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A New Bronchodilator Response Grading Strategy Identifies Distinct Patient Populations

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Abstract

Rationale: A positive bronchodilator response (BDR) according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines require both 200 ml and 12% increase in forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) after bronchodilator inhalation. This dual criterion is insensitive in those with high or low FEV_1.

Objectives: To establish BDR criteria with volume or percentage FEV_1 change.

Methods: The largest FEV_1 and FVC were identified from three pre- and three post-bronchodilator maneuvers in COPDGene (Genetic Epidemiology of COPD) participants. A total of 7,741 individuals with coefficient of variation less than 15% for both FEV_1 and FVC formed bronchodilator categories of FEV_1 response: negative ($\leq$0.00% or $\leq$0.00 L), minimal ($>$0.00% to $\leq$9.00% or $>$0.00 L to $\leq$0.09 L), mild ($>$9.00% to $\leq$16.00% or $>$0.09 L to $\leq$0.16 L), moderate ($>$16.00% to $\leq$26.00% or $>$0.16 L to $\leq$0.26 L), and marked ($>$26.00% or $>$0.26 L). These response size categories are based on empirical limits considering average FEV_1 increase of approximately 160 ml and the clinically important difference for FEV_1. To compare flow and volume response characteristics, BDR-FEV_1 category assignments were applied for the BDR-FVC response.

Results: Twenty percent met mild and 31% met moderate or marked BDR-FEV_1 criteria, whereas 12% met mild and 33% met moderate or marked BDR-FVC criteria. In contrast, only 20.6% met ATS/ERS positive criteria. Compared with the negative BDR-FEV_1 category, the minimal, mild, moderate, and marked BDR-FEV_1 categories were associated with greater 6-minute-walk distance and lower St. George's Respiratory Questionnaire and modified Medical Research Council dyspnea scale scores. Compared with negative BDR, moderate and marked BDR-FEV_1 categories were associated with fewer exacerbations, and minimal BDR was associated with lower computed tomography airway wall thickness. Compared with the negative category, all BDR-FVC categories were associated with increasing emphysema percentage and gas trapping percentage. Moderate and marked BDR-FVC categories were associated with higher St. George's Respiratory Questionnaire scores but fewer exacerbations and lower dyspnea scores.

Conclusions: BDR grading by FEV_1 volume or percentage response identified subjects otherwise missed by ATS/ERS criteria. BDR grades were associated with functional exercise performance, quality of life, exacerbation frequency, dyspnea, and radiological airway measures. BDR grades in FEV_1 and FVC indicate different clinical and radiological characteristics.

Keywords: airflow obstruction; bronchodilator responsiveness; forced expiratory volume in 1 second

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Current criteria for identifying a positive spirometric bronchodilator response (BDR) based on American Thoracic Society (ATS) and European Respiratory Society (ERS) (1) guidelines require both 200 ml and 12% increase in forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC). If these dual criteria are not met, BDR is categorized as negative. These guidelines may not identify many individuals with potentially clinically important BDR, especially those with low baseline FEV_1 who do not meet change greater than or equal to 200 ml or those with high baseline FEV_1 who do not meet change greater than or equal to 12% (2–4). Both Pellegrino and Brusasco (5) and Calverley and colleagues (6) emphasized that FEV_1 BDR is a continuous variable; no threshold adequately separates responders from nonresponders. Hansen and colleagues (4), analyzing BDR in a sample of clinical pre- and post-bronchodilator tests, showed that 224 (71.6%) of 313 patients failed ATS/ERS FEV_1 criteria, but 89 (39.7%) of those 224 who failed showed statistically significant ΔFEV_1 greater than or equal to 100 ml or greater than or equal to 6.0% improvement. Of those with baseline FEV_1 less than 1 L ($n = 44$), 52.3% had ΔFEV_1 greater than or equal to 100 ml or greater than or equal to 6.0%, whereas only 11.4% were ATS/ERS positive (3). These results suggest the need to revise BDR evaluation.

The COPDGene (Genetic Epidemiology of COPD) population, with 10,311 current smokers or ex-smokers with or without spirometrically defined chronic obstructive pulmonary disease (COPD), is uniquely positioned to evaluate BDR (7) and formed the basis of the present evaluation. We aimed to *1*) develop a new grading system based on BDR volume or percentage increase for comparison with ATS/ERS guidelines, *2*) evaluate ATS/ERS recommended ΔFEV_1 versus ΔFVC values, and *3*) explore the clinical relevance of the new BDR grades by comparing them with clinical outcomes and pulmonary structural characteristics. Some of the results of this study have been reported previously in the form of an abstract (8).

Methods

We used the COPDGene cohort enrolled between 2007 and 2011 (7). This cohort included 10,311 non-Hispanic white and African American subjects, 45–80 years old, with a greater than or equal to 10–pack-year smoking history. Key exclusion criteria were history of other lung disease (except asthma) or previous lung resection (*see* online supplement) (7). Participants underwent spirometry, 6-minute-walk test, quantitative computed tomography (CT), and standard questionnaires to assess symptoms and medical history. From this population, participants who did not have FEV_1, FEV_6, and FVC values from three prebronchodilator and three post-bronchodilator maneuvers were excluded ($n = 2{,}084$), as were those with coefficient of variation (standard deviation [SD]/mean) of either prebronchodilator or post-bronchodilator blows greater than 15% ($n = 486$) (9), reducing the study population to 7,741. The COPDGene protocol was approved by institutional review boards at 21 participating centers. Written informed consent was obtained from all participants.

Spirometry and Proposed BDR Grades

Spirometry was performed in accordance with ATS/ERS recommendations and using an ultrasound-based spirometer (EasyOne; ndd Medical Technologies) before and after two puffs of albuterol using a spacer (10). Before bronchodilator reversibility testing, short-acting and long-acting inhaled bronchodilators were withheld 4 and 12 hours; short-acting and long-acting oral bronchodilators were withheld 8 and 12 hours before testing, respectively. The largest of three acceptable FEV_1 and FVC measurements was reported. Spirometric measurements were graded (range, 0–4) by a centralized quality control process: grade 4 = fully met ATS criteria, reproducible to within 50 ml; grade 3 = fully met ATS criteria, reproducible to between 50 and 100 ml; grade 2 = fully met ATS criteria, reproducible between 100 and 150 ml; grade 1 = partly meeting ATS criteria and/or reproducible between 150 and 200 ml; grade 0 = failure to meet ATS criteria and/or reproducible greater than 200 ml (11). In the study group, prebronchodilator quality control grades for FEV_1 and FVC were 3.54 ± 0.78 and 3.35 ± 0.92, respectively, whereas post-bronchodilator quality control grades were 3.62 ± 0.70 and 3.46 ± 0.81, respectively. These grades did not differ markedly among BDR categories (Table 1).

BDR was evaluated as absolute change from baseline FEV_1 (ΔFEV_1L) and percentage change from baseline FEV_1 ($\Delta FEV_1\%$). BDR is a continuous variable with a unimodal, not bimodal, response pattern (12). Using fixed population-based criteria for both volume and percentage change in BDR is not optimal, especially considering differences in drug, dosage, and administration methods in published studies (4). We used five bronchodilator categories of FEV_1-BDR by using volume or percentage FEV_1 change: negative ($\leq 0.00\%$ or ≤ 0.00 L), minimal ($>0.00\%$ to $\leq 9.00\%$ or >0.00 L to ≤ 0.09 L), mild ($>9.00\%$ to $\leq 16.00\%$ or >0.09 L to ≤ 0.16 L), moderate ($>16.00\%$ to $\leq 26.00\%$ or >0.16 L to ≤ 0.26 L), and marked ($>26.00\%$ or >0.26 L). The rationale for the 5-point grading system including nonresponders (negative) and minimal, mild, moderate, and marked responders is based on several considerations: ΔFEV_1L less than or equal to 0 clearly defines the nonresponder and negative responder category. We have previously asserted that $\Delta FEV_1\%$ of 6% or 7% might be clinically important because it is associated with about a 90- to 100-ml increase in FEV_1 (3), which has been suggested as the minimal clinically important difference (MCID) for ΔFEV_1 (13). We use 90 ml or 9% to separate minimal from mild response. A 9% threshold, corresponding to the upper 95th percentile of BDR in FEV_1, was previously proposed to define clinical "abnormality," based on BDR in a large group of asymptomatic never-smokers (14). After excluding nonresponders, when we ordered responses by baseline FEV_1, average ΔFEV_1 in groups of 100 persons seemed to stabilize at approximately 160 ml (ΔFEV_1L and $\Delta FEV_1\%$ profiles in Figure 1). This value (and the corresponding 16% change) was chosen to separate the mild and moderate categories. Previously, absolute increase in FEV_1 required to exclude natural variability with 95% confidence was reported as 160 ml in obstructive airway disease (OAD) (15). In distinguishing between moderate and marked response, it seemed practical to use a further 100-ml MCID step size and use 260 ml or 26% increase. For ATS/ERS guideline comparison, we placed participants into ATS/ERS groups for ΔFEV_1: *1*) positive, defined as ΔFEV_1L greater than or equal to 0.2 L and $\Delta FEV_1\%$ greater than or equal to 12% and *2*) negative, defined as all others. To compare flow and volume response characteristics in bronchodilator testing, we also evaluated BDR in FVC (BDR-FVC).

