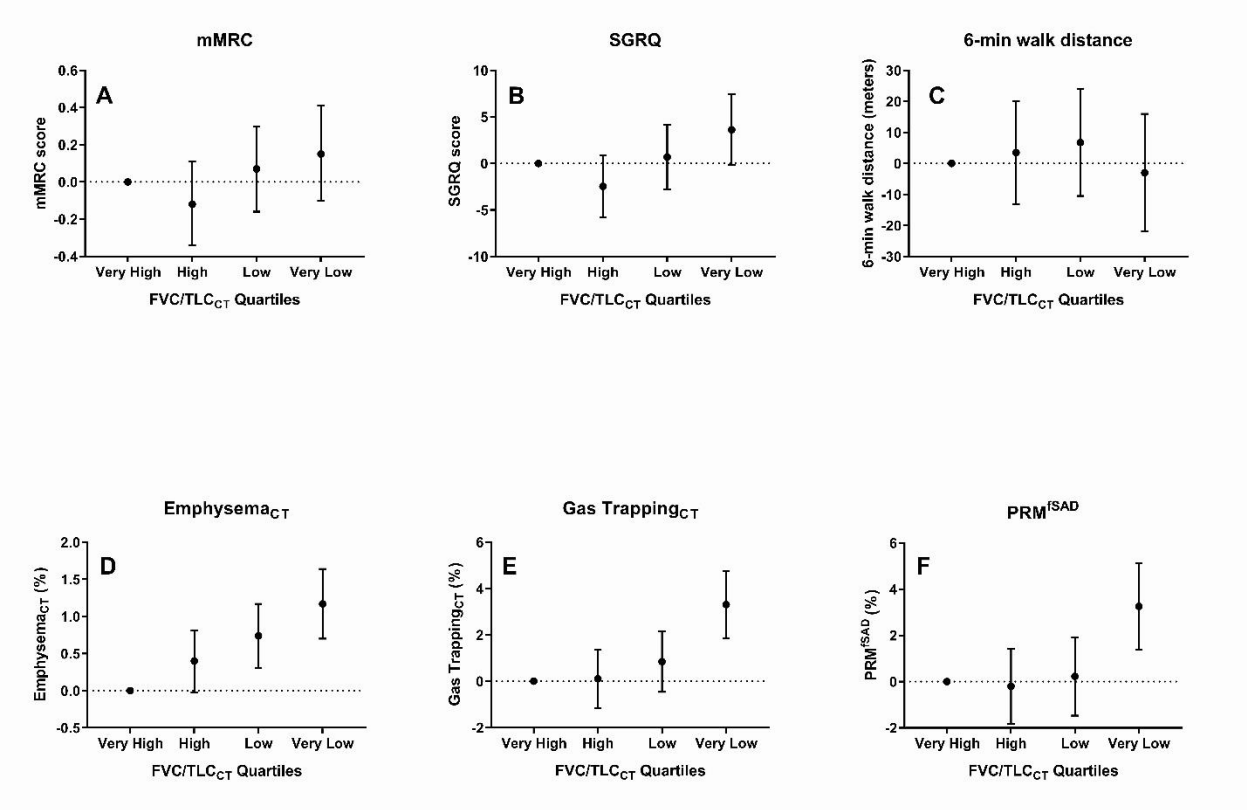
‡ For PRM data analysis, data were available for 932 subjects.

For 6-MWT data analysis, data were available for 1,121 subjects.

BDR = bronchodilator response; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; DM = diabetes mellitus; FRC_{CT}% = functional residual capacity % predicted; HTN = hypertension; ICS = inhaled glucocorticosteroids, LABA = long-acting beta-agonist, LAMA = long-acting muscarinic antagonist, mMRC = modified Medical Research Council dyspnea score; OSA = obstructive sleep apnea; post-FEV1% = post-bronchodilator FEV1% predicted; post-FVC% = post-bronchodilator FVC% predicted; PRM^{fSAD} = parametric response mapping functional small airways disease; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire score; TLC_{CT}% = total lung capacity % predicted and 6-MWD = 6-min walk test.

In multivariable-adjusted analyses, the very low FVC/TLC_{CT} quartile was associated with an average of 3.31% higher radiographic gas trapping (95%CI=1.85-4.76; p<0.001), and 3.26% higher PRM^{fSAD} (95%CI=1.40-5.12; p<0.001) relative to the very high quartile (**Figure 1**). Lower quartiles were also associated with higher % emphysema. The very low quartile was associated with a trend towards higher SGRQ (3.63; 95%CI = -0.17 to 7.44; p=0.06) (**Table 2**).

Figure 1. Associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with dyspnea and health-related quality of life scores, chest CT % emphysema and % gas trapping, functional small airway disease, and 6-min walk test distance at baseline among smokers with Preserved Ratio Impaired Spirometry (PRISm; n=1,131).



Each panel in the figure represents a separate linear regression model with categorical post-bronchodilator FVC/TLC_{CT} quartile as the main independent variable (exposure) with the "very high" quartile used as the reference category. The dependent variable (outcome) in each model was (A) modified Medical Research Council (mMRC) dyspnea score, (B) St. George's Respiratory Questionnaire total score (SGRQ), (C) 6-minute walk test distance (6-MWT in meters), (D) % Emphysema, (E) % Gas trapping, and (F) functional small airways disease (PRM^{fSAD}). All models were adjusted for the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI), history of asthma and congestive heart failure, and diabetes mellitus. FVC/TLC_{CT} quartile is plotted on the x-axis while the regression coefficient (and 95% CI) for each category is plotted on the y-axis.

* For % GT analysis, n= 936 subjects.

† For PRM^{fsad} data analysis, n= 932 subjects.

#For 6-min walk test distance analysis, n=1,121 subjects.

Table 2. Associations of post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with chronic bronchitis, dyspnea and health-related quality of life scores, chest CT % emphysema and % gas trapping, functional small airway disease, and 6-min walk test distance in smokers with preserved ratio impaired spirometry (n=1,131).

	FVC/TLC_{CT}			
Chronic Bronchitis	OR	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	1.49	0.94	2.38	0.09
Low	1.36	0.84	2.20	0.21
Very Low	1.43	0.85	2.42	0.18
mMRC	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	-0.12	-0.34	0.11	0.30
Low	0.07	-0.16	0.30	0.55
Very Low	0.15	-0.10	0.41	0.24
SGRQ	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	-2.46	-5.80	0.88	0.15
Low	0.69	-2.78	4.17	0.70
Very Low	3.63	-0.17	7.44	0.06
% Emphysema	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.40	-0.02	0.81	0.06
Low	0.74	0.31	1.17	<0.001
Very Low	1.17	0.70	1.64	<0.001
***% Gas trapping**	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.11	-1.16	1.38	0.86
Low	0.85	-0.46	2.16	0.20
Very Low	3.31	1.85	4.76	<0.001
† %PRM^{fSAD}	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	-0.20	-1.83	1.43	0.81
Low	0.23	-1.47	1.92	0.79
Very Low	3.26	1.40	5.12	<0.001
#6-MWT distance, meters	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	3.50	-13.15	20.15	0.68
Low	6.79	-10.46	24.03	0.44
Very Low	-2.96	-21.90	15.97	0.76

Binary logistic regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and chronic bronchitis as the dependent variables (outcome) were performed. Linear regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and mMRC, SGRQ, % Emphysema, % Gas trapping, PRM^{fSAD}, and 6-MWT distance as the dependent variables (outcome) were performed. All models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure.

* For % GT analysis, data were available for 936 participants.

† For PRM^{fSAD}data analysis, data were available for 932 participants.

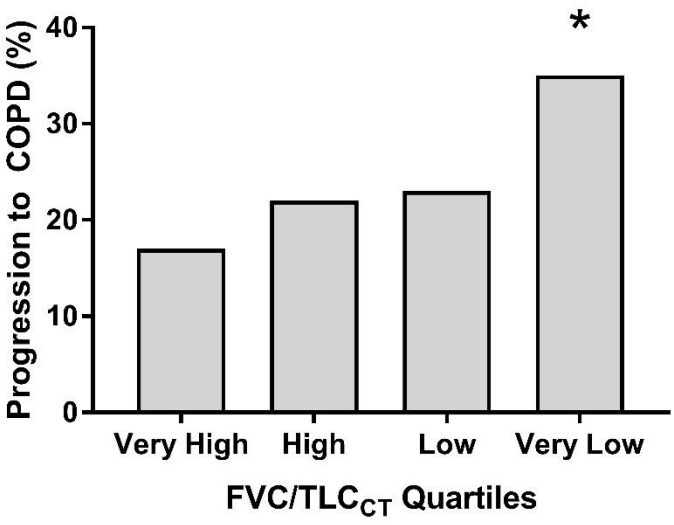
#For 6-MWT distance analysis, data were available for 1,121 participants.

mMRC = modified Medical Research Council dyspnea score; OR=odds ratio; PRM^{fSAD}= parametric response mapping functional small airways disease; SGRQ = St. George's Respiratory Questionnaire score; 6-MWT = 6-min walk test.

Progression to COPD at 5-year follow-up

Among participants with valid spirometry at the 5-year follow up visit (n=617), approximately 35.9% (56 of 156) of individuals in very low FVC/TLC_{CT} quartile progressed to COPD, while 23% (37 of 160), 22% (35 of 156), and 17% (25 of 145) of individuals in the low, high, and very high FVC/TLC_{CT} quartiles, respectively, progressed to COPD (**Figure 2**; Cochran-Armitage test for trend p<0.001). In the multivariable-adjusted analysis, the very low FVC/TLC_{CT} quartile at enrollment was associated with progression to COPD with an OR of 2.67 (95%CI=1.45-5.00; p<0.001) relative to the highest quartile (**Table 3**).

Figure 2. Progression to COPD ($FEV_1/FVC<0.7$) at the 5-year follow-up visit by post-bronchodilator forced vital capacity /total lung capacity ratio (FVC/TLC_{CT}) quartiles at enrollment in smokers with preserved ratio impaired spirometry (n=617).



Cochran Armitage Trend test $p<0.001$

Pairwise comparisons between quartiles performed using Chi-squared test. *$p = 0.026$ vs Very High FVC/TLC_{CT} Quartile

Table 3. Change in FEV_1, 6-MWT distance, % emphysema and gas trapping between enrollment and follow-up, and progression to COPD at 5-year follow-up visit in smokers with Preserved Ratio Impaired Spirometry (PRISm) across post-bronchodilator forced vital capacity /total lung capacity ratio (FVC/TLC_{CT}) quartiles (n=617).

