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Combined Forced Expiratory Volume in 1 Second and Forced Vital Capacity Bronchodilator Response, Exacerbations, and Mortality in Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: The American Thoracic Society (ATS)/European Respiratory Society defines a positive bronchodilator response (BDR) by a composite of BDR in either forced expiratory volume in 1 second (FEV_1) and/or forced vital capacity (FVC) greater than or equal to 12% and 200 ml (ATS-BDR). We hypothesized that ATS-BDR components would be differentially associated with important chronic obstructive pulmonary disease (COPD) outcomes.

Objectives: 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: *1*) No-BDR, no BDR in either FEV_1 or FVC; *2*) FEV_1-BDR, BDR in FEV_1 but no BDR in FVC; *3*) FVC-BDR, BDR in FVC but no BDR in FEV_1; and *4*) 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 with No-BDR. Compared with No-BDR, both ATS-BDR and Combined-BDR were associated with higher functional residual capacity %predicted, greater internal perimeter of 10 mm, and greater 6-minute-walk distance. In contrast to ATS-BDR, Combined-BDR was independently associated with less emphysema (adjusted beta regression coefficient, −1.67; 95% confidence interval [CI], −2.68 to −0.65; $P = 0.001$), more frequent respiratory exacerbations (incidence rate ratio, 1.25; 95% CI, 1.03–1.50; $P = 0.02$) and severe exacerbations (incidence rate ratio, 1.34; 95% CI, 1.05–1.71; $P = 0.02$), and lower mortality (adjusted hazards ratio, 0.76; 95% CI, 0.58–0.99; $P = 0.046$). 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.

Keywords: asthma; chronic obstructive pulmonary disease; bronchodilator agents; mortality; spirometry

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Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that persists after bronchodilator administration. According to the American Thoracic Society/European Respiratory Society (ATS-ERS), bronchodilator response (BDR) is defined by an increase in forced expiratory volume in 1 second (FEV_1) and/or forced vital capacity (FVC) greater than or equal to 12% and 200 ml after bronchodilator administration (1). This definition is simple and easily applicable (2) but its value for phenotyping and for predicting outcomes and treatment response is debatable (1, 3, 4). BDR prevalence rates in COPD range from 4% to 65% (5–9], and the accuracy of BDR in distinguishing between asthma and COPD is low (10–13). The clinical relevance of BDR in COPD is not clear. Some reports have showed that BDR is associated with worse respiratory symptoms (14), reduced exercise capacity (15), greater frequency of respiratory exacerbations (16), lesser amount of emphysema (5, 7, 8), and FEV_1 decline (17), whereas others have found no association of BDR with COPD symptoms and outcomes (6, 8, 18).

BDR has also been defined either as an increase in FEV_1 alone, or an increase in FEV_1 and/or FVC after bronchodilator administration with various cutoffs (3). BDR according to ATS-ERS guidelines (ATS-BDR) is a composite of a positive response in FEV_1 and/or FVC. Because ATS-BDR is defined by BDR in either FEV_1 and/or FVC, subjects with ATS-BDR may represent a heterogeneous population. BDR in FEV_1 may indicate different disease processes associated with COPD than BDR in FVC. BDR in FVC is more common in small airway disease (19), whereas BDR in FEV_1 is associated with both large and small airway disease (20). We hypothesized that BDR components would be differentially associated with important COPD outcomes. To test our hypothesis, we analyzed data from the Genetic Epidemiology of COPD study (COPDGene), a large cohort of current and former smokers. We compared the association of BDR components with chronic bronchitis, dyspnea, exercise capacity, and structural lung disease at enrollment. We also examined their predictive value for FEV_1 reduction over time, respiratory exacerbations, and mortality.