Table 1. Demographic characteristics, spirometry, functional exercise capacity, and quantitative CT measures of airway abnormality among FEV_1 BDR grades ($N = 7{,}741$)

	Negative	Minimal	Mild	Moderate	Marked
Category range for ΔFEV_1L (L)	$\Delta FEV_1 \leq 0$	$0 < \Delta FEV_1 \leq 0.09$	$0.09 < \Delta FEV_1 \leq 0.16$	$0.16 < \Delta FEV_1 \leq 0.26$	$0.26 > \Delta FEV_1$
Category range for ΔFEV_1% (%)	$\Delta\%FEV_1 \leq 0$	$0 < \Delta\%FEV_1 \leq 9$	$9 < \Delta\%FEV_1 \leq 16$	$16 < \Delta\%FEV_1 \leq 26$	$26 > \Delta\%FEV_1$
n (%)	1,634 (21.1)	2,159 (27.9)	1,549 (20)	1,399 (18.1)	1,000 (12.9)
Demographics					
Age, yr	59.1 ± 8.6	60.8 ± 8.9	60.9 ± 9.0	60.6 ± 9.1	59.0 ± 8.7
BMI, kg/m^2	28.8 ± 6.2	28.5 ± 6.3	28.5 ± 6.1	28.7 ± 6.1	28.7 ± 6.0
Smoking history, pack-years	39.1 (27.7–54.2)	40.0 (28.0–55.5)	40.0 (27.0–55.5)	40.0 (28.5–55.5)	40.5 (30.0–58.0)
Sex, male, %	55.3	48.1	47.8	57.2	66.8
Race, white, %	64.8	72.7	76.2	76.6	74.8
ICS use, %	6.7	6.2	5.5	6.9	9.3
Spirometry					
Pre-BD FEV_1, L	2.37 ± 0.95	2.07 ± 0.92	2.05 ± 0.88	2.13 ± 0.91	2.08 ± 0.95
Post-BD FEV_1, L	2.28 ± 0.93	2.12 ± 0.93	2.17 ± 0.88	2.32 ± 0.93	2.43 ± 0.98
Pre-BD FVC, L	3.46 ± 1.03	3.17 ± 0.99	3.17 ± 0.96	3.29 ± 1.04	3.36 ± 1.14
Post-BD FVC, L	3.33 ± 1.01	3.18 ± 0.97	3.29 ± 0.93	3.50 ± 1.00	3.78 ± 1.12
ΔFEV_1, L	−0.09 ± 0.09	0.04 ± 0.02	0.12 ± 0.02	0.20 ± 0.04	0.36 ± 0.12
ΔFVC, L	−0.14 ± 0.24	0.02 ± 0.19	0.12 ± 0.21	0.21 ± 0.24	0.41 ± 0.37
ΔFEV_1, %	−3.93 ± 3.99	2.64 ± 1.96	6.95 ± 3.18	11.17 ± 5.13	21.12 ± 11.65
ΔFVC, %	−3.81 ± 7.04	1.09 ± 6.63	4.61 ± 7.78	7.95 ± 9.68	14.84 ± 13.86
Pre-BD FEV_1/FVC, %	66.87 ± 15.29	63.59 ± 16.14	63.13 ± 15.21	63.02 ± 14.73	59.87 ± 14.21
Post-BD FEV_1/FVC, %	67.09 ± 15.98	64.83 ± 16.89	64.80 ± 15.99	65.65 ± 15.19	63.21 ± 14.63
Pre-BD FEV_1, QC	3.15 ± 1.05	3.60 ± 0.67	3.71 ± 0.59	3.66 ± 0.65	3.61 ± 0.72
Post-BD FEV_1, QC	3.68 ± 0.68	3.74 ± 0.58	3.68 ± 0.60	3.55 ± 0.69	3.26 ± 0.97
Pre-BD FVC, QC	3.07 ± 1.14	3.42 ± 0.82	3.48 ± 0.77	3.43 ± 0.85	3.34 ± 0.89
Post-BD FVC, QC	3.46 ± 0.82	3.57 ± 0.68	3.51 ± 0.73	3.41 ± 0.86	3.21 ± 1.02
Functional exercise performance, quality of life, and exacerbation frequency					
6MWD, m	413 ± 123	408 ± 123	418 ± 118	429 ± 120	431 ± 117
SGRQ score	20.61 (5.96–43.27)	22.55 (6.30–44.79)	21.74 (7.12–43.50)	20.53 (6.45–40.82)	25.35 (8.36–46.27)
mMRC	1.34 ± 1.48	1.38 ± 1.44	1.31 ± 1.42	1.23 ± 1.41	1.38 ± 1.43
Exacerbations/yr	0.39 ± 1.00	0.42 ± 0.93	0.43 ± 0.99	0.38 ± 0.93	0.38 ± 0.89
Quantitative CT					
$WA_{segmental}$, %	61.13 ± 3.32	61.17 ± 3.21	61.26 ± 3.19	61.40 ± 3.14	62.12 ± 3.38
Pi_{15}	5.14 ± 0.19	5.13 ± 0.19	5.14 ± 0.20	5.15 ± 0.20	5.21 ± 0.21
Emphysema %	1.75 (0.56–6.17)	2.40 (0.74–9.49)	2.70 (0.76–7.93)	2.61 (0.79–8.01)	2.81 (0.97–7.12)
Gas trapping %	13.54 (6.01–29.90)	15.10 (6.99–35.47)	16.06 (7.54–34.46)	16.47 (7.77–34.14)	19.35 (9.99–36.12)

Definition of abbreviations: 6MWD = 6-minute-walk distance; BD = bronchodilator; BDR = bronchodilator response; BMI = body mass index; CT = computed tomography; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroids; mMRC = modified Medical Research Council dyspnea scale; Pi_{15} = square root wall area of a 15-mm diameter airway; QC = quality control grades for spirometry maneuver (ranging from 0 to 4); SGRQ = St. George's Respiratory Questionnaire; WA = wall area.
Data are presented as mean ± SD or median (25th–75th interquartile range) or as percentages.

BDR-FVC was evaluated as absolute change from baseline FVC (ΔFVCL) and percentage change from baseline FVC (ΔFVC%). We used the same BDR category assignments we derived for FEV_1 for the BDR-FVC response.

Clinical and Functional Correlates

As clinical and functional correlates, we used the St. George's Respiratory Questionnaire (SGRQ) to assess health-related quality of life (scores ranging from 0 to 100, with a greater score indicating worse health status) (16), modified Medical Research Council (mMRC) dyspnea scale to quantify dyspnea (scores ranging from 0 to 4, with a greater score indicating worse dyspnea perception) (17), and 6-minute-walk distance (6MWD) to assess functional exercise performance. The 6-minute-walk test was performed according to ATS standards (18) and at least 20 minutes after albuterol administration for post-bronchodilator spirometry. Exacerbation frequency in the prior year was recorded at enrollment, with exacerbations defined as acute worsening of respiratory symptoms requiring antibiotics and/or systemic corticosteroids (19). CT scans were acquired at full inspiration and end expiration (*see* online supplement). CT scans were obtained after bronchodilator testing. Airway wall thickness was assessed by segmental airway wall area percentage (segmental WA% = [outer bronchus area − airway luminal area]/outer bronchus area) and square root wall area of a 15-mm diameter airway (Pi_{15}) (20). Emphysema percentage on CT was defined as the percentage of low-attenuation areas below −950 Hounsfield units (HU) on an end-inspiratory CT scan (21). Gas trapping percentage was defined as percentage of lung voxels below −856 HU on expiratory scans (22).