	Very Low quartile (n=156)	**Low quartile (n=160)**	**High quartile (n=156)**	**Very High quartile (n=145)**	**P for trend**
FVC/TLC_{CT}	**<0.53**	**0.53 - 0.59**	**0.59-0.66**	**>0.66**	
Change in FEV1 (ml/yr)	-18.26 ± 53.68	-18.03 ± 49.98	-26.15 ± 47.94	-18.27 ± 55.49	0.17
Change in 6-MWT (meters/year)*	-43.0 ± 94.03	-41.13 ± 101.75	-37.07 ± 117.17	-34.83± 105.47	0.066
Change in %Emph per year§	0.06 ± 2.03	-0.18 ± 1.79	-0.12 ± 2.01	0.07 ± 1.71	0.63
Change in %GT per year ‡	2.07 ± 6.58	0.11 ± 6.02	0.01 ± 6.52	-0.03 ± 5.46	0.073
COPD at follow-up visit	56 (38.9%)	37 (23.1%)	35 (22.4%)	25 (17.2%)	<0.001

* For Change in 6-MWT analysis, data were available for 154,155,154, and 144 participants for very low, low, high, and very high quartile, respectively.

§ For % Emp analysis, data were available for 123,120,128, and 108 participants for very low, lo, high, and very high quartile, respectively.

‡ For Change in %GT analysis, data were available for 92, 95, 94, and 72 participants for very low, lo, high, and very high quartile, respectively.

Longitudinal changes in spirometry, functional capacity, and radiographic features

Table 3 shows changes in spirometry, functional capacity, and radiographic features between enrollment and follow-up visit. In the adjusted analysis, the very low FVC/TLC_{CT} quartile at enrollment was associated with increase of 2.74% radiographic gas trapping (95%CI=0.55-4.93; p=0.014) relative to the highest quartile (**Table 4**). FVC/TLC_{CT} was not associated with change in FEV1, 6-MWT distance or % emphysema over time. There were no differences in the rate of decline in FEV1 by current smoking status at enrollment (combined and by FVC/TLC quartile - data not shown).

Table 4. Multivariable-adjusted associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with change in FEV_1, 6-MWT distance, % emphysema and gas trapping between enrollment and follow-up, and progression to COPD at 5-year follow-up visit in smokers with preserved ratio impaired spirometry(n=617).

	FVC/TLC_{CT}			
Change in FEV1, ml/year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	-0.20	-8.95	3.97	0.20
Low	3.85	-7.85	15.55	0.52
Very Low	3.75	-8.95	16.45	0.56
Change in 6-MWT distance, meters/year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	-0.54	-24.47	23.40	0.96
Low	-1.87	-26.57	22.83	0.88
Very Low	4.09	-22.55	30.73	0.76
Change in % Emphysema pe yer	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	-0.08	-0.58	0.41	0.75
Low	-0.07	-0.59	0.45	0.79
Very Low	0.19	-0.37	0.75	0.51
Change in % Gas trapping per year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	0.32	-1.60	2.24	0.74
Low	1.02	-0.96	3.00	0.31
Very Low	2.74	0.55	4.93	0.014
COPD at 5 years	OR	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	1.49	0.83	2.72	0.18
Low	1.54	0.85	2.83	0.16
Very Low	2.67	1.45	5.00	0.002

Linear regression models with post-bronchodilator FVC/ quartiles as independent variables (exposure) change in FEV1, 6-MWT distance, % emphysema and gas trapping between enrollment and follow-up as the dependent variables(outcomes) were performed. Binary logistic regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and progression to COPD at follow-up visit as the dependent variables (outcome) were performed. All models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure.

For change in FEV_1 mL/year, data were available for 617 participants.

For change in 6-MWT distance analysis, data were available for 606 participants.

For change in % emphysema analysis, data were available for 478 participants.

For change in % gas trapping analysis, data were available for 352 participants.

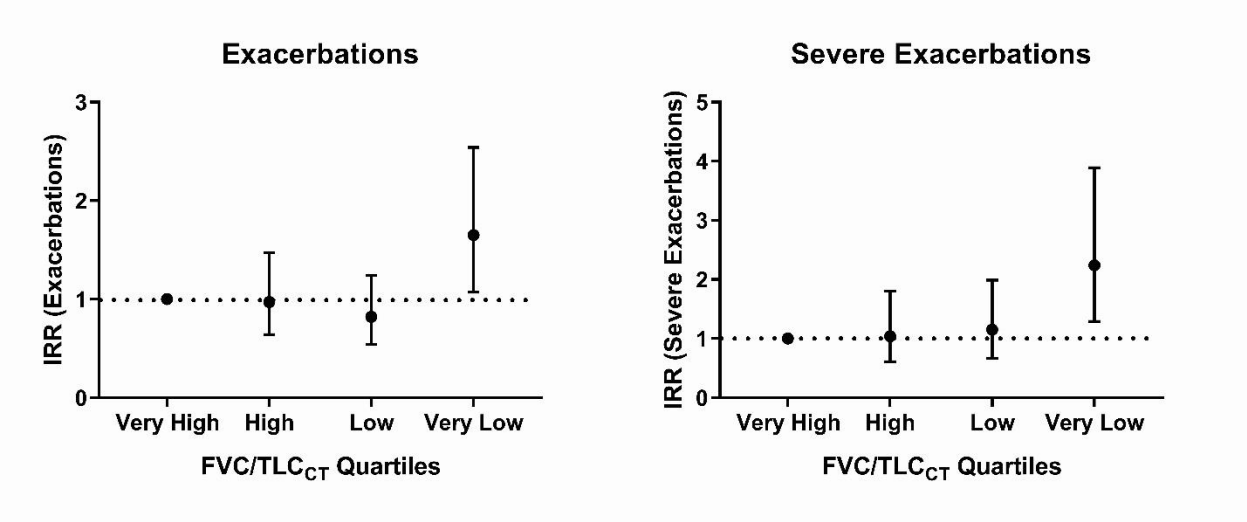
OR= odds ratio; 6-MWT = 6-min walk test.

Respiratory Exacerbations

Of 967 subjects with exacerbation data available, 349 (36.1%) reported at least one exacerbation and 196 (20.3 %) reported at least one severe exacerbation during a median follow-up time of 6.4 years (IQR= 3.8 to 7.4). Approximately, 44% (115 of 262), 37% (93 of 250), 31% (72 of 232), and 31% (69 of 223) in the very low, low, high, and very high Quartiles had at least one exacerbation during the time period (Cochran-Armitage trend test $p<0.001$). In the

very low, low, high, and very high Quartiles, 26% (67 of 262), 18% (46 of 250), 16% (38 of 232), and 20% (45 of 223) of participants, respectively, had at least one severe respiratory exacerbation, with a trend towards significance (Cochran-Armitage p=0.095). We created multivariable zero-inflated negative binomial models to examine the association of FVC/TLC_{CT} quartile with respiratory exacerbations (**Figure 3**). The very low FVC/TLC_{CT} quartile was associated with increased relative risk for total exacerbations (IRR=1.65; 95%CI=1.07-2.54; p=0.023) and severe (IRR=2.24; 95%CI=1.29-3.89; p=0.004) exacerbations (**Table 5**).

Figure 3. Associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with prospective exacerbations and severe exacerbations in smokers with Preserved Ratio Impaired Spirometry (PRISm; n=967).



For exacerbation analysis, data for 967 subjects with PRISm at enrollment were available. Zero-inflated negative binomial regression models with post-bronchodilator FVC/TLC_{CT} as independent variable (exposure) and total exacerbations and severe exacerbations as the dependent variables (outcome) were performed. All regression models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure, and chronic bronchitis in the count negative binomial regression and an intercept-only model in the zero component. Follow-up time was included as an offset in the models. FVC/TLC_{CT} quartile is plotted on the x-axis while the IRR (and 95% CI) for each category is plotted on the y-axis.

IRR = incidence rate ratio, FVC/TLC_{CT} = forced vital capacity /total lung capacity.

Table 5. Multivariable-adjusted associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with prospective total exacerbations and severe exacerbations in smokers with preserved ratio impaired spirometry (n=967).

	FVC/TLC_{CT}			
Exacerbations	IRR	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	0.97	0.64	1.47	0.88
Low	0.82	0.54	1.24	0.34
Very low	1.65	1.07	2.54	0.023
Severe Exacerbations	IRR	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	1.04	0.61	1.80	0.88
Low	1.15	0.67	1.99	0.61
Very Low	2.24	1.29	3.89	0.004

For exacerbation analysis, data for 967 of total 1131participants were available. Zero-inflated negative binomial regression models with post-bronchodilator FVC/TLC_{CT} quartile as independent variables (exposure) and total exacerbations and severe exacerbations as the dependent variables (outcome) were performed. All regression models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure, and chronic bronchitis in the count negative binomial regression and an intercept-only model in the zero component. Follow-up time was included as an offset in the models.

IRR= incident rate ratio.