Methods

Subjects

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 (21). Briefly, all subjects provided informed consent before participation in the study. Subjects were self-identified as 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 scale (21). Subjects performed prebronchodilator and post-bronchodilator spirometry according to ATS-ERS guidelines (22). Subjects were instructed to withhold only short-acting bronchodilators before their visits. After prebronchodilator spirometric maneuvers, post-bronchodilator maneuvers were performed between 15 and 40 minutes after two puffs of albuterol dose inhaler were administered using a spacer (23). We used the National Health and Nutrition Examination Survey III spirometric reference values to calculate % predicted values (24). 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 prebronchodilator and post-bronchodilator spirometry data at enrollment. Subjects performed inspiratory and expiratory chest computed tomography (CT) scans using multidetector CT scanners per protocol (21). Total lung capacity (TLC) was measured at maximal inspiration. Functional residual capacity (FRC) was measured at end expiration. FRC and TLC% predicted were calculated based on the predicted values (25). Emphysema and gas trapping were quantitated using 3D Slicer software (www.airwayinspector.org), and airway dimensions were measured using Pulmonary Workstation 2 (VIDA Diagnostics,) (21). Parametric response mapping was used to calculate functional small airways disease (26, 27).

Approximately 5 years after the enrollment 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.

Variables and Outcomes

BDR was defined as an increase in prebronchodilator FEV_1 and/or FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration (ATS-BDR). We categorized ATS-BDR into the following BDR categories: *1*) No-BDR, no BDR by any criteria; *2*) FEV_1-BDR, BDR in FEV_1 but no BDR in FVC; *3*) FVC-BDR, BDR in FVC but no BDR in FEV_1; and *4*) 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 an increase in FEV_1 and/or FVC greater than or equal to 12% (relative percent change), and an increase in FEV_1 and/or FVC greater than or equal 200 ml (volume change).

Chronic bronchitis was defined as productive cough for at least 3 consecutive months in the last 2 years (28). Emphysema was defined by the percentage of lung

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volume at maximal inspiration with attenuation less than −950 HU. Gas trapping was quantified as the percentage of lung volume at end expiration with attenuation less than −856 HU (29). The square root of wall area for a hypothetical airway with an internal perimeter of 10 mm (Pi10) was derived (30). Respiratory exacerbation was defined as an episode of increased cough, phlegm, or shortness of breath that lasted more than 48 hours 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/yr between enrollment and follow-up and visits.

Statistical Analysis

We categorized subjects at enrollment into four groups based on BDR category: No-BDR, FEV_1-BDR, FVC-BDR, and Combined-BDR. First, we compared the characteristics at enrollment between ATS-BDR and No-BDR subjects. Then we compared characteristics of subjects in FEV1-BDR, FVC-BDR, and Combined-BDR groups with the characteristics of subjects in the No-BDR group. We used Student's *t* test or Wilcoxon rank sum test for normal and nonnormal continuous variables, respectively, and Fischer exact or chi-square test for categorical variables. We performed multivariable logistic and generalized linear regression models as appropriate for associations between BDR categories and chronic bronchitis, modified Medical Research Council, CT emphysema and gas trapping, 6-MWT distance, and FEV_1 change. For exacerbation analysis, we created zero-inflated negative binomial models because exacerbations followed a Poisson distribution and data were overdispersed. Follow-up time was included in the models as an offset. All models included the following covariates: age, sex, race, smoking status, smoking pack-years, body mass index 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, body mass index, and post-bronchodilator FEV_1% predicted.

We conducted a sensitivity analysis including subjects with self-reported history of asthma (*see* online supplement). Moreover, because the subjects in the various BDR groups may have a wide range of lung function, we tested additional models by including only subjects with post-bronchodilator FEV_1% predicted less than 80% by excluding those with Global Initiative for Chronic Obstructive Lung Disease stage I disease severity. We also tested similar associations for BDR defined as relative percent change and relative volume change in separate models. Finally, we tested additional models adjusted for medication usage. 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.

Results

The cohort included 4,458 subjects with COPD (*see* Figure E1 in the online supplement 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.