Statistical Analyses

IBM SPSS Statistics version 22.0 (IBM) and Stata version 15 (StataCorp) software was used. Univariate analyses were performed between BDR grades using chi-square test for proportions and one-way analysis of variance or Kruskal-Wallis test for continuous variables (Table 1; *see also* Table E1 in the online supplement). *P* values for

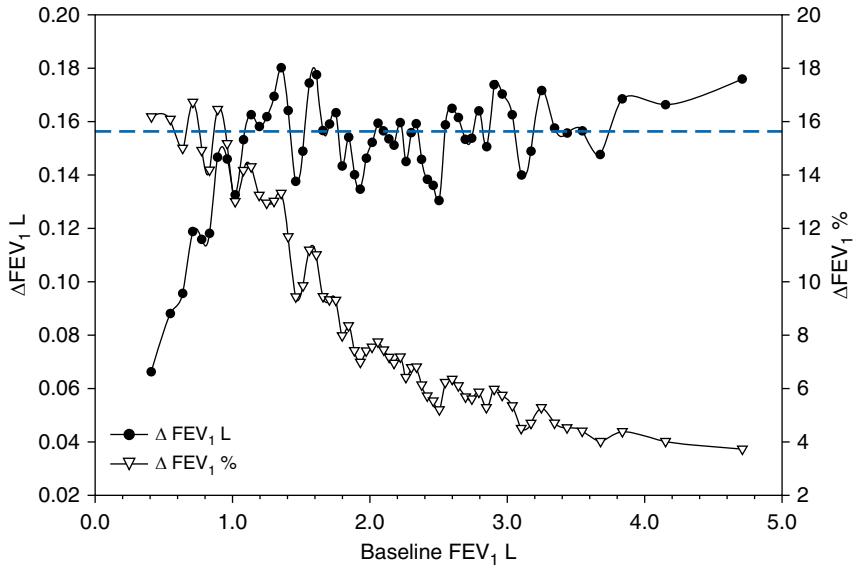

Figure 1. Mean forced expiratory volume in 1 second (FEV_1) bronchodilator response in volume (in L) and as a percentage by clusters of 100 individuals at each point as baseline FEV_1 percent predicted value increases for the 6,107 participants with positive bronchodilator response. Changes in volume (left axis, ΔFEV_1L) and percent predicted (right axis, $\Delta FEV_1\%$) differ markedly. Although ΔFEV_1L increases rapidly to approximately 0.16 L and stabilizes at that level (represented with the dashed line on the graph), $\Delta FEV_1\%$ fraction gradually declines in a hyperbolic fashion from 16% to 4%.

pairwise comparisons were adjusted for overall type II error rate (5%) using Tukey's method. Relationships between BDR grades (independent variable) and quantitative CT, SGRQ, and 6MWD (dependent variables) were assessed by generalized linear regression models using age, sex, race, smoking history, body mass index, baseline FEV_1, and CT scanner type (only for CT measures) as covariates (separately for BDR-FEV_1 and BDR-FVC response) (Tables 2 and 3). A proportional odds model was used for mMRC (Tables 2 and 3). A generalized linear regression model with negative binomial link function assessed BDR grade's independent effect on exacerbation frequency (23) (Tables 2 and 3). SGRQ, emphysema percentage, and gas trapping percentage were natural log transformed; regression coefficients for natural log–transformed variables were back transformed, and exponentiated β-values were presented to aid interpretation. Finally, to assess the relationship between BDR (ΔFEV_1L, $\Delta FEV_1\%$, ΔFVCL, ΔFVC% as separate continuous variables) and 6MWD, SGRQ, and quantitative CT measures, we modeled 6MWD, SGRQ, and quantitative CT measures against ΔFEV_1L, $\Delta FEV_1\%$, ΔFVCL, and ΔFVC% in the whole study population. ΔFEV_1L, $\Delta FEV_1\%$, ΔFVCL, and ΔFVC% were coded using a restricted cubic spline function with three knots located at the 5th, 50th, and 95th percentiles (Figures 2A and 2B). All these models were adjusted for age, sex, race, smoking history, body mass index, baseline FEV_1 or FVC, and CT scanner type (for CT measures).

Analyses were performed for the whole study population. ATS/ERS criteria identified most of the participants in the marked BDR category as positive BDR. Accordingly, analyses were performed in the subgroup after excluding ATS/ERS positives (Table 3). Excluding ATS/ERS positives causes a substantial loss in sample size of the marked BDR group, however; for that reason, marked BDRs were excluded from the subgroup analysis.

Results

Characteristics of the 7,741 participants are summarized in Table 4. Within-subject coefficients of variation for pre- and post-bronchodilator FEV_1 were 4.12 ± 2.77% and 3.52 ± 2.54%, respectively. Distributions of absolute and percentage FEV_1 BDR are presented in Figure 3. Mean ΔFEV_1L and ΔFVCL were 0.099 L and 0.092 L, respectively. However, ΔFEV_1L and $\Delta FEV_1\%$ distributions were dramatically different (Figure 3). This emphasizes that volume and percentage changes need to be considered separately from each other. Table 1 shows study participants graded by BDR intensity categories. Total BDR positives were 78.9%.

ΔFEV_1L and ΔFVCL after bronchodilator inhalation are presented in Figure 4. Despite similarity of mean and SD (Table 4), ΔFVCL increased more rapidly than ΔFEV_1L above a BDR of 0.1 L (Figure 4A). In contrast, $\Delta FEV_1\%$ and ΔFVC% increased similarly over the full BDR range (Figure 4B).

In Figure 1, ΔFEV_1L and $\Delta FEV_1\%$ of positive BDR participants are ordered by increasing prebronchodilator FEV_1 volumes to compare volume and percentage increase patterns. Conspicuously, BDR patterns expressed as ΔFEV_1L and $\Delta FEV_1\%$ differed markedly as prebronchodilator FEV_1 increased. Below prebronchodilator FEV_1 percent predicted of 40% (FEV_1, ~1 L), ΔFEV_1L increased rapidly up to approximately 0.160 L and then stabilized, whereas $\Delta FEV_1\%$ averaged approximately 16%, then gradually declined in a hyperbolic fashion to approximately 4% as FEV_1 increased.

BDR Categories by FEV_1 Response

Using proposed BDR cutoffs, 27.9%, 20.0%, 18.1%, and 12.9% of the population had minimal, mild, moderate, and marked BDR, respectively (Table 1). One hundred percent of the minimal responders had a minimal FEV_1-BDR by both ΔFEV_1L and $\Delta FEV_1\%$. Of the mild responders 93.1% and 25.6% had mild BDR by ΔFEV_1L and $\Delta FEV_1\%$, respectively. Of the moderate responders, 91.6% and 20.7% had moderate BDR by ΔFEV_1L and $\Delta FEV_1\%$, respectively. Of the marked responders, 91.0% and 27.7% had marked BDR by ΔFEV_1L and $\Delta FEV_1\%$, respectively. However, 21.1% of the population had a negative BDR. Mean ages of marked bronchodilator responders and nonresponders were lower than those of minimal, mild, and moderate responders. Female sex was more prominent in minimal and mild BDR, whereas male sex was more prominent in marked and nonresponse categories. Negative responders had greater pre- and post-bronchodilator FEV_1/FVC than all other response categories.

In the univariate analyses, there was progressive increase in segmental WA% from negative to marked BDR ($P < 0.0001$).

Table 2. Adjusted multivariable analysis for functional exercise performance, QOL, exacerbation frequency, dyspnea, and quantitative CT measures with increasing FEV_1 and FVC BDR grades

		Bronchodilator Response Grades, FEV_1 Response				
		Negative (*n* = 634 [21.1%])	**Minimal (*n* = 2,159 [27.9%])**	**Mild (*n* = 1,549 [20.0%])**	**Moderate (*n* = 1,399 [18.1%])**	**Marked (*n* = 1,000 [12.9%])**
6MWD	Mean difference (95% CI)	1 (ref)	**8.46* (2.01 to 14.91)**	**17.60† (10.61 to 24.58)**	**26.94† (19.81 to 34.07)**	**37.00† (29.14 to 44.86)**
SGRQ	% Difference (95% CI), e^{β}	1 (ref)	**−7.30* (−13.00 to −1.20), 0.927**	**−8.30* (−14.40 to −1.80), 0.917**	**−12.20† (−18.20 to −5.80), 0.878**	**−12.40† (−18.90 to −5.30), 0.876**
mMRC	OR (95% CI)	1 (ref)	**0.81* (0.71 to 0.93)**	**0.74† (0.64 to 0.86)**	**0.62† (0.53 to 0.73)**	**0.63† (0.53 to 0.75)**
Exacerbations/yr	RR (95% CI)	1 (ref)	0.89 (0.78 to 1.01)	0.91 (0.79 to 1.05)	**0.86* (0.74 to 0.99)**	**0.74† (0.63 to 0.87)**
$WA_{segmental}$, %	Mean difference (95% CI)	1 (ref)	**−0.24* (−0.43 to −0.06)**	−0.18 (−0.38 to 0.01)	−0.08 (−0.28 to 0.12)	**0.29* (0.06 to 0.51)**
Pi_{15}	Mean difference (95% CI)	1 (ref)	**−0.01* (−0.03 to −0.00)**	−0.00 (−0.02 to 0.01)	−0.00 (−0.01 to 0.01)	**0.03† (0.01 to 0.04)**
Emphysema %	% Difference (95% CI), e^{β}	1 (ref)	7.62 (−1.62 to 12.71), 1.08	5.30 (−4.41 to 15.99), 1.05	3.75 (−6.06 to 14.60), 1.04	−6.00 (−15.83 to 4.97), 0.95
Gas trapping, %	% Difference (95% CI), e^{β}	1 (ref)	−2.69 (−8.57 to 3.57), 0.97	1.54 (−5.06 to 8.60), 1.01	4.00 (−2.92 to 11.41), 1.04	**10.50 (2.37 to 19.28), 1.10***