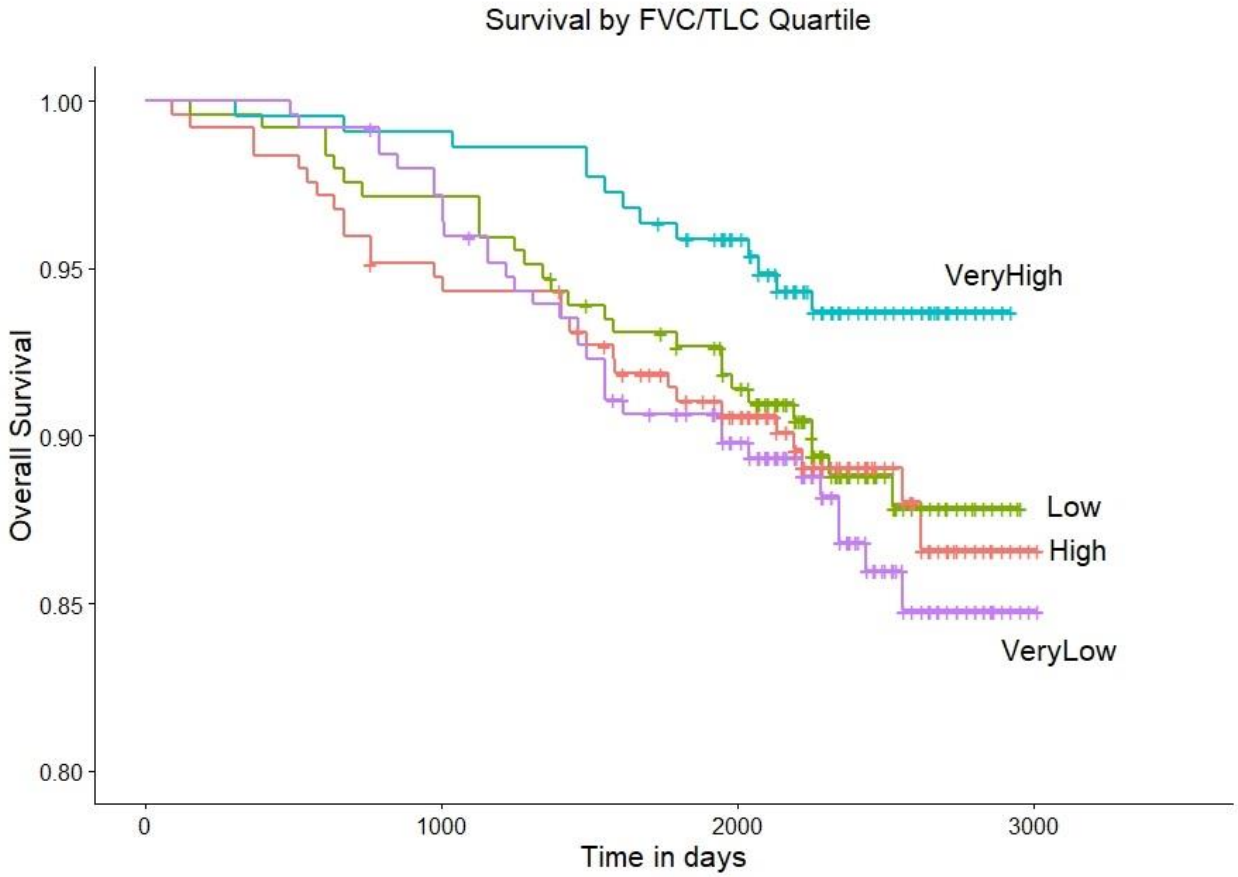
Mortality (n = 960)

During a median follow-up time of 2,408 days (IQR= 2158 to 2622), 12.9 % (32 of 248) subjects died in the Very Low quartile, 11 % (27 of 246) died in the low quartile, 11.3 % (28 of 247) died in the High quartile, and 5.9 % (13 of 219) died in the very high quartile (Cochran-Armitage trend test p=0.02). A Kaplan-Meier plot of mortality by FVC/TLC_{CT} quartile at enrollment is shown in **Figure 4**.

In Cox proportional hazards models adjusted for age at enrollment, sex, race, BMI, current smoking at enrollment, cumulative smoking exposure, diabetes, history of asthma and congestive heart failure, increased mortality in the high quartile with a trends towards an increased mortality in the low and very low quartiles relative to the very high quartile was observed (**Table 6**). In a Cox proportional hazards model examining individuals in the very high

quartile relative to all other quartiles (high, low, very low) combined, a reduced risk of mortality was observed (HR=0.53, 95% CI=0.28-0.97,p=0.040).

Figure 4. Kaplan-Meier Plot of overall survival by forced vital capacity /total lung capacity ratio (FVC/TLC_{CT}) quartiles at enrollment in smokers with Preserved Ratio Impaired Spirometry (PRISm, n=960).



Chi-squared p-value for differences in mortality by quartile = 0.07.

Table 6. Associations of post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with mortality in smokers with Preserved Ratio Impaired Spirometry (PRISm; n=960).

	FVC/TLC_{CT}			
Quartile	**HR**	**2.5%**	**9.75%**	**P value**
Very High	ref	ref	ref	ref
High	2.12	1.09	4.13	0.028
Low	1.68	0.84	3.36	0.14
Very Low	1.87	0.89	3.87	0.10

Cox Hazard regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and mortality as the dependent variable(outcome) were performed.

All models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI), history of asthma and congestive heart failure, and diabetes mellitus.

HR= Hazard Ratio

Sensitivity analysis

When PRISm was defined using LLN criteria, we observed similar findings with those in main analysis except that FVC/TLC_{CT} was significantly associated with chronic bronchitis, increased mMRC and SGRQ and the association with mortality was attenuated (**Table 7-11 and Figure 5)**. There were 1,096 participants with PRISm defined as post-bronchodilator $FEV_1/FVC \geq$ the lower limit of normal (LLN) and FEV1< LLN. After excluding 3 with bronchiectasis, 9 with interstitial lung disease, 106 with no available TLC, and 5 that FVC/TLC≥1, 973 participants were included in the analyses.

Table 7. Baseline characteristics of smokers with preserved ratio impaired spirometry defined based on the lower limit of normal across post-bronchodilator forced vital capacity /total lung capacity ratio (FVC/TLC_{CT}) quartiles (n=973).

	Very Low quartile (n=244)	Low quartile (n=243)	High quartile (n=243)	Very High quartile (n=243)	P for trend
FVC/TLC_{CT}	**<0.52**	**0.52 - 0.58**	**0.58-0.65**	**>0.65**	
Age, y ± SD	63.93 ± 8.39	58.81 ± 7.55	56.36 ± 7.41	53.27 ± 6.7	<0.001
Female, n(%)	127 (52.0%)	124 (51.0%)	108 (44.4%)	79 (32.5%)	<0.001
African American, n(%)	49 (20.1%)	59 (24.3%)	74 (30.5%)	109 (44.9%)	<0.001
BMI, Kg/m^2 ± SD	33.02 ± 7.13	33.64 ± 7.54	30.75 ± 6.93	31.14 ± 7.02	<0.001
Pack-Years ± SD	52.53 ± 28.60	48.48 ± 24.93	44.69 ± 29.05	37.70 ± 20.20	<0.001
Active Smoker, n(%)	123 (50.4%)	141 (58.0%)	145 (59.7%)	170 (70.0%)	<0.001
Chronic Bronchitis, n(%)	56 (23.0%)	46 (18.9%)	58 (23.9%)	29 (11.9%)	<0.001
mMRC ± SD	1.85 ± 1.48	1.47 ± 1.45	1.30 ± 1.40	1.30 ± 1.45	<0.001
SGRQ ± SD	34.65 ± 21.94	31.03 ± 24.22	27.48 ± 22.40	28.25 ± 23.24	<0.001
Asthma, n(%)	65 (26.6%)	53 (21.8%)	45 (18.5%)	48 (19.8%)	0.042
CHF, n(%)	23 (9.4%)	13 (5.3%)	8 (3.3%)	8 (3.3%)	0.001
DM, n(%)	71 (29.1%)	72 (29.6%)	51 (21.0%)	35 (14.4%)	<0.001
HTN, n(%)	138 (56.6%)	132 (54.3%)	107 (44.0%)	97 (39.9%)	<0.001
CAD, n(%)	36 (14.8%)	31 (12.8%)	21 (8.6%)	10 (4.1%)	<0.001
OSA, n(%)	72 (29.5%)	60 (24.7%)	58 (23.9%)	42 (17.3%)	0.002
CVA, n(%)	10 (4.1%)	13 (5.3%)	7 (2.9%)	5 (2.1%)	0.11
LAMA, n(%)	35 (15%)	19 (8.1%)	17 (7.1%)	14 (5.9%)	<0.001
ICS, n(%)	24 (10.1%)	17 (7.2%)	15 (6.3%)	10 (4.2%)	0.011
LABA, n(%)	11 (4.6%)	2 (0.9%)	2 (0.8%)	5 (2.1%)	0.067
ICS/LABA, n(%)	61 (25.7%)	38 (16.0%)	22 (9.2%)	21 (8.7%)	<0.001
Post-FEV1% ± SD	61.20 ± 8.73	67.94 ± 7.00	69.79 ± 6.37	70.26 ± 6.21	<0.001
Post-FVC% ± SD	64.03 ± 9.48	70.44 ± 7.47	72.27 ± 7.68	72.88 ± 7.20	<0.001
BDR, n(%)	41 (17.1%)	30 (12.5%)	36 (15.0%)	39 (16.1%)	0.97
§% Emphysema ± SD	2.78 ± 4.25	1.84 ± 2.39	1.73 ± 2.39	1.23 ± 1.79	<0.001
§% Gas trapping ± SD	15.90 ± 10.54	11.30 ± 9.00	9.46 ± 7.50	7.83 ± 6.36	<0.001
‡PRM^{fSAD}, % ± SD	18.00 ± 11.23	13.07 ± 9.91	10.80 ± 8.26	10. 01 ± 8.39	<0.001
§FRC_{CT}% ± SD	100.32 ± 19.07	90.28 ± 15.53	83.52 ± 14.70	75.78 ± 12.06	<0.001
TLC_{CT} % ± SD	90.12 ± 13.22	85.64 ± 10.45	80.01 ± 10.65	69.81 ± 9.61	<0.001
#6-MWT, meters ± SD	366.65 ± 112.41	383.49 ± 104.38	413.74 ± 112.99	413.71 ± 112.13	<0.001

§ For % GT and FRC_{CT}% analysis, data were available for 819 participants.

‡ For PRM data analysis, data were available for 806 participants.

For 6-MWT data analysis, data were available for 962 participants.

BDR = bronchodilator response; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; DM = diabetes mellitus; FRC_{CT}% = functional residual capacity % predicted; HTN = hypertension; ICS = inhaled glucocorticosteroids, LABA = long-acting beta-agonist, LAMA = long-acting muscarinic antagonist, mMRC = modified Medical Research Council dyspnea score; OSA = obstructive sleep apnea; post-FEV1% = post-bronchodilator FEV1% predicted; post-FVC% = post-bronchodilator FVC% predicted; PRM^{fSAD} = parametric response mapping functional small airways disease; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire score; TLC_{CT}% = total lung capacity % predicted and 6-MWD = 6-min walk test.

Table 8. Multivariable-adjusted associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with chronic bronchitis, dyspnea and health-related quality of life scores, chest CT % emphysema and % gas trapping, functional small airway disease, and 6-min walk test distance in smokers with preserved ratio impaired spirometry defined based on the lower limit of normal (n=973).