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 modified Medical Research Council and lower post-bronchodilator FEV_1% predicted (*see* Table E1). In ATS-BDR subjects, there were more Global Initiative for Chronic Obstructive Lung Disease stage III and IV 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.

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 1). Table 1 shows the characteristics of subjects at enrollment categorized into BDR groups.

Compared with No-BDR subjects, FEV_1-BDR subjects were younger and had higher body mass index and post-bronchodilator FEV_1% predicted and FVC% predicted, had less advanced COPD stage, less CT emphysema and CT gas trapping, less functional small airways disease, lower FRC% predicted and TLC% predicted by CT, and covered greater 6-MWT distance. Compared with 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 with 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% predicted, and TLC% predicted (Table 2). Combined-BDR was associated with lower % emphysema, greater functional small airway disease (*see* Table E2) 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.

Change in FEV_1 between Enrollment and 5-Year Follow-up Visit ($n = 1,702$)

The mean FEV_1 decline for the cohort was -40.39 ± 54.52 ml/yr. In adjusted analysis, FEV_1-BDR (adjusted beta regression coefficient [Coef], −18.34; 95% confidence interval [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 3). 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.

Respiratory exacerbations (n = 2,980). FEV_1-BDR and FVC-BDR were not associated with respiratory exacerbations (Table 3). 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 3). 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