		Bronchodilator Response Grades, FVC Response				
		Negative (*n* = 2,885 [37.3%])	**Minimal (*n* = 1,273 [16.4%])**	**Mild (*n* = 928 [12.0%])**	**Moderate (*n* = 935 [12.1%])**	**Marked (*n* = 1,720 [22.2%])**
6MWD	Mean difference (95% CI)	1 (ref)	4.65 (−2.17 to 11.48)	2.38 (−5.27 to 10.03)	4.42 (−3.26 to 12.10)	**13.91† (7.56 to 20.27)**
SGRQ	% Difference (95% CI), e^{β}	1 (ref)	4.97 (−2.28 to 12.63), 1.05	4.37 (−3.50 to 12.89), 1.04	**9.39 (1.16 to 18.29), 1.09***	**14.33 (7.19 to 21.95), 1.14***
mMRC	OR (95% CI)	1 (ref)	−0.03 (−0.09 to 0.03)	0.07 (−0.01 to 0.15)	**0.12* (0.03 to 0.21)**	**0.20† (0.09 to 0.30)**
Exacerbations/yr	RR (95% CI)	1 (ref)	0.06 (−0.07 to 0.19)	**0.16* (0.01 to 0.30)**	**0.20* (0.05 to 0.34)**	**0.17* (0.05 to 0.29)**
$WA_{segmental}$, %	Mean difference (95% CI)	1 (ref)	−0.10 (−0.29 to 0.09)	0.11 (−0.10 to 0.33)	0.27 (0.05 to 0.49)	**0.67† (0.49 to 0.85)**
Pi_{15}	Mean difference (95% CI)	1 (ref)	**−0.02* (−0.03 to −0.01)**	−0.01 (−0.02 to 0.01)	0.12 (−0.00 to 0.03)	**0.04† (0.03 to 0.05)**
Emphysema, %	% Difference (95% CI), e^{β}	1 (ref)	**23.82 (12.03 to 36.84), 1.24†**	**27.44 (13.99 to 42.47), 1.27†**	**40.50 (25.70 to 57.04), 1.40†**	**50.29 (37.00 to 64.88), 1.50***
Gas trapping, %	% Difference (95% CI), e^{β}	1 (ref)	**10.33 (2.90 to 18.31), 1.10***	**19.83 (10.75 to 29.65), 1.20†**	**26.51 (17.07 to 36.71), 1.26†**	**46.21 (37.09 to 55.94)†, 1.46**

Definition of abbreviations: 6MWD = 6-minute-walk distance; BDR = bronchodilator response; CI = confidence interval; CT = computed tomography; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; mMRC = modified Medical Research Council dyspnea scale; OR = odds ratio; Pi_{15} = square root wall area of a 15-mm diameter airway; QOL = quality of life; ref = reference; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire; WA = wall area.

Mean value of the outcome is modeled; regression coefficient corresponds to mean difference of the outcome. The mean value of the outcome variables (6MWD, WA%, and Pi_{15}) increases/decreases by the amount of the regression coefficient in the particular BDR category compared with the reference category (negative response to bronchodilator). SGRQ, emphysema percentage, and gas trapping percentage were natural log transformed. The displayed coefficients (percentage difference and 95% CI) for SGRQ, emphysema percentage, and gas trapping percentage were back-transformed regression coefficients (e^{β}) that correspond to the relative ratio between the two groups in percent. For example, for SGRQ, the mean SGRQ total score of marked bronchodilator responders is 12.4% lower than that of the reference category. OR indicates the relative odds increase for a higher score of mMRC between the two groups. For example, the estimated odds of having a one-unit-higher score of mMRC dyspnea score for marked bronchodilator responders is 0.63 of the odds compared with participants with a negative bronchodilator response. RR indicates the relative risk decrease in number of exacerbations per year between the risk group and the reference category. For example, relative risk of number of exacerbations per year is 26% decreased in marked bronchodilator responders compared with that of the reference category. Participants with a negative bronchodilator response are stated as the reference category. All models were controlled for sex, age, race, body mass index, smoking history, and initial prebronchodilator FEV_1. In addition, models with CT outcomes were adjusted for CT scanner type. Significant associations are marked in bold. Negative response group was set as the reference category.

*$P < 0.05$.

†$P < 0.0001$.

Table 3. Adjusted multivariable analysis for functional exercise performance, QOL, exacerbation frequency, dyspnea, and CT measures with increasing FEV_1 BDR grade in the subgroup excluding all marked bronchodilator responders and participants with a positive response by ATS/ERS BDR criteria ($N = 5{,}937$)

		Bronchodilator Response Grades			
Number of participants		**Negative 1,608**	**Minimal 2,048**	**Mild 1,334**	**Moderate 947**
6MWD	Mean difference (95% CI)	1 (ref)	**7.94* (1.39 to 14.49)**	**18.50† (10.79 to 25.31)**	**24.97† (16.98 to 32.96)**
SGRQ	% difference (95% CI), e^{β}	1 (ref)	**−7.20* (−13.20 to −0.08), 0.928**	**−9.00* (−15.40 to −2.00), 0.910**	**−12.70† (−19.60 to −5.30), 0.873**
mMRC	OR (95% CI)	1 (ref)	**0.81* (0.70 to 0.93)**	**0.72† (0.61 to 0.84)**	**0.59† (0.49 to 0.72)**
Exacerbations/yr	RR (95% CI)	1 (ref)	0.88 (0.77 to 1.00)	0.89 (0.76 to 1.03)	0.87 (0.73 to 1.04)
$WA_{segmental}$, %	Mean difference (95% CI)	1 (ref)	−0.20 (−0.42 to 0.03)	−0.24 (−0.49 to 0.01)	−0.27 (−0.55 to 0.02)
Pi_{15}	Mean difference (95% CI)	1 (ref)	**−0.01* (−0.02 to −0.002)**	−0.00 (−0.02 to 0.01)	−0.01 (−0.02 to 0.00)
Emphysema, %	Mean difference (95% CI)	1 (ref)	8.17 (−1.33 to 18.57), 1.082	3.38 (−6.59 to 14.41), 1.034	4.12 (−6.92 to 16.53), 1.041
Gas trapping, %	Mean difference (95% CI)	1 (ref)	−2.18 (−8.33 to 4.59), 0.97	−0.01 (−7.08 to 7.50), 0.99	5.86 (−2.32 to 14.71), 1.06

Definition of abbreviations: 6MWD = 6-minute-walk distance; ATS/ERS = American Thoracic Society/European Respiratory Society; BDR = bronchodilator responders; CI = confidence interval; CT = computed tomography; FEV_1 = forced expiratory volume in 1 second; mMRC = modified Medical Research dyspnea scale; OR = odds ratio; Pi_{15} = square root wall area of a 15-mm diameter airway; QOL = quality of life; ref = reference; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire; WA = wall area.
Mean value of the outcome is modeled; regression coefficient corresponds to mean difference of the outcome. The displayed coefficients (percentage difference and 95% CI) for SGRQ are back-transformed regression coefficients (e^{β}) that correspond to the relative ratio between the two groups in percent. All models were controlled for sex, age, race, body mass index, smoking history, and initial prebronchodilator FEV_1. In addition, models with CT outcomes were adjusted for CT scanner type. Significant associations are marked in bold. Negative response group was set as the reference category.
* $P < 0.05$.
† $P < 0.0001$.