	FVC/TLC_{CT}			
Chronic Bronchitis	OR	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	2.54	1.53	4.28	<0.001
Low	1.72	1.00	3.00	0.053
Very Low	2.53	1.42	4.57	0.002
mMRC	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.03	-0.22	0.27	0.83
Low	0.03	-0.23	0.29	0.82
Very Low	0.40	0.12	0.68	0.006
SGRQ	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.51	-3.23	4.26	0.79
Low	1.92	-2.02	5.86	0.34
Very Low	6.04	1.73	10.36	0.006
% Emphysema	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.44	-0.06	0.95	0.081
Low	0.71	0.18	1.23	0.009
Very Low	1.51	0.93	2.08	<0.001
***% Gas trapping**	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.74	-0.81	2.28	0.35
Low	2.52	0.88	4.15	0.003
Very Low	5.54	3.74	7.34	<0.001
† $\%PRM^{fSAD}$	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	0.02	-1.76	1.80	0.98
Low	2.04	0.16	3.92	0.033
Very Low	5.23	3.18	7.29	<0.001
#6-MWT distance, meters	coef	2.5%	97.5%	P value
Very High	ref	ref	ref	ref
High	11.57	-48.54	71.67	0.71
Low	-20.45	-83.53	42.62	0.52
Very Low	-36.44	-105.74	32.85	0.30

Binary logistic regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and chronic bronchitis as the dependent variables (outcome) were performed. Linear regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and mMRC, SGRQ, % Emphysema, % Gas trapping, PRM^{fSAD}, and 6-MWT distance as the dependent variables (outcome) were performed. All models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure.

* For % GT analysis, data were available for 819 participants.

† For PRM^{fSAD}data analysis, data were available for 806 participants.

#For 6-MWT distance analysis, data were available for 962 participants.

mMRC = modified Medical Research Council dyspnea score; OR=odds ratio; PRM^{fSAD}= parametric response mapping functional small airways disease; SGRQ = St. George's Respiratory Questionnaire score; 6-MWT = 6-min walk test.

Table 9. Multivariable-adjusted associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with change in FEV_1, 6-MWT distance, % emphysema and gas trapping between enrollment and follow-up, and progression to COPD (defined as $FEV_1/FVC<LLN$) at 5-year follow-up visit in smokers with preserved ratio impaired spirometry defined based on the lower limit of normal.

	FVC/TLC_{CT}			
Change in FEV1, ml/year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	1.70	-11.45	14.84	0.80
Low	2.42	-11.44	16.29	0.73
Very Low	5.57	-9.64	20.78	0.47
Change in 6-MWT distance, meters/year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	-7.75	-31.83	16.33	0.53
Low	9.28	-16.08	34.65	0.47
Very Low	6.16	-21.72	34.04	0.66
Change in % Emphysema per year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	-0.02	-0.60	0.56	0.93
Low	0.01	-0.63	0.64	0.98
Very Low	0.21	-0.49	0.91	0.56
Change in % Gas trapping per year	coef	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	1.19	-0.79	3.18	0.24
Low	3.39	1.20	5.58	0.003
Very Low	2.53	0.03	5.03	0.047
COPD at 5 years	OR	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	0.97	0.50	1.88	0.93
Low	1.63	0.85	3.15	0.15
Very Low	3.18	1.62	6.40	<0.001

Linear regression models with post-bronchodilator FVC/ quartiles as independent variables (exposure) change in FEV1, 6-MWT distance, % emphysema and gas trapping between enrollment and follow-up as the dependent variables(outcomes) were performed. Binary logistic regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and progression to COPD at follow-up visit as the dependent variables (outcome) were performed. All models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure.

For change in FEV_1, data were available for 530 participants.

For change in 6-MWT distance analysis, data were available for 521participants.

For change in % emphysema analysis, data were available for 420 participants.

For change in % gas trapping analysis, data were available for 325 participants.

OR= odds ratio; 6-MWT = 6-min walk test.

Table 10. Multivariable-adjusted associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with prospective total exacerbations and severe exacerbations in smokers with preserved ratio impaired spirometry defined based on the lower limit of normal (n= 851).

	FVC/TLC_{CT}			
Exacerbations	IRR	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	1.07	0.70	1.63	0.75
Low	1.07	0.69	1.65	0.77
Very low	2.23	1.44	3.45	<0.001
Severe Exacerbations	IRR	2.5%	9.75%	P value
Very High	ref	ref	ref	ref
High	1.18	0.68	2.04	0.55
Low	1.32	0.74	2.36	0.34
Very Low	2.98	1.65	5.36	<0.001

For exacerbation analysis, data for 851 of total 973 participants with PRISm were available. Zero-inflated negative binomial regression models with post-bronchodilator FVC/TLC_{CT} quartile as independent variables (exposure) and total exacerbations and severe exacerbations as the dependent variables (outcome) were performed. All regression models included the following co-variates: age, sex, race, body mass index, smoking status at the enrollment, smoking pack-years, history of asthma and congestive heart failure, and chronic bronchitis in the count negative binomial regression and an intercept-only model in the zero component. Follow-up time was included as an offset in the models.

IRR= incident rate ratio.

Table 11. Multivariable-adjusted associations between post-bronchodilator forced vital capacity /total lung capacity (FVC/TLC_{CT}) quartiles at enrollment with mortality in smokers with Preserved Ratio Impaired Spirometry defined based on the lower limit of normal (n=839).

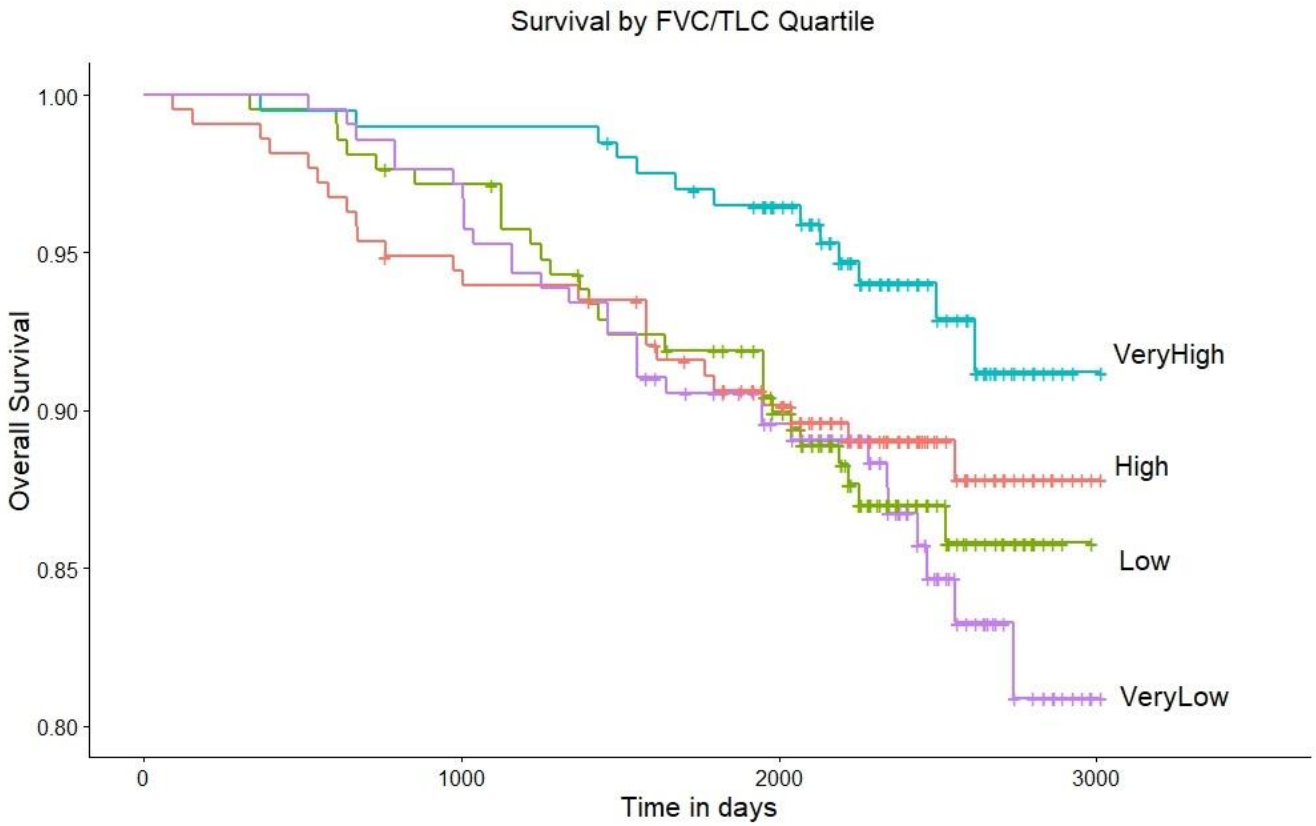
	FVC/TLC_{CT}			
Quartile	**HR**	**2.5%**	**9.75%**	**P value**
Very High	ref	ref	ref	ref
High	1.59	0.79	3.19	0.19
Low	1.78	0.89	3.57	0.10
Very Low	1.78	0.84	3.75	0.13

Cox Hazard regression models with post-bronchodilator FVC/TLC_{CT} quartiles as independent variables (exposure) and mortality as the dependent variable(outcome) were performed.

All models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI), history of asthma and congestive heart failure, and diabetes mellitus.

HR= Hazard Ratio

Figure 5. Kaplan-Meier Plot of overall survival by forced vital capacity /total lung capacity ratio (FVC/TLC_{CT}) quartiles at enrollment in smokers with Preserved Ratio Impaired Spirometry (PRISm) defined based on the lower limit of normal (n=839).



Chi-squared p-value for differences in mortality by quartile = 0.07.

5. Discussion

5.1. Aim 1 Discussion

In a cohort of current and former smokers with COPD, we demonstrated that using a more stringent combined bronchodilator response in both FEV_1 and FVC criterion can identify subjects with lower emphysema who are also at greater risk for exacerbations and lung function decline but are at lower mortality risk than subjects with no bronchodilator response.

Bronchodilator response is often evaluated in patients with respiratory symptoms. Although asthmatics have a greater degree of bronchodilator response than subjects with COPD(9), and BDR in COPD declines over time as the disease progresses(90), its clinical utility has been debated as BDR does not sufficiently distinguish between asthma and COPD. Current definitions of BDR also do not identify a useful COPD phenotype(21, 91). Multiple prior studies have attempted to identify BDR subtypes with clinical utility. BDR in FVC has been suggested as being a more clinically relevant marker in COPD as it is more common than BDR in FEV_1. BDR-FVC is associated with hyperinflation(92-94) which results in dyspnea and lower exercise capacity(95). BDR in FVC has also been shown to be more strongly associated with gas trapping than BDR in FEV_1(96). These findings are in agreement with our results that FVC-BDR is associated with %gas trapping while FEV_1-BDR and Combined-BDR are not. The change in FVC after bronchodilator administration is less affected by gas compression during the forced exhalation maneuver while change in FEV_1 after bronchodilator administration may be overestimated by gas compression(97). In addition, data from impulse oscillometry and body plethysmography suggest that FEV_1-BDR underestimates the change in volume and airway resistance after bronchodilation(98). Newton et al. found that in patients with severe COPD and lung hyperinflation, only 11% had a positive FEV_1 response, whereas the FVC response was 53%(92). Further, Ben Saad et al showed that in COPD patients with reversibility by ATS criteria, FVC

response was seen in an additional 45% who did not have FEV_1 response(99). Thus, FVC response appears to be more common in COPD than FEV_1 response.