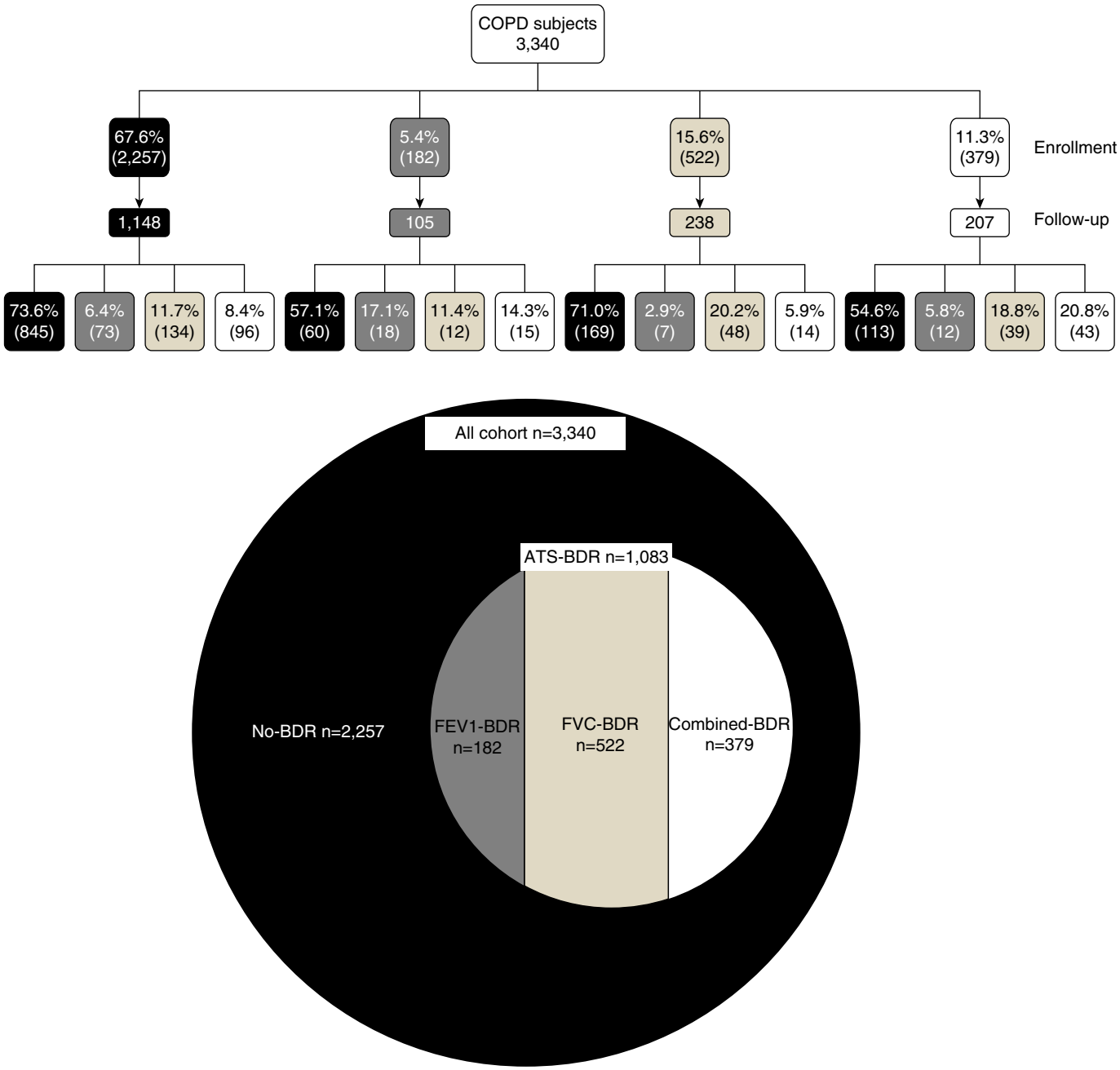

Figure 1. Bronchodilator response rates in subjects with chronic obstructive pulmonary disease at enrollment and follow-up visit. ATS = American Thoracic Society; ATS-BDR = increase in prebronchodilator FEV_1 and/or FVC ⩾12% and ⩾200 ml after bronchodilator administration; BDR = bronchodilator response; Combined-BDR = an increase in both FEV_1 and FVC ⩾12% and ⩾200 ml after bronchodilator administration; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; FEV_1-BDR = increase in FEV_1 ⩾12% and ⩾200 ml but a change in FVC <12% and 200 ml after bronchodilator administration; FVC-BDR = increase in FVC ⩾12% and ⩾200 ml but a change in FEV_1 <12% and 200 ml after bronchodilator administration; No-BDR = a change in both FEV_1 and FVC <12% and <200 ml after bronchodilator administration.

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 2,371 (interquartile range, 2,073–2,652) 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;

Table 1. Characteristics of subjects with chronic obstructive pulmonary disease at enrollment by BDR groups ($n = 3,340$)

	FEV_1-BDR ($n = 182$)	FVC-BDR ($n = 522$)	Combined-BDR ($n = 379$)	No-BDR ($n = 2,257$)
Age, yr	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				
I, mild	34 (18.68)	80 (15.33)	53 (13.98)	497 (22.02)
II, moderate	124 (68.13)	168 (32.18)	192 (50.66)	958 (42.45)
III, severe	23 (12.64)	153 (29.31)	119 (31.40)	532 (23.57)
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, ft	1,363 ± 370.07*	1,175 ± 407.35	1,312 ± 347.35	1,249 ± 414.91

Definition of abbreviations: BD = bronchodilator; BDR = bronchodilator response; Combined-BDR = an increase in both FEV_1 and FVC ⩾12% and ⩾200 ml after bronchodilator administration; FEV_1 = forced expiratory volume in 1 second; FEV_1-BDR = increase in FEV_1 ⩾12% and ⩾200 ml but a change in FVC <12% and 200 ml after bronchodilator administration; FRC = functional residual capacity; FVC = forced vital capacity; FVC-BDR = increase in FVC ⩾12% and ⩾200 ml but a change in FEV_1 <12% and 200 ml after bronchodilator administration; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled glucocorticosteroids; LABA = long-acting β agonist; LAMA = long-acting muscarinic antagonist; MMRC = Modified Medical Research Council; No-BDR = a change in both FEV_1 and FVC <12% and <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; Ref = reference; TLC = total lung capacity. Continue variables are presented as mean ± SD.