Pi_{15} increased from minimal to marked BDR ($P < 0.0001$). The marked BDR-FEV_1 group had significantly greater segmental WA% and Pi_{15} than minimal, mild, and moderate BDR-FEV_1 groups and nonresponders (adjusted $P = 0.0005$ for *post hoc* comparisons; not shown). 6MWD increased from 408 ± 123 m to 431 ± 117 m as BDR-FEV_1 increased from minimal to marked ($P < 0.0001$). We also observed significant differences in SGRQ and mMRC scores and in exacerbation frequency between BDR-FEV_1 groups (Table 2).

After adjusting for potential confounders, including sex, age, and baseline FEV_1, patients with greater BDR-FEV_1 had greater 6MWD, better SGRQ, fewer exacerbations, and lower mMRC (Table 2). There was a significant decrease in the odds of being in a higher mMRC category as BDR-FEV_1 category increased from minimal to marked. Mean WA% and Pi_{15} of marked BDR-FEV_1 were 0.29% and 0.03 mm greater than among negative responders, respectively. 6MWD was 37 m greater in marked BDR than in negative responders. SGRQ was 12% less in moderate and marked BDR-FEV_1 groups than in negative responders. Relative risks of annualized exacerbation rates were 26% and 14% decreased in marked and moderate FEV_1 bronchodilator responders compared with the negative category, respectively (relative risk, 0.86 [$P = 0.044$] and 0.74 [$P < 0.00001$], respectively). However, mean WA% and Pi_{15} were 0.24% and 0.01 mm less in minimal FEV_1 bronchodilator responders than in negative responders. In models assessing the relationship between ΔFEV_1L and $\Delta FEV_1\%$ as continuous variables (Figure 2A), 6MWD increased with an upward slope as ΔFEV_1L increased, whereas 6MWD decreased with a downward slope as $\Delta FEV_1\%$ increased, in participants with a positive BDR. The relation between SGRQ score with $\Delta FEV_1\%$ had an upward slope in positive BDR. The relationship of $\Delta FEV_1\%$ with both WA segmental percentage and Pi_{15} was more pronounced with a steeper upward slope than for ΔFEV_1L.

Comparison of BDR-FEV_1 Grading Strategy with BDR by ATS/ERS Criteria

Comparison of BDR using ATS/ERS criteria with the proposed BDR grades shows striking differences (Table 5). ATS/ERS criteria identify only 20.6% of patients as

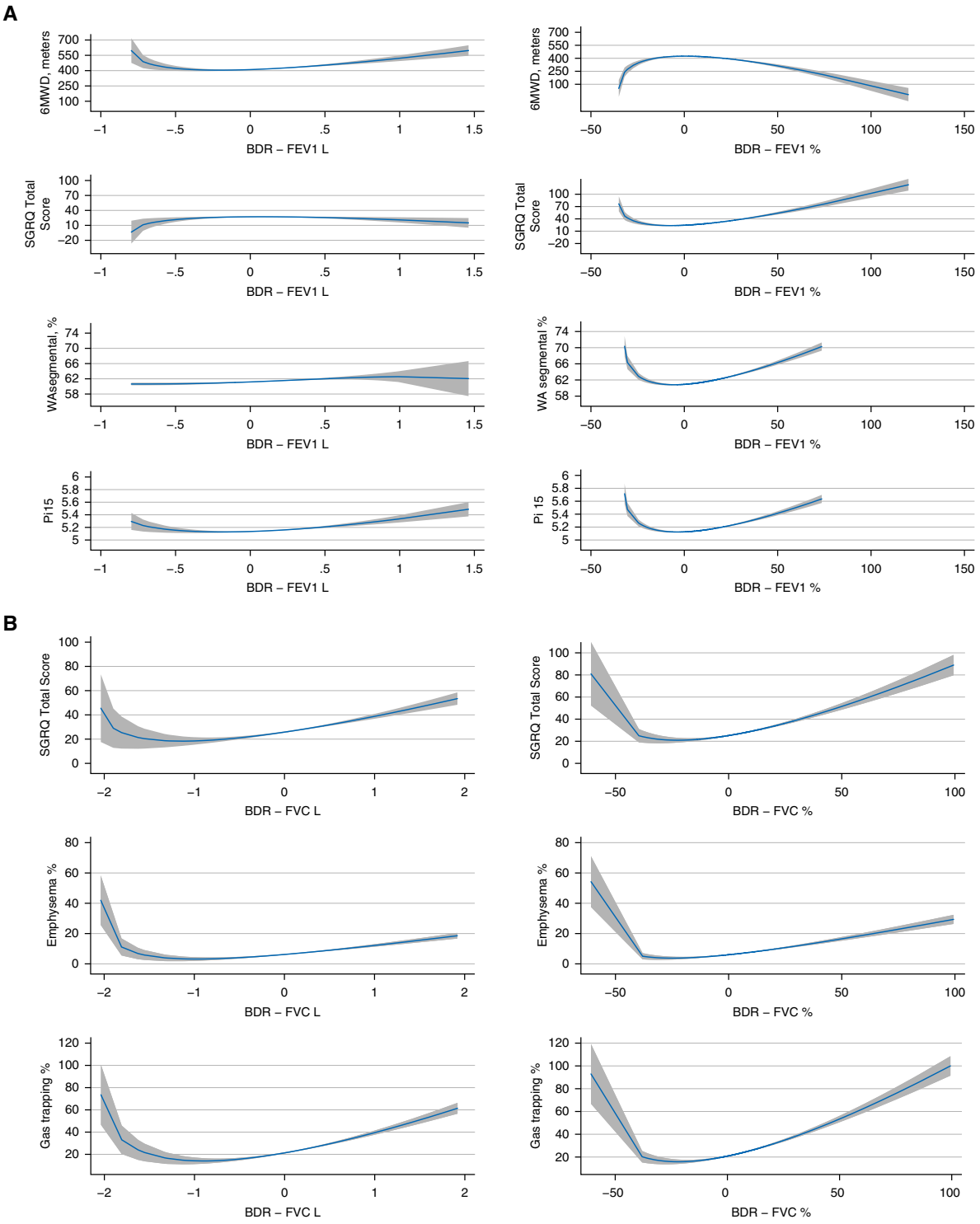

Figure 2. Restricted cubic spline models of bronchodilator response (BDR; as separate continuous variables change in forced expiratory volume in 1 second in liters [ΔFEV_1 L], change in forced expiratory volume in 1 second percent predicted [$\Delta FEV_1\%$], change in forced vital capacity in liters [ΔFVC L], and change in forced vital capacity percent predicted [ΔFVC%]), with 95% confidence intervals (in gray), for 6-minute-walk distance (6MWD), total St. George's Respiratory Questionnaire (SGRQ) score, and quantitative computed tomography (CT) measures in the total study population. (*A*) The adjusted models of BDR (FEV_1L and BDR − $FEV_1\%$) for 6MWD, SGRQ, wall area (WA) segmental percentage, and square root wall area of a 15-mm diameter airway (Pi_{15}). (*B*) The adjusted models of BDR − FVCL and BDR − FVC% for SGRQ, emphysema percentage, and gas trapping percentage. ΔFEV_1L, $\Delta FEV_1\%$, ΔFVCL, and ΔFVC% were coded using a restricted cubic spline function with three knots, located at the 5th, 50th, and 95th percentiles. Models were adjusted for age, sex, race, smoking history, body mass index, baseline FEV_1 or FVC, and CT scanner type (for CT measures).

Table 4. Characteristics of the study population

Variables	Study Population (*N* = 7,741)
Age, yr	60.2 ± 8.9
Sex, male, %	54.5
Race, white/African American, %	72.7/27.3
BMI, kg/m^2	28.6 ± 6.1
Smoking history, pack-years (IQR)	40.0 (28.0–55.5)
Prebronchodilator spirometry	
FEV, L	2.14 ± 0.93
FEV_1, % predicted	72.2 ± 26.0
FVC, L	3.28 ± 1.03
FVC, % predicted	85.4 ± 19.2
FEV_1/FVC, %	63.6 ± 15.4
FEV_1/FVC <70%, *n* (%)	4,298 (55.5)
Post-bronchodilator spirometry	
FEV_1, L	2.24 ± 0.93
FEV_1, % predicted	75.6 ± 25.8
FVC, L	3.37 ± 1.01
FVC, % predicted	87.8 ± 18.5
FEV_1/FVC, %	65.1 ± 16.0
FEV_1/FVC <70%, *n* (%)	3,864 (49.9)
Within-subject coefficient of variation among 3 forced exhalations	
CV for 3 pre-BD FEV_1, %	4.12 ± 2.77
CV for 3 pre-BD FVC, %	3.54 ± 2.46
CV for 3 post-BD FEV_1, %	3.52 ± 2.54
CV for 3 post-BD FVC, %	3.02 ± 2.18
Change after bronchodilator	
ΔFEV_1, L	0.099 ± 0.015
ΔFVC, L	0.092 ± 0.030
ΔFEV_1, %	6.04 ± 9.34
ΔFVC, %	3.78 ± 10.48

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; CV = coefficient of variation; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range. Mean ± SD or median (25th–75th IQR) presented as appropriate. Reported pulmonary function values are based on largest measurements.

positive BDR, 79.4% in the marked category, 32.3% in the moderate category, and only 8.8% in minimal and mild BDR-FEV_1 categories. Almost four-fifths of the marked BDR group (794 of 1,000) was also ATS/ERS positive. When we analyzed correlates of BDR grades after excluding ATS/ERS positives in the minimal, mild, and moderate BDR categories, we observed that minimal, mild, and moderate BDR-FEV_1 were associated with greater 6MWD and lower SGRQ than in the negative BDR category. Odds of being in a higher mMRC category decreased as BDR-FEV_1 increased from minimal to moderate when compared with nonresponders (Table 3).