In a COPD cohort, we demonstrated that BDR categories are differentially associated with clinical, functional and radiographic features of obstructive lung disease. This may reflect different pathophysiological processes. When emphysema and poor elastic recoil play an important role, FVC-BDR is more common(92, 100). Although the mechanisms underlying isolated FVC response in COPD are not clear, it may be the result of longitudinal traction of airways not being supported by the radial traction of parenchymal tethering which is impaired at higher lung volumes in emphysema(101). On the other hand, in pathophysiological processes with flow limitation that affect peripheral and central airways(102), FEV_1-BDR is more prominent(103). The current ATS-BDR definitions, by stipulating that a positive response in either FEV_1 or FVC be met, likely introduce considerable heterogeneity of underlying disease processes, making them less specific. Although, both ATS-BDR and Combined-BDR were associated with thicker airway wall, which is in agreement with prior literature (104), as well as with higher FRC% predicted, and greater 6-minute walk distance compared to No-BDR, Combined-BDR identifies subjects with lower %emphysema, low risk for mortality but with a heightened exacerbation risk whereas ATS-BDR does not. This combination of features in the Combined-BDR groups suggests that this is an inherently less impaired group by disease severity and more impaired by disease activity. The inverse association of this “Combined-BDR phenotype” with mortality despite its increased risk for respiratory exacerbations contrasts the prior literature that exacerbations are associated with increased mortality(105). This disagreement could be due to the fact that the Combined-BDR group had a lower degree of emphysema compared with No-BDR group, and emphysema is a strong predictor of mortality and maybe the main driver of survival(106).

We also found that although all the BDR subtypes are associated with FEV_1 change over time, Combined-BDR was associated with the greatest decline. Calverley et al reported that BDR in

FEV_1 is not associated with FEV_1 decline (14) whereas other investigators have shown that BDR in FEV_1 is a predictor of FEV_1 decline in COPD(19). However, the latter have been criticized because baseline FEV_1 was not taken into consideration(20, 21). The mechanisms underlying the stronger association of FEV_1 decline with Combined-BDR are not clear, but it should be noted that frequent exacerbations, as noted in this group, are associated with a faster decline in lung function(107).

Further, BDR definitions that include percentage response alone or volume response alone have been proposed(21), but they suffer from the likelihood of meeting BDR criteria easily in mild and severe disease, respectively. For example, a subject with mild disease and a greater than 200 ml response in either FEV_1 or FVC, will be deemed to have BDR. Similarly, a subject with severe disease and low baseline lung function, is more likely to meet the percent criteria for FEV_1 or FVC. For this reason, ATS_ERS guidelines recommend an increase ≥12% and ≥200ml after bronchodilator administration. We extend the literature by demonstrating that a percentage response coupled with a volume response is superior to either one alone to predict respiratory exacerbations and mortality (Supplement).

Although, BDR has been used to define asthma-COPD overlap in the past, it does not provide any clinically meaningful information, and currently, there is no consensus definition for the asthma-COPD overlap. Based on our findings, Combined-BDR may prove to be a useful criterion to identify patients with asthma-COPD overlap, although more research is needed to test this criterion. Whether these subjects will be more responsive to inhaled corticosteroids with lower risk for pneumonia remains to be tested. We do note that BDR is limited by its variability over time in our study, which is in agreement with previous reports(12, 14). BDR variability may be due to variability in the spirometric maneuvers such as differences in coaching and spirometers used, or due to factors intrinsic to the subject such as diurnal variability and changes in mucus production.

However, Combined-BDR was more stable than other BDR categories, and its fluctuation over time may be a reflection of the variability in airflow obstruction of this putative COPD phenotype.

Our study has several limitations. First, the cohort included current and former smokers and hence the results may not be generalizable. However, we did perform a number of sensitivity analyses, including subjects with asthma, and by excluding subjects with mild disease. Second, subjects did not withhold long-acting bronchodilators prior to the study but did withhold short-acting bronchodilators. Although there were some baseline differences in the use of chronic inhaled medications between BDR categories, models adjusting for their use showed similar associations between BDR categories and outcomes as those in the primary analysis. We did not, however, confirm compliance with use of long-acting medications, and this may introduce some bias. The association of combined-BDR with poorer outcomes is unlikely to be due to undertreatment as participants with FVC-BDR, despite having a greater proportion of participants on long-acting medications, did not have improved outcomes compared with No-BDR. Third, the repeatability analysis was limited by the fact that we had follow-up spirometry for only half the subjects. Fourth, we did not have data to test asthma-like features including eosinophil counts in blood or sputum, and immunoglobulin levels. Finally, spirometry data was not available at follow-up in some participants due to attrition or mortality. However, as has been previously shown using data from the same cohort by Dransfield et al., completers, late, and deceased subjects in the COPDGene study were fairly similar in regards to demographic characteristics and baseline lung function(107). In addition, the rate of change of FEV_1 is very heterogeneous and imputation methods may not reliably capture this change. These limitations do not undermine the strengths of our study that includes data from a large cohort of participants in whom we had CT and spirometry data that were subject to stringent quality control. The cohort also included a substantial number of women and African Americans.

In conclusion, Combined-BDR is associated with less emphysema and lower mortality but with greater frequency of exacerbations, indicating a putative COPD phenotype with asthma-like characteristics. More research is needed to test whether the Combined-BDR phenotype helps identify patients with the asthma-COPD overlap, and whether targeting patients with this phenotype will result in improved outcomes.

5.2. Aim 2 Discussion

Among smoked tobacco-exposed people with or without COPD, both inconsistent and consistent BDR was associated with a self-reported history of asthma. Consistent BDR was also associated with evidence of small airway disease on high resolution chest CT and greater lung function decline relative to never BDR regardless of the BDR definition applied. There was no association between blood eosinophil counts and BDR. Participants with consistent and inconsistent ATS-BDR or FVC-BDR had more air trapping than participants with never BDR. Among smoked tobacco-exposed people with normal spirometry, both consistent and inconsistent BDR were associated with progression to COPD over time.

BDR has been advocated to identify clinical phenotypes in COPD. Earlier studies failed to show convincing clinical utility; likely because the BDR definition applied is not specific.(12, 20) Three recent reports from COPDGene and SPIROMICS showed that FEV_1-BDR and FVC-BDR are differentially associated with clinical and radiographic features of obstructive lung disease.(77, 78, 108) However, an important limitation of BDR to identify a COPD phenotype is that BDR is not necessarily stable over time.(21) To our knowledge, this is the first study in smoked tobacco-exposed people with or without COPD examining the association of BDR over time with clinical and radiographic features.

Patients with asthma more often have BDR and typically greater BDR than patients with COPD but BDR is common in both diseases.(9) GINA guidelines are often misinterpreted and BDR is considered equivalent to the diagnosis of asthma. It is no surprise that BDR was associated with asthma diagnosis as the presence of BDR may have led the health care providers of the participants to give them the diagnosis of asthma, perhaps even erroneously. Childhood asthma diagnosis is unlikely to be confounded based on the presence of BDR as it manifests in childhood with respiratory symptoms prior to spirometric evaluation. We have extended the literature by

showing that, in current and former smoked tobacco-exposed people with or without COPD, BDR was not only associated with asthma diagnosis but also with childhood asthma.

We observed that BDR was not associated with airway wall thickness measured by Pi10 while a previous report by Kim and colleagues found an association in patients with COPD.(109) This discrepancy can be explained by the fact that in our study we included some participants without a spirometric diagnosis of COPD as well as due to differences in the protocols used to evaluate BDR. In SPIROMICS we aimed to elicit "Maximal bronchodilatation" by administering both albuterol and ipratropium as opposed to only albuterol.

Our findings complement previous reports in COPD patients showing that the various BDR types (e.g. FEV_1-BDR, FVC-BDR) are differentially associated with chest CT findings of obstructive lung disease.(77, 78, 108) We showed FEV_1-BDR was inversely associated with emphysema which is a pathological definition of disease distal to small airways.(110) The association of FEV_1-BDR with emphysema is the opposite of the association of FEV_1-BDR with gas trapping due to small airway disease (PRM^{fSAD}). That may explain why we found no association of FEV_1-BDR with chest CT % gas trapping by traditional chest CT. Gas trapping by traditional chest CT cannot distinguish emphysema from true gas trapping due to small airway disease.

Pathological hallmarks of COPD include destruction of lung parenchyma (emphysema) and small airways disease, which affects predominantly the end of expiration, thus reducing the FVC. BDR is typically present in both FEV_1 and FVC in COPD patients with no severe lung function impairment.(78) This is likely the reason that we observed that both FEV_1-BDR and FVC-BDR were associated with emphysema in GOLD 0. However, an isolated BDR in FVC is usually present in patients with significant amount of emphysema.(92) Bronchodilators do not affect airflow when the lungs are inflated close to total lung capacity at the beginning of exhalation (BDR in FEV_1) because the airway resistance and diameter is mostly determined by airway-parenchyma interdependence and airway smooth muscle does not play a significant role.(101)

Previous studies have shown that BDR is weakly correlated with sputum and blood eosinophil levels(111-113). Our findings, in the SPIROMICS cohort, failed to show that either inconsistent BDR or consistent BDR are associated with blood eosinophils. This may also reflect that eosinophil levels vary over time and one-time measurement may not be informative.(114, 115)

We also found that BDR was associated with greater FEV_1 decline over time. Other reports have shown that lung function decline over time in COPD is associated with methacholine reactivity and BDR, (116) (19) but these reports could have been confounded by less severe lung function at baseline.(21, 117, 118) The higher the FEV_1, the higher the chance of BDR.(14) Nevertheless, a recent report showed an association of BDR with FEV_1 decline even after adjusting for baseline lung function.(78) Consistent BDR was associated with greater lung function decline relative to those with never BDR after taking into account the baseline lung function. Moreover, BDR in participants with normal spirometry, in particular those with consistent BDR, are at higher risk for progression to COPD .This important finding may be due to the fact that individuals with consistent BDR have greater small airway disease and hence are at higher risk for lung function decline.(81) Finding BDR may indicate small airway smooth muscle pathology playing a role in the inflammatory and remodeling process of the airway.(119)

Our observations suggest that the presence of BDR even at one visit (inconsistent BDR) describes an obstructive lung disease phenotype with a history of asthma and small airway disease, while consistent BDR provides additional characterization of this phenotyping by indicating a high risk for lung function decline over time. Smoked tobacco-exposed with or without COPD and consistent BDR had a higher risk for lung function decline and greater severe small airway disease than individuals with never BDR independent of their post-bronchodilator FEV_1% predicted.