*$P < 0.05$ versus No-BDR using Student's *t* test, Wilcoxon, Fischer, or chi-square tests when appropriate.

†Data were available for a subset of subjects: For % emphysema and TLC% predicted analysis, data were available for 3,127 subjects. For % gas trapping and FRC% analysis, data were available for 2,788 subjects. For Pi10 data analysis, data were available for 3,102 subjects. For 6-minute-walk-test data analysis, data were available for 3,264 subjects.

‡Across all GOLD stages shown (vs. No-BDR using chi-square test).

$P = 0.97$), 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 4).

Bronchodilator Response at Follow-up Visit

1,702 subjects completed a spirometry at follow-up visit. Of all subjects with prebronchodilator 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 enrollment, 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 1). Of FVC-BDR subjects at enrollment, 20.2% had FVC-BDR at follow-up. Of Combined-BDR subjects at enrollment, 20.8% had Combined-BDR at follow-up visit.

Sensitivity Analyses

We repeated the analyses in subjects with COPD with and without history of asthma with similar findings (*see* Tables E3–E5). When subjects with Global Initiative for Chronic Obstructive Lung Disease stage I were excluded from the analyses, Combined-BDR remained associated with less emphysema, higher frequency of exacerbations, and lower mortality (*see* Tables E6–E8).

When we defined BDR as an increase greater than or equal 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 (*see* Table E10) but not with mortality (*see* Table E11). When we defined BDR as an increase greater than or equal 200 ml (without the requirement of a 12% change) in $FEV_1$and/or FVC (absolute change), we observed that combined-volume-BDR was associated with

Table 2. Associations of BDR categories with clinical, functional, and radiographic features at enrollment in subjects with chronic obstructive pulmonary disease ($n = 3,340$)

	Chronic Bronchitis		MMRC		6-MWT (*ft*)		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 to 1.85)	0.15	0.09 (−0.09 to 0.27)	0.31	30.6 (−19.6 to 80.7)	0.23	0.01 (−0.01 to 0.03)	0.34
FVC-BDR	0.94 (0.73 to 1.18)	0.58	0.05 (−0.07 to 0.16)	0.41	6.1 (−25.88 to 38.1)	0.71	0.01 (−0.003 to 0.02)	0.16
Combined-BDR	1.24 (0.96 to 1.59)	0.09	−0.09 (−0.22 to 0.04)	0.17	70.8 (35.09 to 106.4)	<0.001	0.04 (0.02 to 0.05)	<0.001
ATS-BDR*	1.10 (0.92 to 1.31)	0.28	0.01 (−0.08 to 0.09)	0.87	33.5 (9.5 to 57.5)	0.01	0.02 (0.01 to 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 to 0.67)	0.30	−−0.16 (−2.27 to 1.96)	0.88	1.41 (−2.52 to 5.35)	0.48	0.26 (−2.18 to 2.70)	0.84
FVC-BDR	0.13 (−0.76 to 1.02)	0.77	1.47 (0.15 to 2.78)	0.03	4.37 (1.91 to 6.82)	<0.001	1.53 (0.003 to 3.05)	0.0496
Combined-BDR	−1.67 (−2.68 to −0.65)	0.001	1.41 (−0.08 to 2.89)	0.06	5.10 (2.33 to 7.87)	<0.001	1.78 (0.05 to 3.51)	0.043
ATS-BDR*	−0.65 (−1.32 to 0.03)	0.059	1.18 (0.18 to 2.17)	0.02	4.14 (2.28 to 5.99)	<0.001	1.40 (0.25 to 2.55)	0.02