BDR Grading Strategy Applied for BDR in FVC

By using proposed BDR cutoffs, 16.4%, 12.0%, 12.1%, and 22.2% of the population had minimal, mild, moderate, and marked FVC-BDR, respectively (Table 2). Of the study population, 37.3% had a negative BDR in FVC. Prebronchodilator FEV_1, FVC, and FEV_1/FVC decreased as volume response increased from minimal to marked FVC-BDR. In the univariate analyses (Table E1), total SGRQ and dyspnea scores, exacerbation frequency, segmental WA%, emphysema percentage, and gas trapping percentage increased as FVC-BDR increased from negative to marked ($P < 0.0001$).

After adjusting for potential confounders, including baseline FVC, patients with greater BDR-FVC had greater emphysema and gas trapping and fewer exacerbations and lower mMRC (Table 2). Emphysema and gas trapping were 50% and 46% greater, respectively, in marked BDR than in negative responders. Mean WA% and Pi_{15} of marked BDR-FVC were 0.67% and 0.04 mm greater than in negative responders, respectively. 6MWD was approximately 14 m greater in marked BDR-FVC than in negative responders. SGRQ was 9% and 14% higher in moderate and marked BDR-FVC than in negative responders. Participants in mild, moderate, and marked BDR-FVC categories were less likely than negative responders to experience exacerbations. There were significantly decreased odds of being in a higher mMRC category in moderate and marked BDR-FVC categories. However, mean Pi_{15} was 0.02 mm less in minimal BDR-FVC group than in negative BDR-FVC responders.

In models assessing the relationship between ΔFVCL and ΔFVC% as continuous variables (Figure 2B), total SGRQ score, emphysema percentage, and gas trapping percentage were lowest in the region of ΔFVCL and ΔFVC% levels around −1.5 L and −40%, respectively. After those regions, there was a trend of increasing total SGRQ score, emphysema percentage, and gas trapping percentage with an upward slope as ΔFVCL and ΔFVC% increased.

Discussion

Our approach of identifying distribution characteristics of BDR is an improvement in evaluating clinical and radiological associations of bronchodilator responsiveness. Grading systems using several categories might be more useful than those yielding only positive/negative categories. These data demonstrate the importance of separating volume and percentage BDR change rather than requiring both simultaneously, which biases against identifying meaningful BDR in subjects with small or large FEV_1.

Our categorization employs identical numerical fractions for ΔFEV_1 in liters and in percentage units. It yields many more positive responders than ATS/ERS positive criteria do (Table 5). Logically, patients with low FEV_1 should benefit more from small FEV_1 volume increases than those with large FEV_1. Advantageously, for the 7,741 individuals studied, our grading method identified 80% with at least minimal and 50% with moderate or greater FEV_1 BDR, whereas the ATS/ERS method identified only 20.6% positive.

Interpretation of BDR for patients with OAD in pulmonary laboratories has long been disputed. Nearly 50 years ago, Freedman and colleagues suggested that most physicians would agree that an FEV_1 increase less than 10% is valueless and that a 20–30% increase was likely useful (24). In 1974, a *Chest* advisory committee

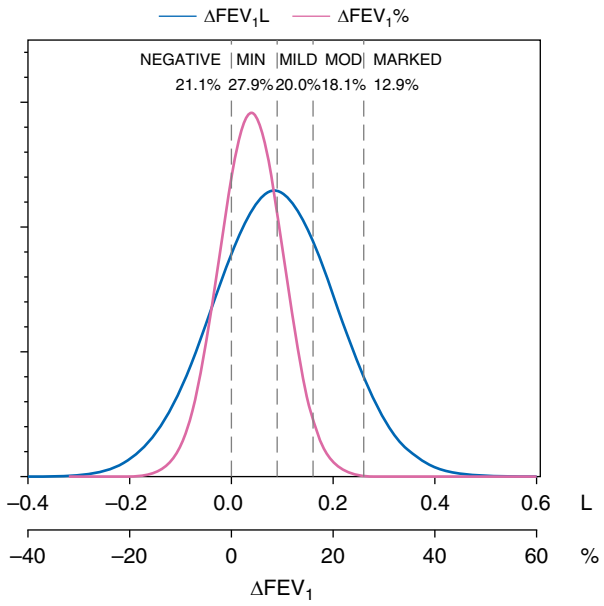

Figure 3. Distribution of change in absolute volume for largest of three pre- to post-bronchodilator forced expiratory volume in 1 second (FEV_1) differences (ΔFEV_1L) and change in FEV_1 percent predicted after bronchodilator in the whole study population ($N = 7,741$). Dashed vertical lines represent the limits of the new bronchodilator response (BDR) grading system (negative, ⩽0.00% or ⩽0.00 L; minimal [MIN], >0.00% to ⩽9.00% or >0.00 L to ⩽0.09 L; mild, >9.00% to ⩽16.00% or >0.09 L to ⩽0.16 L; moderate [MOD], >16.00% to ⩽26.00% or >0.16 L to ⩽0.26 L; and marked, >26.00% or >0.26 L). Percentages of participants in each BDR category are given between vertical lines that represent the limits of the BDR grading system. Curves were constructed as Gaussian fits on the histogram points consisting of 24 bins with equal distance of 0.0905 L spanning from −0.63 L to 1.45 L for ΔFEV_1L and 6.46% wide bins from −31.8 to 116.8% for ΔFEV_1% change. N.B.: To demonstrate the similarities and differences in distributions, only the segments from −0.4 L to 0.6 L and from −40% to 60% changes are shown.

recommended positive BDR required FEV_1 change in both percent and absolute volume (25). In 1982, Reis recommended an FEV_1 increase of both 15% and 200 ml (26). Eliasson and colleagues (27), reviewing 66 asthma and COPD papers, found that 14 papers used seven different BDR criteria. In 1991, an ATS committee recommended increase in FEV_1 or FVC greater than or equal to 200 ml and 12% (28). This criterion was reinforced in the 2005 ATS/ERS guidelines (1). Considering that baseline FEV_1 values of individuals assessed for BDR vary over a wide range (29), to exceed healthy population-based confidence intervals (30) for both volume and percentage values to establish positive BDR may be too restrictive.

In a 2011 review, Hanania and colleagues (31) examined the five most prevalent recommendations: including FEV_1 percent predicted greater than 10% (ERS [32]), FEV_1 increase greater than 15% (American College of Chest Physicians [25]) and greater than 12% and 200-ml increase (ATS [28], ATS/ERS [1], and Global Initiative for Chronic Obstructive Lung Disease [19]). In response to a letter by Hansen and colleagues (33), Hanania and colleagues agreed that BDR less than 200 ml in those with low baseline FEV_1 was clinically valuable (34). In 2005, Donohue (13) recommended that greater than 100 ml FEV_1 increase in patients with OAD is likely to be clinically important.

BDR may be expressed in alternate ways: as absolute change in values, as percentage change from baseline, or as change as a percentage of the subject's predicted value (35, 36). Using change in FEV_1 as percent predicted was recently shown to avoid sex and size bias in the assessment of BDR (35). Although there is no consensus on how a BDR should be expressed in the literature, most guidelines express BDR as absolute change in values and as percentage change from baseline, so we employed this strategy. In addition, in the presence of severe airway disease such as COPD, the baseline FEV_1 may be far off the predicted value, which may cause an underestimation of the BDR as compared with performance of the subject variable (change in FEV_1 as percent predicted) in relatively healthier or nonsmoker populations.