Our study has several limitations. Our study included individuals with at least 20 pack-years cumulative smoking exposure, so that our results may not be generalizable in individuals with no

or mild smoking exposure. Our main independent variable, BDR group, was based on spirometry in several visits but most of the outcomes were based on baseline characteristics. We did not examine the new ATS-ERS BDR definition (2021).(120) Nevetheless, the new definition has not been adopted yet in clinical practice and there is no evidence that it is superior to that previous one (2005).(61, 121) Post-brobronchodilator spirometry performed after administration of both albuterol and ipratropium rather than only albuterol but this reduces the chance of submaximal bronchodilation and potential BDR variation. In the adjusted analysis, we did not include medications (e.g. long-acting bronchodilators) as covariates in the models because we could not confirm adherence and durations of those treatments. Medications were likely confounded by indication based on the unadjusted analysis. Participants with consistent BDR had worse lung function and more medication usage. Finally, not all the participants had all five annual spirometries. Most of those in the inconsistent BDR groups had 4 or 5 visits while the majority of the participants in the never and consistent BDR groups had only 2 visits, thereby reducing the likelihood of demonstrating inconsistent BDR. **Nonetheless, in our adjusted analysis we adjusted for number of visits that a participant completed.** These limitations do not undermine the strengths of the study, which include sequential spirometry with stringent quality controls and a tightly defined chest CT protocol yielding a wealth of CT metrics which relate to lung structure.

In conclusion, in smoked tobacco-exposed people with or without COPD, the presence of BDR even on one visit describes an obstructive lung disease phenotype with a greater likelihood of a history of asthma, and more small airway disease. BDR in people with normal spirometry was associated with progression to COPD over time. Moreover, consistent BDR at every visit was associated with greater small airway disease and higher risk for lung function decline relative to those with no BDR.

5.3. Aim 3 Discussion

Among COPD participants with mild-to-moderate spirometric impairment, we showed that the top 5% of patients with the most exacerbations (frequent exacerbators) are responsible for 34.3% and 31.8% of total and severe exacerbations, respectively. The mortality of COPD patients with frequent exacerbators is approximately double the mortality of the rest of the mild-to-moderate COPD participants in the study. Furthermore, in current or former smokers with normal spirometry, the frequent exacerbators are responsible for more than half of the total and severe exacerbations, respectively, and also have increased adjusted mortality relative to those with no exacerbations. An increase in frequency of exacerbations in COPD and current or former smokers with normal spirometry by one exacerbation a year was associated with increased mortality.

COPD patients with 2 or more exacerbations every year were defined as “frequent exacerbators” based on the landmark ECLIPSE study(83). Since then, this cut-off has been used to identify high-risk COPD patients where escalation of treatment may be needed (122). Using a hypothesis-free approach, Le Rouzic and colleagues found that frequent exacerbators have an average of 2.89 exacerbations/year as opposed to “infrequent exacerbators” who have an average of 0.71 exacerbations/year(123). Two exacerbations in a given year is not a highly stable COPD exacerbation phenotype as exacerbations tend to occur in clusters. However, a patient with ≥2 exacerbations/year in the previous year has more than 46% chance to have at least 2 exacerbations in the subsequent year(124). As the number of exacerbations increase, the probability of a subsequent exacerbation increases and the frequent exacerbator phenotype becomes more “stable”(125). Suissa et al showed that the median time to subsequent hospitalization is 5.4 years after the first hospitalization, 1.6 years after the second one, and 0.3 years after the seventh one.[12] In the current study, we found that the top 5% in exacerbation frequency among COPD patients with mild-to-moderate lung function impairment has ≥1.8

exacerbations/year which indicates that 2 exacerbation/year is likely the appropriate cut-off even among COPD patients with mild-to-moderate lung function impairment. Our findings also suggest that in current or former smokers with preserved spirometry, one exacerbation a year may indicate a “high-risk phenotype”.

In the ECLIPSE study, which included COPD participants with moderate or severe lung function impairment and an average FEV1%predicted of 48%, every year about a quarter of them had at least 2 exacerbations but they were not always the same individuals. Twelve percent of the entire cohort consistently had ≥ 2 exacerbations every year (83). In the SPIROMICs cohort that includes COPD subjects across a wide spectrum of lung function with an average of FEV1%predicted of 63%, Han et al found that every year 10-15% of the participants had 2 or more exacerbations but only 2.1% of them consistently had ≥ 2 exacerbations/year for 3 consecutive years (124). The frequent exacerbator phenotype is relatively uncommon (126, 127).

Nonetheless, the frequent exacerbator phenotype is associated with a high burden of disease. In a cohort of COPD patients with post-bronchodilator FEV1%predicted below 70%, Beeh et al demonstrated that 13.6% of COPD participants classified as frequent exacerbators were responsible for 50% of total hospitalizations.(48) Similarly, we found that among COPD participants with mild-to-moderate lung impairment, the top 5% in exacerbation frequency is responsible for approximately one third of all exacerbations. Moreover, we showed that the top 5% in exacerbation frequency among former or current smokers with normal spirometry is responsible for more than half of exacerbations.

COPD-related hospitalizations are associated with increased mortality (128-130) which increases further with each hospitalization(131). In our study, frequent exacerbators (not necessarily with hospitalizations) have increased mortality after adjustment for demographics, smoking exposure, body mass index (BMI), and lung function relative to the mortality in

individuals with no exacerbations. This association remains even when we defined frequent exacerbators as those with 2 or more exacerbations a year. An increase in frequency of exacerbations in COPD patients with mild-to-moderate lung impairment by one exacerbation a year is associated with 41% increase in mortality. This is the first study showing that frequent exacerbator phenotype is associated with increased mortality even among current or former smokers with preserved spirometry. An increase in frequency of exacerbations in smokers with normal spirometry by one exacerbation a year is associated with 62% increase in mortality.

History of asthma, gastroesophageal reflux disease, prior exacerbations, increased respiratory symptoms, poor health status, worsening lung function, increased fibrinogen and white blood cells, certain cytokines, and evidence of small airway disease in the chest CT have been reported as risk factors for frequent exacerbators (83, 124, 132). Poor lung function and prior exacerbations are the most consistent risk factors. Chronic bronchitis is also associated with high risk for exacerbations (133) but the association between chronic bronchitis with frequent exacerbations is inconsistent(83). In our analysis, poor lung function, poor exercise capacity, increased radiographic emphysema, dyspnea, chronic bronchitis, history of asthma, history of prior exacerbations and pneumonia, and history of cancer were risk factors for frequent exacerbators among COPD participants. Cancer may be related with immunodeficiencies(134), a known risk factor for COPD exacerbations(52). Among current or former smokers with normal spirometry, smoking pack-years, dyspnea, history of asthma, history of prior exacerbation and pneumonia, and obstructive sleep apnea were associated with frequent exacerbations. Obstructive sleep apnea may be confounded by obesity hypoventilation syndrome (135). Patients with obesity hypoventilation syndrome may be frequently hospitalized with acute respiratory failure and misdiagnosed with COPD(136). For thar reason, in the mortality analysis obstructive sleep apnea was included in the models as a co-variate.

Our study has several limitations. First, we examined the average of exacerbations per year in a study period with a duration ≥3 years as opposed to annual exacerbations. Nevertheless, the definition of frequent exacerbation as 2 exacerbations a year for several consecutive years has limited clinical value as health care providers do not have the luxury of longitudinal data to decide the appropriate treatment plan. Secondly, our mortality analysis in the participants with preserved spirometry is limited by the low death rates and the relatively small sample size. Third, our mortality analysis is inherently biased as we selected patients with ≥3 years follow-up and therefore all the participants were alive for at least 3 years. Another limitation is the variable participation in the Longitudinal Follow-Up program (exacerbations). In addition, we did not have data regarding plasma eosinophilic counts and carbon dioxide in arterial blood gases that may provide additional information regarding the exacerbation risk. Racial minorities other than black individuals did not participate in the study. The above do not undermine the strength of our study which are the wealth of our demographic and medical history data, and the stringent quality control of our questionnaires, spirometry and radiographic measurements. Moreover, the large number of women and black individuals in our study makes our findings more externally applicable.

The frequent exacerbator phenotype is potentially a clinically relevant phenotype as it may indicate specialized COPD treatments. e.g. COPD patients with chronic hypercapnic respiratory failure have a median of 5 exacerbations per year and one-year mortality of 33%(41, 42) benefit from domiciliary nocturnal non-invasive ventilation. Non-invasive ventilation in those patients can reduce exacerbations and mortality by one third. Another example is COPD patients with antibody deficiency syndrome that have a median rate of 4 exacerbations a year and their exacerbation rate drops to a median of 0.75 a year after treatment with immunoglobin replacement treatment and/or prophylactic antibiotics (52).

In conclusion, the top 5% with the most exacerbations in COPD participants with mild-to-moderate lung impairment is responsible for approximately one third of all exacerbations. Among current or former smokers with preserved spirometry, the top 5% of those with the most exacerbations is responsible for more than half of the exacerbations in the cohort. COPD participants and current or former individuals with preserved spirometry have increased mortality compared to those with no exacerbations. These findings demonstrate for the first time that even in the absence of severe lung function impairment, the frequent exacerbator phenotype is associated with increased mortality. An increase in frequency of exacerbations by one exacerbation a year is associated with increased mortality. Future studies should investigate disease mechanisms associated with frequent exacerbations with the goal to develop interventions with great impact on disease burden.

5.4. Aim 4 Discussion

In a cohort of individuals with normal spirometry and current or former smoking exposure, respiratory exacerbations between visit 1 and visit 2 were associated with and lung function decline between visit 1 and visit 2 (concurrent lung function decline) but they were not associated with lung function decline between visit 2 and visit 3 (future lung function decline) among those participants that had normal spirometry at visit 2. Respiratory exacerbations between visit 1 and visit 2 were associated with long-term mortality but the interaction between respiratory exacerbations and COPD at visit 2 was not associated with increased mortality.