Definition of abbreviations: 6-MWT = 6-minute-walk test; ATS = American Thoracic Society; ATS-BDR = increase in prebronchodilator FEV_1 and/or FVC ⩾12% and ⩾200 ml after bronchodilator administration; BDR = bronchodilator response; CI = confidence interval; Coef = coefficient; combined-BDR = an increase in both FEV_1 and FVC ⩾12% and ⩾200 ml after bronchodilator administration; FEV_1 = forced expiratory volume in 1 second; FEV_1-BDR = increase in FEV_1 ⩾12% and ⩾200 ml but a change in FVC <12% and 200 ml after bronchodilator administration; FRC = functional residual capacity; FVC = forced vital capacity; FVC-BDR = increase in FVC ⩾12% and ⩾200 ml but a change in FEV_1 <12% and 200 ml after bronchodilator administration; MMRC = Modified Medical Research Council; no-BDR = a change in both FEV_1 and FVC <12% and <200 ml after bronchodilator administration; OR = odds ratio; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; Ref = reference; TLC = total lung capacity.
For % emphysema and TLC% predicted analysis, data were available for 3,127 subjects. For % gas trapping and FRC% analysis, data were available for 2,788 subjects. For 6-MWT data analysis, data were available for 3,264 subjects.
All models included the following covariates: age, sex, race, smoking status, smoking pack-years, body mass index, and post-bronchodilator FEV_1% predicted.
*Multivariable linear and logistic regression models with ATS-BDR binary variable = BDR according to ATS guidelines; Yes or No as the independent variable.

mortality (*see* Table E14) but not with respiratory exacerbations (*see* Table E13). 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 (*see* Table E15).

Discussion

In a cohort of current and former smokers with COPD, we demonstrated that using a more stringent combined BDR 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 BDR.

BDR is often evaluated in patients with respiratory symptoms. Although subjects with asthma have a greater degree of BDR than subjects with COPD (10), and BDR in COPD declines over time as the disease progresses (31), its clinical utility has been debated because BDR does not sufficiently distinguish between asthma and COPD. Current definitions of BDR also do not identify a useful COPD phenotype (3, 32). 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 because it is more common than BDR in FEV_1. BDR-FVC is associated with hyperinflation (33–35), which results in dyspnea and lower exercise capacity (36). BDR in FVC has also been shown to be more strongly associated with gas trapping than BDR in FEV_1 (37). These findings are in agreement with our results that FVC-BDR is associated with %gas trapping, whereas 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, whereas change in FEV_1 after bronchodilator administration may be overestimated by gas compression (2). In addition, data from impulse oscillometry and body plethysmography suggest that FEV_1-BDR underestimates the change in volume and airway resistance after bronchodilation (38). Newton and colleagues (33) found that in patients with severe COPD and lung hyperinflation, only 11% had a positive FEV_1 response, whereas the FVC response was 53%. Furthermore, Ben Saad and coworkers (39) showed that in patients with COPD with reversibility by ATS criteria, FVC response was seen in an additional 45% who did not have FEV_1 response. Thus, FVC response seems 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 pathophysiologic processes. When emphysema and poor elastic recoil play an important role, FVC-BDR is more common (33, 40). 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 (41). However, in pathophysiologic processes with flow limitation that affect peripheral and central airways (42), FEV_1-BDR is more prominent (20). 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 (43), and with higher FRC% predicted, and greater 6-MWT

Table 3. Association of BDR categories at enrollment with drop in FEV_1 between baseline and follow-up visit and respiratory exacerbations in subjects with chronic obstructive pulmonary disease

	Change in FEV_1 (*n* = 1,702) (*ml/yr*)		Exacerbations (*n* = 2,980)		Severe Exacerbations (*n* = 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 to −7.90)	<0.001	1.18 (0.90 to 1.55)	0.26	0.97 (0.68 to 1.40)	0.88
FVC-BDR	−8.11 (−15.49 to −0.73)	0.03	1.10 (0.93 to 1.30)	0.29	1.09 (0.88 to 1.35)	0.42
Combined-BDR	−21.86 (−29.60 to −14.11)	<0.001	1.25 (1.03 to 1.50)	0.02	1.34 (1.05 to 1.71)	0.02
ATS-BDR*	−15.32 (−20.66 to −9.98)	<0.001	1.16 (1.02 to 1.32)	0.02	1.16 (0.98 to 1.37)	0.08