BDR Category Assignments

Dividing BDR data into grades has often used only mean and SD values. In our study population, using a grading approach based on ΔFEV_1L or ΔFEV_1% distribution and means (Figure 3) might cause an unbalanced strategy, because ±1 SD of volume change would assimilate approximately 68% of participants into one BDR class, with the remaining approximately 32% divided into several much smaller classes (e.g., ±2 SD, ±3 SD). Instead, our grading strategy is based on profile of changes in volume and percentage change in FEV_1 (Figure 1) and other considerations to establish grading category cutoffs. This resulted in BDR of this population being classified 21% negative, 28% minimal, 20% mild, 18% moderate, and 13% marked.

Of the 7,741 participants, 21.1% had negative BDR by FEV_1 compared with 37.3% by BDR-FVC. Although BDR-FVC was reported more frequently than BDR-FEV_1 in patients with COPD (37, 38), we observed that BDR by FEV_1 was more common than BDR by FVC in our study population. FVC has the disadvantage of being dependent on expiratory time (39). Therefore, evaluation of BDR by FVC may be noisy (40). Figure 4 shows that, for ΔFEV_1L BDR greater than 100 ml, the number of individuals meeting any specific volume criterion is much greater for FVC than for FEV_1, whereas for those meeting ΔFEV_1% criteria greater than 10% are similar for FVC and FEV_1. In patients with COPD, the magnitude of the flow (ΔFEV_1) and volume (ΔFVC) responses after administration of albuterol differs. A particular flow response is accompanied by a higher volume response as the severity of airflow obstruction worsens in COPD. In our study, ΔFEV_1 and ΔFVC responses were similar between BDR categories (Table 1). This finding may be a result of our study population consisting of smokers, with almost 50% without airflow obstruction.

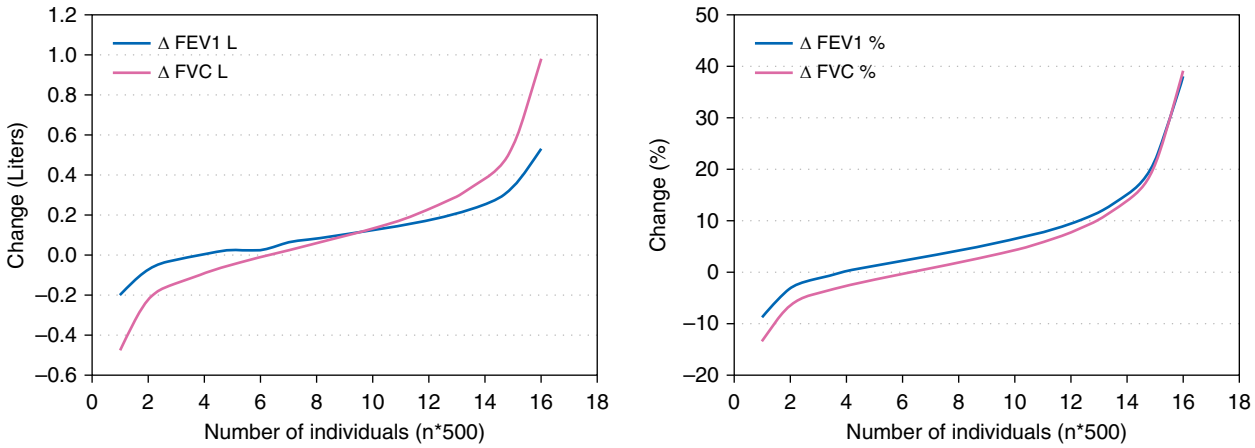

Figure 4. Response trend of change in forced expiratory volume in 1 second (ΔFEV_1) and change in forced vital capacity (ΔFVC) after bronchodilator in the total study population ($N = 7{,}741$). (*A*) Response trend of mean change in absolute volume of ΔFEV_1L and $\Delta FVCL$ in 500 individuals at each point. (*B*) Response trend of mean change in $\Delta FEV_1\%$ and $\Delta FVC\%$ in 500 individuals at each point. In both *A* and *B*, individuals are ordered by size of response.

Clinical Implications of BDR Grades

Our results indicate that spirometric indices and CT measures of airway wall thickness increase as BDR increases. In accordance with reports suggesting inverse correlation between spirometric obstruction and BDR, baseline FEV_1/FVC decreased as BDR increased (27). We observed significant increase in segmental WA% and Pi_{15} as BDR increased from minimal to marked (Table 1). Similar trends persisted when we adjusted CT outcomes for baseline FEV_1 and other potential confounders. Kim and colleagues found that airway wall thickness independently predicted BDR in COPD and suggested that increased CT airway wall thickness in the BDR positive COPD group represented airway pathology dominated by smooth muscle hypertrophy (41). Morphometric studies in patients with asthma revealed bronchial tree zones with significant muscular hypertrophy, reflecting hyperreactivity of these segments (42). Both the segmental WA% and Pi_{15} mainly reflect large airways. We believe that our findings showing significant BDR dependence in segmental WA% and Pi_{15} may reflect an increased bronchomotor tone due to smooth muscle hypertrophy in the large airways of smokers with marked BDR.

To our knowledge, our results indicate for the first time that 6MWD, a marker of functional exercise performance, significantly and continuously increases as acute BDR grade increases. This finding is in agreement with Anthonisen and Wright's initial observations of a relatively well-preserved exercise tolerance in patients with COPD with large BDRs (43). The mechanism underlying this observation is not known, but one possible explanation is that patients with a larger BDR are able to bronchodilate during the hyperpnea of exercise. Despite the relationship between 6MWD and ΔFEV_1L being similar to that of 6MWD and BDR-FEV_1 response grades, the relationship between 6MWD and $\Delta FEV_1\%$ was inverse (Figure 2A). One possible explanation for the difference between results of continuous modeling of 6MWD versus $FEV_1\%$ and $\Delta FEV_1\%$ may be that greater than 90% of the responders in each BDR category were positive by volume change in FEV_1. For that reason, associations with BDR grades may be dominated by associations with volume change in FEV_1.

Recently, Quanjer and colleagues suggested that an ideal BDR measure should be based on clinical outcomes, such as exacerbations, quality of life, and hospitalizations (12). Not long before, Albert and colleagues suggested that BDR did not distinguish clinical outcomes such as mortality or exacerbation rates in the ECLIPSE COPD (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort (44). We observed a significant increase in quality of life as BDR grade increased from minimal to marked. In support of this, a higher SGRQ score was reported in poorly responsive patients with moderate to very severe COPD in the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial (45). Moreover, to our knowledge, our analysis is the first to show exacerbation frequency reduction without regard to baseline FEV_1 in patients with moderate and marked BDR compared with negative responders. Our analysis characterizes a group of marked BDR with more airway disease, evidenced by greater segmental WA% and Pi_{15}, better-preserved exercise performance and dyspnea, better quality of life, and fewer exacerbations than in negative responders. Associations observed for 6MWD in the multivariable models are greater than their MCIDs (46, 47). Associations for exacerbations and CT measures can only be evaluated statistically, because validated MCIDs for those outcomes do not yet exist (48).

When we applied a BDR grading strategy for an FVC-based BDR, we observed that emphysema percentage and gas trapping percentage increased as BDR in FVC increased from minimal to marked category. Emphysema and gas trapping were prominent features of BDR-FVC responders in accordance with previous reports (49–51). Cerveri and colleagues have shown that FVC responder patients with COPD have more severe emphysema than both FEV_1 and FVC responders (49). Furthermore, Deesomchok and colleagues have shown that patients with COPD with greatest resting lung hyperinflation show the largest bronchodilator-induced volume

Table 5. Comparison of bronchodilator responses using ATS/ERS guidelines and proposed bronchodilator response grades

	BDR Grades				
	Negative	Minimal	Mild	Moderate	Marked
Total number of participants	1,634	2,159	1,549	1,399	1,000
Only $\Delta FEV_1\% \geq 12\%$	0	0	146	489	769
Only $\Delta FVC\% \geq 12\%$	27	121	216	345	505
Only $\Delta FEV_1L \geq 0.2$ L	0	0	0	632	955
Only $\Delta FVCL \geq 0.2$ L	88	269	448	663	761
$\Delta FEV_1L \geq 0.2L$ and $\Delta FEV_1\% \geq 12\%$	0	0	0	224	724
$\Delta FVCL \geq 0.2L$ and $\Delta FVC\% \geq 12\%$	26	111	215	338	501
BDR(+) by ATS/ERS $\Delta FEV_1L \geq 0.2L$ and $\Delta FEV_1\% \geq 12\%$ or $\Delta FVCL \geq 0.2L$ and $\Delta FVC\% \geq 12\%$	26	111	215	452	794

Definition of abbreviations: ATS/ERS = American Thoracic Society/European Respiratory Society; BDR = bronchodilator response; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
Number of participants in each category is presented. ATS/ERS guidelines ($\Delta FEV_1L \geq 0.2L$ and $\Delta FEV_1\% \geq 12\%$ or $\Delta FVC \geq 0.2L$ and $\Delta FVC\% \geq 12\%$) and proposed BDR grades (based on range of ΔFEV_1L or $\Delta FEV_1\%$). All models were controlled for sex, age, race, body mass index, smoking history, and initial pre-bronchodilator FEV_1. In addition, models with computed tomography (CT) outcomes were adjusted for CT scanner type.

response in reversibility testing (50). The greater volume response than flow response in patients with COPD was explained by the presence of a higher loss of lung elastic recoil due to emphysema and compression of small airways by the enlarged airspaces as the airflow obstruction worsened (49). In addition to previously reported findings, the BDR grading strategy defined in the present study was successful in capturing an increasing trend in emphysema and gas trapping extent as BDR in FVC increased from minimal to marked response categories compared with nonresponders.

