




# Bronchodilator Responsiveness Defined by the 2005 and 2021 ERS/ATS Criteria in Patients with Asthma as Well as Chronic Obstructive Pulmonary Disease

Yun Li , Junfeng Lin\*, Zihui Wang\*, Zhufeng Wang, Lunfang Tan, Shuyi Liu, Jinhai Huang, Yi Gao , Jinping Zheng 

National Clinical Research Center for Respiratory Disease, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Yi Gao; Jinping Zheng, National Clinical Research Center for Respiratory Disease, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Road, Yuexiu District, Guangzhou, 510120, People's Republic of China, Tel +86 20 83062869, Fax +86 20 83062729, Email misstall2@163.com; jpzhenggy@163.com

**Background:** In the 2021 ERS/ATS interpretive strategies for routine lung function tests, a positive bronchodilator response (BDR) was updated as a change of >10% relative to the predicted value in forced expiratory volume in 1 second (FEV<sub>1</sub>) or forced vital capacity (FVC). We aimed to explore the differences between the 2005 and 2021 ERS/ATS criteria applied to patients with asthma as well as chronic obstructive pulmonary disease (COPD).

**Methods:** BDR test data about asthma patients aged 6–80 years and COPD patients aged 18–80 years were derived from the National Respiratory Medicine Center, First Affiliated Hospital of Guangzhou Medical University, from January 2017 to March 2022. BDR results defined by the 2005 and 2021 ERS/ATS criteria were named 2005-BDR and 2021-BDR, respectively. We compared differences between 2005-BDR and 2021-BDR and analyzed the trend in the proportion of positive BDR (BDR+) with the level of airflow obstruction.

**Results:** A total of 4457 patients with asthma and 7764 patients with COPD were included in the analysis. The percentages of 2005-BDR+ and 2021-BDR+ were 63.32% and 52.84% for asthma, 30.92% and 22.94% for COPD, respectively. Of patients with 2005-BDR+, 81.86% for asthma and 70.18% for COPD showed 2021-BDR+ results, and these patients had higher FEV<sub>1</sub>%pred, FVC%pred (all  $P < 0.05$ ). Whichever BDR criterion was adopted, the proportion of BDR+ had an upward linear trend with the increased degree of airflow obstruction in COPD, but exhibited an approximate inverted U-shaped curve in asthma. In COPD, the proportion of BDR<sub>FEV<sub>1</sub></sub> was negatively associated with the degree of airflow obstruction, while BDR<sub>FVC</sub> was positively associated (all  $P < 0.05$ ).

**Conclusion:** Compared with 2005-BDR+, the proportion of 2021-BDR+ reduced markedly in patients with asthma and COPD, but their trends with the degree of airflow obstruction did not change. Patients with consistent BDR+ had higher initial FEV<sub>1</sub>%pred and FVC%pred.

**Keywords:** pulmonary function test, bronchodilator responsiveness testing, asthma, chronic obstructive pulmonary disease, European Respiratory Society, ERS, American Thoracic Society, ATS

## Introduction

Pulmonary function tests (PFTs) have played a vital role in the screening, diagnosis and management of respiratory diseases. In order to improve the quality control and interpretation of PFTs, a series of technical documents have been jointly published by the American Thoracic Society (ATS) and European Respiratory Society (ERS).<sup>1–7</sup> Bronchodilator responsiveness (BDR) testing, widely used to assess the degree of volume and airflow improvement in response to an

inhaled short-acting bronchodilator, is considered to be a key diagnostic criterion for asthma,<sup>8</sup> as well as differentiating asthma from chronic obstructive pulmonary disease (COPD).

However, recommendations on how to express a bronchodilator response are still controversial. Three approaches are commonly used to express BDR, including an absolute change from the initial value, a relative change to the initial value, and a change relative to the predicted value. The 2005 ERS/ATS interpretive strategies for routine lung function tests recommended that a change in forced expiratory volume in 1 second (FEV<sub>1</sub>) or forced vital capacity (FVC)  $\geq 12\%$  and  $\geq 200\text{mL}$  of the initial value was defined as significant BDR.<sup>3</sup> Nevertheless, the absolute and relative changes in FEV<sub>1</sub> and FVC are closely associated with initial lung function, and biased toward height, age and sex in both health and disease.<sup>9–11</sup> Furthermore, requiring a fixed minimum change in FEV<sub>1</sub>  $\geq 200\text{mL}$  seems unrealistic, since in many subjects with a low baseline FEV<sub>1</sub>, especially children and elder adults, the FEV<sub>1</sub> increased  $>12\%$  of baseline but  $<200\text{mL}$ .<sup>11</sup>