Respiratory exacerbations are critical events in course of COPD. In a prior work of our group, a respiratory exacerbation resulted in lung function decline between 8 and 23 ml/year with greater lung function decline observed in patients with COPD stage Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1.(137) A severe respiratory exacerbation was associated with further lung function decline , which could be as high as 87 ml/year. Severe respiratory exacerbations are associated with 23-26% 1-year(138, 139) and 50-76% 5-year mortality.(128, 131, 139-143) Because of the significant impact of respiratory exacerbation on COPD progression and the fact that are responsible for more than 70% of direct health care costs,(144, 145) patients with frequent exacerbations, known also as “frequent exacerbators” have been the focus of several investigations.(48, 49, 83, 124)

Respiratory exacerbations are not well studied beyond the “COPD range” e.g. individuals with preserved lung function and history of heavy smoking exposure, perhaps because historically respiratory exacerbations were considered integral part of COPD. Recently, several investigations have targeted populations with mild disease or disease at early stage.(146, 147) Our study is the first one showing that respiratory exacerbations in individuals with normal spirometry and smoking exposure are associated with progression to COPD (and abnormal spirometry), and lung function decline. A prior study of our group found no association between

exacerbations and lung function decline in individuals with normal spirometry and preserved ratio impaired spirometry likely due to its smaller sample size.(137) Severe exacerbations were associated with greater lung function decline than total exacerbations (moderate or severe) but there was no association between severe respiratory exacerbations and progression to COPD. The former was likely due the fact that were underpowered to detect an association as severe exacerbations are rare events in those with normal spirometry.

Further, we showed that despite respiratory exacerbations being associated with concurrent lung function decline, they were not associated with future lung function decline in those individuals that did not experience concurrent lung function decline. We are uncertain whether there is a biological explanation of this finding, and whether those individuals are less prone to lung function decline. It could be related to the smaller sample size in the future lung function decline analysis. It is also possible that participants who did not experience concurrent lung function decline with respiratory exacerbations may have received treatment for upper respiratory symptoms or conditions like cardiogenic pulmonary edema that should not result in lung function decline.

Our previous work has shown that respiratory exacerbations are associated with increased mortality in individuals with normal spirometry. In the current work, we extended the literature by showing that exacerbations were associated with mortality without progression to COPD or abnormal spirometry. Although participants that died may have developed COPD after visit 2 and more frequent spirometric testing may have captured that, such an explanation is unlikely as we found not association of respiratory exacerbations with future lung function decline. Regardless of the explanation, our findings indicate that respiratory exacerbations may be key events in individuals with normal spirometry that may occur long time before progression to COPD or death.

The mechanism through which respiratory exacerbations result in lung function impairment and death in individuals with normal spirometry is unknown. Chronic bronchitis was more prevalent in participants with frequent respiratory exacerbations than those with fever exacerbations. Chronic bronchitis is characterized by increase in airway goblet cells, increase and alterations in the composition of mucus, reduction in ciliated results, impaired mucociliary clearance, and thus higher risk for respiratory infections.(133, 148) Chronic sputum production in people with history of smoking and normal spirometry (non-obstructive chronic bronchitis) is associated with respiratory exacerbations, lung function impairment, and increased mortality.(53, 149)

Our findings add more fuel in the discussion whether more sensitive diagnostic criteria for COPD are needed,(3, 150) and interventions that target patients with COPD at early stages or perhaps even interventions in asymptomatic individuals before develop COPD should be investigated. Diagnostic testing in asymptomatic individuals is controversial but recent studies showed that asymptomatic COPD is associated with COPD-related hospitalizations and mortality. (151) Screening in high-risk individuals e.g. significant smoking exposure may be cost-effective. (151, 152)

Our study has several limitations. Our cohort included only people with smoking exposure and out findings may not be generalizable. Respiratory exacerbations may be confounded by undiagnosed asthma. Nevertheless, we included asthma as a covariate in all the analyses. Medication usage was not considered as a co-variate in the models because participants with exacerbations used medication more often than those with no exacerbations (confounded by indication). Our sample included only Caucasian and African Americans. The above limitations do not undermine the strength of our data which include that approximately half of participants are female and that we adjusted for demographics, smoking exposure, body mass index, and lung function.

In conclusion, respiratory exacerbations in individuals with normal spirometry and history of current or former smoking exposure resulted in lung function decline and progression to COPD. Respiratory exacerbations in individuals with normal spirometry and history of current or former smoking exposure were associated with long-term mortality without necessary progression to COPD first. Future research should examine whether therapeutic interventions in high-risk individuals with normal spirometry can improve clinical outcomes and perhaps prevent progression to COPD.

5.5. Aim 5 Discussion

Our study explores the utility of FVC/TLC_{CT} ratio in former and current smokers with PRISm as a potential tool to identify individuals with features of and possible increased risk for progression to obstructive lung disease. In our cohort, very low FVC/ TLC_{CT} was associated with radiographic findings traditionally associated with COPD as well as progression to COPD and respiratory exacerbations while very high FVC/ TLC_{CT} was associated with reduced mortality.

PRISm is a common spirometric pattern with a prevalence between 5% and 20%(58, 153-155). Although often referred to as a "restrictive spirometric pattern", 30-40% of patients with PRISm do not have reduced TLC(156, 157). On average, individuals PRISm have higher BMI, but obesity alone does not decrease vital capacity or TLC below the LLN in most individuals (158). Notably, only about 5% of patients undergoing bariatric surgery for extreme obesity have PRISm at preoperative assessment(159).

PRISm is comprised of a heterogeneous population with a wide range of BMI, degree of lung function impairment, and radiographic emphysema likely due to different underlying pathological processes in each individual(56). Subgroups within PRISm may have increased risk for FEV_1 decline progression to COPD, exacerbations, and mortality. In this manuscript, we utilize FVC/TLC, which decreases in obstructive lung disease(65), as a conceptual surrogate for RV (which was not directly measured in our cohort) to identify individuals with features obstructive lung disease within PRISm. Our finding that individuals with PRISm with low FVC/TLC have increased radiographic emphysema and gas trapping complements work from the SPIROMICS cohort, where that RV/TLC was shown to be associated with increased radiographic emphysema and gas trapping in smokers with normal lung function(5). Apart from the fact that RV/TLC was not available in our cohort, we used FVC/TLC as it may be more sensitive to identify the presence of small airway disease than RV/TLC because FVC, a dynamic measure

obtained at forced expiration, will capture dynamic collapse and air trapping not present during slow exhalation maneuver(160, 161). Future studies should examine the role of RV/TLC in PRISm. In addition, we did not examine FRC/TLC as FRC can be reduced remarkably in obesity(158) which may render difficult to interpret those measures when an obstructive lung diseases coexists.

Our findings suggest that low FVC/TLC_{CT} may be a possible a marker of early obstructive pulmonary disease. Nevertheless, participants in the very low FVC/TLC_{CT} quartile have higher BMI; this contrasts with the common knowledge that patients with established obstructive pulmonary disease have often lower BMI. Previous studies have shown an inverse relationship of BMI with mortality in COPD, known also as the "obesity paradox" with confounders such as exercise capacity and muscle mass possibly contributing towards favorable outcomes(162, 163). In addition, despite the fact that obesity does not typically reduce the FVC below the LLN in subjects without lung disease (159), higher BMI decreases FVC and increases the FEV_1/FVC ratio which can lead to underdiagnosis of obstructive pulmonary disease(160, 164). In COPD subjects with established airflow obstruction, increasing BMI is associated with higher FEV_1/FVC(164).

We acknowledge that the fixed threshold FEV1/FVC<0.7 diagnostic criterion for COPD endorsed by Global Initiative for Chronic Obstructive Lung Disease(GOLD) may have also misclassified individuals with obstructive lung disease as PRISm. In a recent large population-based sample (n=24,207), Bhatt and colleagues showed that the discriminative accuracy of $FEV_1/FVC<0.7$ to predict COPD-related death and/or hospitalization was not inferior to $FEV_1/FVC<LLN$(165). We assert that because the majority of our findings remained robust on sensitivity analyses using LLN-defined lung function categories. FVC/TLC ratio can be utilized to identify individuals with features of obstructive lung disease regardless of whether fixed-threshold or LLN criteria are used.

In COPDGene, 40.5% of PRISm individuals and 32.5% of smokers with normal lung function are African American(56). Differences in the reliability of prediction equations may lead to the "overdiagnosis" of African American with PRISm in the absence of true pathology; this may contribute to the lower rates of African Americans in the low FVC/TLC_{CT} quartiles. It is also unclear why females were relatively over-represented in the lower FVC/TLC_{CT} quartiles. Whether PRISm represents a gender-specific pathway to COPD, or whether traditional FEV_1/FVC criteria systematically misclassify women with COPD is not known(166, 167). Our sensitivity analysis using gender and race specific spirometric criteria to define PRISm showed similar findings. Future studies, especially in cohorts of diverse ancestry and ethnicity, are warranted to further explore these findings.

Previous studies have shown that air trapping is associated with FEV_1 decline. In current and former smokers with at least 20 pack-years smoking and normal lung function, RV/TLC is associated with FEV_1 decline (5). We have extended these finding by showing that air trapping (low FVC/TLC) in individuals with PRISm is associated with progression to COPD. General population studies have also shown that individuals with abnormal non-obstructed lung function are at risk for developing COPD(168, 169). It may seem counterintuitive that low FVC/TLC_{CT} in PRISm was associated with progression to COPD and respiratory exacerbations, but was not associated with FEV_1 decline, increase in emphysema, and change in 6-MWT distance over time(170). Within COPDGene, individuals with PRISm are at increased risk for respiratory exacerbations relative to smokers with normal lung function(171). However, respiratory exacerbations in PRISm do not result in significant excess lung function decline in FEV_1 as observed in individuals with established airflow limitation(137). A survivor bias may also be present in FEV1 decline analysis(137). Participants that had poor lung function and low FVC/TLC may have died before the follow-up visit. Similarly, we may have not observed changes in 6-MWT distance likely due to the high variability of the test(172, 173).

Population-based studies have shown that PRISm is associated with increased cardiac(57) and all-cause mortality(58, 62). While the increased average BMI in PRISm as a whole may mediate some of the risk associated with increased mortality, the association between very high FVC/TLC_{CT} and lower mortality relative to all other quartiles despite concurrent adjustment for BMI, congestive heart failure, and diabetes status in our study suggests our composite measure may have utility in the risk-stratification of individuals with PRISm. Previous studies in COPD have shown associations between RV and mortality(174). In Veterans with a history of smoking and normal lung function, Zeng et al. showed that RV/TLC is associated with increased respiratory medication use, hospitalizations, and all-cause mortality(54).