Definition of abbreviations: ATS = American Thoracic Society; ATS-BDR = increase in prebronchodilator FEV_1 and/or FVC ⩾12% and ⩾200 ml after bronchodilator administration; BDR = bronchodilator response; CI = confidence interval; Coef = coefficient; Combined-BDR = an increase in both FEV_1 and FVC ⩾12% and ⩾200 ml after bronchodilator administration; FEV_1 = forced expiratory volume in 1 second; FEV_1-BDR = increase in FEV_1 ⩾12% and ⩾200 ml but a change in FVC <12% and 200 ml after bronchodilator administration; FVC = forced vital capacity; FVC-BDR = increase in FVC ⩾12% and ⩾200 ml but a change in FEV_1 <12% and 200 ml after bronchodilator administration; IRR = incidence rate ratio; No-BDR = a change in both FEV_1 and FVC <12% and <200 ml after bronchodilator administration.
All models included the following covariates: age, sex, race, smoking status, smoking pack-years, body mass index, and post-bronchodilator FEV_1% predicted.
*Multivariable logistic regression models with ATS-BDR binary variable = BDR according to ATS guidelines; Yes or No as the independent variable.

distance compared with 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 (44). This disagreement could be caused by 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 may be the main driver of survival (45).

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 and coworkers (6) reported that BDR in FEV_1 is not associated with FEV_1 decline, whereas other investigators have shown that BDR in FEV_1 is a predictor of FEV_1 decline in COPD (17). However, the latter have been criticized because baseline FEV_1 was not taken into consideration (3, 18). 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 (46).

Furthermore, BDR definitions that include percentage response alone or volume response alone have been proposed (3), 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 is 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 greater than or equal 12% and greater than or equal 200 ml 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 (*see* online 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

Table 4. Association of BDR categories at enrollment with mortality in subjects with chronic obstructive pulmonary disease (*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

Definition of abbreviations: ATS = American Thoracic Society; ATS-BDR = increase in prebronchodilator FEV_1 and/or FVC ⩾12% and ⩾200 ml after bronchodilator administration; BDR = bronchodilator response; CI = confidence interval; combined-BDR = an increase in both FEV_1 and FVC ⩾12% and ⩾200 ml after bronchodilator administration; FEV_1 = forced expiratory volume in 1 second; FEV_1-BDR = increase in FEV_1 ⩾12% and ⩾200 ml but a change in FVC <12% and 200 ml after bronchodilator administration; FVC = forced vital capacity; FVC-BDR = increase in FVC ⩾12% and ⩾200 ml but a change in FEV_1 <12% and 200 ml after bronchodilator administration; HR = hazard ratio; no-BDR = a change in both FEV_1 and FVC <12% and <200 ml after bronchodilator administration; Ref = reference.
Cox hazard regression models for mortality included the following covariates: age, sex, race, smoking status, smoking pack-years, body mass index, and post-bronchodilator FEV_1% predicted.
*Cox hazard regression models with ATS-BDR binary variable = BDR according to ATS guidelines; Yes or No as the independent variable.

these subjects are 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 (6, 8). BDR variability may be caused by variability in the spirometric maneuvers, such as differences in coaching and spirometers used, or by 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 several sensitivity analyses, including subjects with asthma, and by excluding subjects with mild disease. Second, subjects did not withhold long-acting bronchodilators before 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 caused by undertreatment because 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 were not available at follow-up in some participants because of attrition or mortality. However, as has been previously shown using data from the same cohort by Dransfield and colleagues (46), completers, late, and deceased subjects in the COPDGene study were fairly similar in regards to demographic characteristics and baseline lung function. 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, which 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. ■

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