BDR-FVC is associated with gas trapping. This finding is in agreement with literature findings (51, 52). Gas trapping on quantitative CT is accepted as a prominent sign of small airway disease. In support of this, small airway diameter on spiral CT scan was previously shown to narrow in FVC responder patients with COPD (49). There was an inverse association with BDR-FVC response and exacerbation frequency in patients with mild to marked BDR-FVC compared with negative responders. Furthermore, quality of life was impaired in moderate and marked BDR-FVC compared with negative responders. We theorize that impaired quality of life and increased exacerbation frequency observed in these patients may be a consequence of severe hyperinflation and emphysema present in moderate and marked BDR-FVC responders.

In this study, we demonstrate that BDR-FEV_1 and BDR-FVC are associated with different clinical, functional, and radiological characteristics. Although increasing BDR in FEV_1 is primarily associated with improving 6MWD, quality of life, and dyspnea, increasing BDR in FVC is primarily associated with increasing emphysema and gas trapping. Moderate or marked BDR in both measures is associated with a reduction in exacerbation frequency.

A very recent paper aimed to examine clinical, functional, and radiological associations of BDR by ATS/ERS criteria (51). In subjects with spirometrically defined COPD, the authors have shown that ATS-BDR positive participants in the COPDGene population were associated with higher gas trapping percentage, Pi_{10}, functional small airway disease, functional residual capacity and total lung capacity percent predicted, respiratory exacerbations, and 6MWD than the non-BDR group. In our study, in which we examined the responses of subjects with smoking history with and without spirometric evidence of COPD, ATS/ERS criteria identified most of the participants (79.4%) in the marked category as positive BDR. Despite this important clinical association of the ATS/ERS BDR criteria (51), when we excluded BDR positive participants by ATS/ERS criteria, we observed that clinical associations of BDR grading strategy persisted for 6MWD, SGRQ, and mMRC in the adjusted multivariable analysis: Patients with greater BDR had greater exercise performance, better quality of life, and less dyspnea perception (Table 3).

We observed that 21.1% of our study group had a negative response (defined as $\leq$0.00% or $\leq$0.00 L FEV_1 change) to albuterol. Recently, Bhatt and colleagues showed that a paradoxical response to β_2-agonists resulting in bronchoconstriction was associated with respiratory morbidity measured by higher mMRC, frequent exacerbations, and lower 6MWD (53). Probably, some of the participants in the negative response category in our study can be regarded as having a paradoxical response to β_2-agonists. Despite the negative category being set as the reference category in our analyses, our results are partly in accordance with those of Bhatt and colleagues by showing a decreasing quality of life and 6MWD as BDR decreased, increasing odds for experiencing a higher dyspnea level as BDR decreased, and decreasing odds for frequency of exacerbations in patients with marked and moderate BDR compared with the negative response category.

In the whole study group, patients with minimal BDR-FEV_1 compared with those with mild, moderate, and marked BDR-FEV_1 had lower exercise performance, lower quality of life, and more dyspnea perception (Table 2). It seems logical to assume that the minimal BDR-FEV_1 group is likely to have fixed airway obstruction, because their airways respond minimally to albuterol inhalation.

Relevance to Asthma–COPD Overlap Phenotype

Bronchodilator responsiveness is accepted as the key feature of asthma–COPD overlap (ACO) phenotype (54). Although different definitions for ACO are used in various studies, a spirometric component of a widely used ACO definition requires a marked BDR (>400 ml) or at least a positive BDR ($\geq$200 ml and 12%) in addition to persistent airflow limitation (54–56). It might be asked whether the characteristics of the participants with marked BDR in our study resembled clinical features of patients with ACO. Cosentino and colleagues found that subjects with ACO had less severe spirometric and radiological findings (less emphysema and gas trapping) but more segmental airway wall thickening and that

they were more likely to experience frequent exacerbations than subjects with COPD (57). Although there are several published studies aiming to characterize clinical features of ACO phenotype in the COPDGene population (57–59), their analysis is usually limited to comparing features of patients with ACO with either COPD or asthma alone, rather than comparing ACO characteristics with an overall smoker population. Having shown clinical implications of various degrees of BDR (much less than 400 ml), we suggest considering the use of bronchodilator grading, rather than an all-or-none evaluation system, for further ACO phenotyping studies.

Tweeddale and colleagues (15) reported that, in patients with reduced FEV_1/FVC ratio, absolute FEV_1 increase required to exclude natural variability with 95% confidence was 160 ml. In this context, minimal and mild categories in the proposed BDR grading system fall in the range of this natural variability. In our analysis, however, we observed that minimal and mild BDR categories are associated with important patient-centered outcomes in COPD (greater 6MWD, lower SGRQ and mMRC dyspnea scores) compared with negative BDR. The fact that BDR below variability thresholds may associate with symptom and performance improvements (perhaps because BDR may be unpredictably underestimated by FEV_1 and/or FVC changes in some cases) is also acknowledged in ATS/ERS 2005 guidelines (10). Furthermore, BDR to a short-acting bronchodilator is no longer recommended to predict long-term response and is not believed to be helpful in making therapeutic decisions (12). Therefore, we believe that this study's findings are helpful to characterize clinical associations of bronchodilator responsiveness rather than using them to make therapeutic decisions. We hope that our findings, in addition to recently reported studies that characterize BDR (12, 35), will spur guideline committees to revisit current BDR criteria.

Our study has several limitations. Although we used a large population, it includes only current smokers and ex-smokers. A population-based sample of 3,922 healthy nonsmokers showed that the upper 95% confidence limit for BDR was 284 ml for ΔFEV_1 and 12% for ΔFEV_1% (30). In the ECLIPSE cohort, FEV_1 changes after an inhaled bronchodilator in smoking control subjects and patients with COPD were significantly greater than in nonsmoking control subjects (35, 44). Importantly, healthy never-smokers were not included in our cohort, which restricts generalizability of our results to this group. Second, whether other inhaled bronchodilators or other albuterol doses should be similarly graded is untested. Third, observations from various cohorts have shown that the presence of BDR is variable over time (44, 60, 61). Unfortunately, our study does not include longitudinal analysis of the study cohort to allow examination of long-term implications of BDR categorization. Fourth, when defining thresholds for the BDR grading system, in distinguishing between moderate and marked responses, a 100-ml MCID step size was used. However, 100 ml as an MCID for FEV_1 was based on a single study that enrolled only patients with COPD, which limits the generalizability of the 100-ml MCID value to populations other than COPD (13). Fifth, we acknowledge that the thresholds for the BDR grading system were derived for FEV_1 change. These thresholds may not be fully applicable to FVC change. Further study will be necessary to determine whether different thresholds may perform better for FVC response.

Last, blood eosinophils have strong potential as a prognostic and therapeutic biomarker in the clinical management of COPD. Evaluation of the association of bronchodilator responsiveness with blood eosinophil count would be a promising analysis for further research.

In conclusion, BDR in current smokers or ex-smokers can be graded by using either volume or percentage change in FEV_1 or FVC. Our findings, based on the largest smoker population with quantitative CT data, suggest that this BDR grading system identified patients with clinically important differences in exercise performance, quality of life, exacerbation frequency, dyspnea, and pulmonary imaging. BDR-FEV_1 and BDR-FVC are associated with different clinical, functional, and radiological characteristics. Whether these BDR categories have prognostic implications remains to be tested. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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