Our study is the first one showing that a composite measure of lung function may help to identify patients with PRISm who eventually progress to classic airflow obstruction and are at increased risk for respiratory exacerbations and death. The strengths of our study include large sample size, highly granular epidemiological data, axial radiographic imaging data, and longitudinal data on clinically relevant outcomes. Despite this, we acknowledge the following limitations. RV was not available in our cohort. TLC_{CT} was measured in supine position by chest CT, which is usually lower than TLC measured in seated position by plethysmography(67). Another limitation is possible self-selection bias of subjects who returned for a follow-up visit. Since our cohort includes only smokers, our findings cannot be generalized to non-smoking populations and future studies in independent cohorts are warranted. In conclusion, FVC/TLC_{CT} can help to identify individuals with PRISm at increased risk for clinical events and progression to COPD, and who would benefit from smoking cessation and may be a potential target population for treatment trials in the future.

6. Conclusions

The proposed clinically relevant phenotypes describe group of patients with COPD that respond to existing treatment or patients that have a disease with potential therapeutic options. Identifying smaller and more homogenous groups of patients with COPD may lead to "personalize" treatment and increase its effectiveness. This approach has been followed in other areas of medicine e.g. oncology.

In this document, we showed that certain characteristics of BDR (combined BDR in bother FEV_1 and FVC) can help to identify patients with COPD whose their disease resemble asthma. Patients with COPD that have Consistent BDR over time seems to have more "asthmatic" features, greater lung function decline and small airway disease relative to those with absent or inconsistent BDR. These patients may have dramatic response to biological treatment e.g. anti-IL5 similar to the response that patients with asthma have.

Further, we showed that individuals with normal spirometry that have frequent respiratory exacerbations have increase mortality and are high risk for lung function decline and COPD. Further research is needed to assess whether treatment of individuals with normal spirometry, but respiratory symptoms can improve long term outcomes including preventing from progression to COPD. In individuals with PRISm, air trapping identifies patients with burden of exacerbations, increased mortality, and higher risk to progress to COPD. Further research is needed to assess whether individuals with PRISm benefit from existing treatment for COPD.

More granular phenotyping of COPD (asthma-COPD overlap, Hyperinflation, CHRD, Frequent Respiratory Exacerbations) can help to identify patients that respond well to existing treatment. Further research is needed in those individuals with respiratory symptom or at risk for COPD who do not have obstructive spirometry yet (normal spirometry or PRISm) to assess whether

treatment of those individuals can improve outcomes including preventing from progression to COPD.

7. Abstracts and Manuscripts

Combined Bronchodilator Response in both FEV1 and FVC is Associated With High Risk for Exacerbations But Low Mortality in COPD

Journal: *Ann Am Thorac Soc. 2019 Jul;16(7):826-835*

The American Thoracic Society/European Respiratory Society defines a positive bronchodilator response (BDR) by a composite of BDR in either FEV_1 and/or FVC ≥12% and 200ml (ATS-BDR). We hypothesized that ATS-BDR components would be differentially associated with important COPD outcomes.

Objective

To examine whether ATS-BDR components are differentially associated with clinical, functional and radiographic features in COPD.

Methods

We included subjects with COPD enrolled in the COPDGene study. In the main analysis, we excluded subjects with self-reported asthma. We categorized BDR into the following: (i) No-BDR: no BDR in either FEV_1 or FVC, (ii) FEV_1-BDR: BDR in FEV_1 but no BDR in FVC, (iii) FVC-BDR: BDR in FVC but no BDR in FEV_1, and (iv) Combined-BDR: BDR in both FEV_1 and FVC. We constructed multivariable logistic, linear, zero-inflated negative binomial and cox-hazards models to examine the association of BDR categories with symptoms, computed tomography findings, change in FEV_1 over time, respiratory exacerbations and mortality. We also created models using the ATS BDR definition (ATS-BDR) as the main independent variable.

Results

Of 3,340 COPD subjects included in the analysis, 1,083 (32.43%) had ATS-BDR; 182 (5.45%) had FEV_1-BDR; 522 (15.63%) had FVC-BDR and 379 (11.34%) had Combined-BDR. All BDR

categories were associated with FEV_1 decline compared to No-BDR. Compared to No-BDR, both ATS-BDR and Combined-BDR were associated with higher FRC %predicted, greater Pi10, and greater 6-minute walk distance. In contrast to ATS-BDR, Combined-BDR was independently associated with less emphysema (coef = -1.67, 95%CI= -2.68 to -0.65; p=0.001), more frequent respiratory exacerbations (Incidence Rate Ratio IRR 1.25, 95%CI= 1.03 to 1.50;p=0.02) and severe exacerbations (IRR=1.34, 95%CI=1.05 to 1.71; p=0.02) and lower mortality (adjusted hazards ratio HR =0.76, 95%CI=0.58 to 0.99; p=0.046). Sensitivity analysis that included subjects with self-reported history of asthma showed similar findings.

Conclusions

BDR in both FEV_1 and FVC indicates a COPD phenotype with asthma-like characteristics, and provides clinically more meaningful information than current definitions of BDR.

Predictive value of pre- and post-bronchodilator spirometry for COPD features and outcomes

Journal: *BMJ Open Respir Res . 2017 Dec 18;4(1):e000213*

Introduction: We compared the predictive value of pre- and post-bronchodilator spirometry for COPD features and outcomes.

Methods: We analyzed COPDGgene data of 10,192 subjects with smoking history. We created regressions models with the following dependent variables: clinical, functional, and radiographic features, and the following independent variables: pre- (PREO) and post-bronchodilator airflow obstruction (POSTO), pre- and post-bronchodilator FEV1% predicted. We compared the model performance using the Akaike information criterion (AIC).

Results: The COPD prevalence was higher using PREO. About 8.5% had PREO but no POSTO (PREO-POSTN) and 3% of all subjects had no PREO but POSTO (PREN-POSTO). We found no difference in COPD features and outcomes between PREO-POSTN and PREN-POSTO subjects. Although, both pre- and post-bronchodilator spirometries are both associated with chronic bronchitis, dyspnea, exercise capacity, and COPD radiographic findings, models that included post-bronchodilator spirometric measures performed better than models with pre-bronchodilator measures to predict these COPD features. The predictive value of pre- and post-bronchodilator spirometries for respiratory exacerbations, change in FEV1, dyspnea, and exercise capacity during a 5-year period is relatively similar, but post-bronchodilator spirometric measures are better predictors of mortality based on AIC.

Conclusions: Post-bronchodilator spirometry may be a more accurate predictor of COPD features and outcomes.

Increased mortality associated with frequent exacerbations in COPD patients with mild-to-moderate lung function impairment, and smokers with normal spirometry

Journal: *Respir Med X. 2021 Nov;3:100025*

Background

The burden of frequent respiratory exacerbations in COPD patients with mild-to-moderate spirometric impairment and smokers with preserved lung function is unknown.

Methods

We categorized COPD participants in COPDGene with post-bronchodilator FEV1%predicted≥50% by the annual exacerbation frequency into three groups: i)frequent exacerbators(top 5 %;n=109), ii)exacerbators(>0 but less than frequent exacerbators;n=1,009), and iii)No exacerbation(n=981). Exacerbations were defined as respiratory episodes requiring antibiotics and/or systemic steroids. We performed a Cox proportional hazards regression analysis to examine the association with mortality. We repeated the same process in current/former smokers with preserved spirometry(FEV1≥80%predicted and FEV1/FVC≥0.7).

Results

Among 2,099 COPD participants, frequent exacerbators had ≥1.8 exacerbations/year and were responsible for 34.3% of the total exacerbations. There were 102(10.4%) deaths in the group with no exacerbations, 119(11.8%) in the exacerbator group, and 24(22%) in the frequent exacerbators. Adjusted mortality in frequent exacerbators was higher relative to individuals with no exacerbations (hazard ratio(HR)=1.98;95%CI=1.25-3.13). An increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality(HR=1.40,95%CI=1.21-1.62). Among 3,143 participants with preserved spirometry, frequent exacerbators had ≥0.8 exacerbations/year and were responsible for more than half of

the exacerbations. There were 93(4.2%) deaths in the group with no exacerbations, 28(3.8%) in the exacerbator group, and 14(7.6%) in the frequent exacerbators. The adjusted mortality was increased in frequent exacerbators with preserved spirometry relative to those with no exacerbations(HR=2.25;95%CI=1.26-4.01).

Conclusions

In COPD participants with mild-to-moderate spirometric impairment and smokers with preserved spirometry, the frequent exacerbator phenotype is responsible for a large proportion of total exacerbations and associated with high mortality.

Low FVC/TLC in Preserved Ratio Impaired Spirometry (PRISm) is associated with features of and progression to obstructive lung disease

Journal: *Sci Rep . 2020 Mar 20;10(1):5169.*

Background

The FVC/total lung capacity(TLC) ratio may identify obstructive lung disease in Smokers with Preserved Ratio Impaired Spirometry(PRISm;FEV1/FVC≥0.7 and FEV1<80%predicted). We examined the association of FVC/TLC in PRISm with features of obstructive lung disease.

Methods

Current and former smokers with ≥10 pack-years with PRISm in COPDGene were analyzed. FVC was obtained from post-bronchodilator spirometry and TLCCT from chest CT. We stratified PRISm subjects by FVC/TLCCT into quartiles: very high, high, low, and very low. We examined the associations between FVC/TLCCT quartiles and 1)baseline characteristics, 2)respiratory exacerbations, 3)progression to COPD in 5 years, and 4)all-cause mortality.

Results

Of 1,260 participants with PRISm, 1,131 participants were analyzed after excluding individuals with missing data, interstitial lung disease or bronchiectasis. The very low FVC/TLCCT quartile was associated with lower quality of life, gas trapping and emphysema relative to the very high quartile. More individuals in the low FVC/TLCCT quartile than very high quartile individuals progressed to COPD (36% versus 17%;p<0.001). The very low FVC/TLCCT quartile was associated with more total(Incidence Rate Ratio(IRR)=1.73;95%CI=1.12-2.67;p=0.012) and severe(IRR=2.23;95%CI =1.30-3.84;p=0.004) respiratory exacerbations. Mortality was lower in the very high FVC/TLCCT quartile relative to the other quartiles combined.

Conclusions

In PRISm, low FVC/TLCCT ratio is associated with respiratory symptoms, exacerbations, and progression to COPD.

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