Previous studies showed that BDR expressed as the percent change relative to the individual's predicted value might minimize sex and size bias.<sup>10,11</sup> In a study involving 3922 healthy individuals, the 95th percentile of BDR was estimated to be 10.0% (9.5% to 10.5%) of predicted value for FEV<sub>1</sub> and 9.2% (7.9% to 10.5%) of predicted value for FVC.<sup>12</sup> In another study of 2371 healthy non-smokers, the 95th percentiles of BDR in FEV<sub>1</sub> and FVC were 11.6% and 10.2%, respectively.<sup>11</sup> For the preschool children aged 3–5 years, the 95th percentiles of the change in FEV<sub>1</sub>, FEV<sub>0.75</sub>, FEV<sub>0.5</sub>, and FEF<sub>25–75%</sub> relative to the predicted value following bronchodilator were 11.6%, 16.0%, 8.5%, and 35.5%, respectively.<sup>13</sup> Therefore, based on these considerations, the 2021 ERS/ATS interpretive strategies updated the positive response as a change of  $>10\%$  relative to the predicted value for FEV<sub>1</sub> or FVC.<sup>14</sup> For example, a man has a pre-bronchodilator FEV<sub>1</sub> of 2.0L, a post-bronchodilator FEV<sub>1</sub> of 2.4L and his predicted FEV<sub>1</sub> is 3.2L, then the BDR =  $(2.4 - 2.0) \times 100 / 3.2 = 12.5\%$ , which is  $>10\%$  and classified as a positive response.

However, there are limited data about making a comparison between the two criteria applied to clinical practice. Since BDR is mostly used in the diagnosis of obstructive pulmonary diseases, the present study aimed to compare the differences between the two BDR criteria in a large sample of patients with asthma as well as COPD.

## Materials and Methods

### Methods

This was a retrospective study and was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of First Affiliated Hospital of Guangzhou Medical University (2020–124).

### Data Resource and Study Population

The data were derived from the Respiratory Health Big Database of the National Respiratory Medicine Center, First Affiliated Hospital of Guangzhou Medical University. BDR testing reports from January 2017 to March 2022 were extracted from the database and then patients were preliminarily screened according to the International Classification of Diseases Volume 10 (ICD-10) and Systematized Nomenclature of Medicine Clinical Terms (SNOMED) standard terminology. The rationality of the diagnosis was checked by reviewing the electronic medical records. Patients with asthma were clinically diagnosed according to the guideline of the Global Initiative for Asthma (GINA)<sup>8</sup> and aged 6–80 years old. Patients with COPD were diagnosed according to the guideline of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>15</sup> and aged 18–80 years old. Excluded criteria were as followings: patients having a history of interstitial lung diseases or pulmonary tuberculosis or severe bronchiectasis; those with ambiguous diagnosis; those diagnosed with obliterative bronchiolitis; those with missing important parameters such as age, weight, FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC. For the subjects who have performed BDR testing more than once, only the initial report was selected.

### Spirometry Tests

Spirometry tests were performed by trained technicians according to the relevant guidelines by ERS/ATS<sup>2,3,5,7</sup> and Pulmonary Function Group, Respiratory Diseases Society of Chinese Medical Association.<sup>16–18</sup> All the subjects signed consent form before tests. At least three acceptable curves were needed. Each subject inhaled 100 $\mu\text{g}$ /puff sprays of salbutamol (Ventolin, Glaxo Wellcome Products, France) from an inhaler for totally 4 puffs and repeated spirometry after

15 to 30 minutes. Severity of lung function impairment was assessed by FEV<sub>1</sub>%pred with 4 critical values of 70%, 60%, 50% and 35%, namely mild: FEV<sub>1</sub>%pred ≥ 70%, moderate: 60% ≤ FEV<sub>1</sub>%pred < 70%, moderate-severe: 50% ≤ FEV<sub>1</sub>%pred < 60%, severe: 35% ≤ FEV<sub>1</sub>%pred < 50%, extremely severe: FEV<sub>1</sub>%pred < 35%.

## Lung Function Indices and Variable Definitions

Lung function indices were recorded at pre- and post-bronchodilator. The regular indices included FEV<sub>1</sub>, FEV<sub>1</sub>%pred, FVC, FVC%pred and FEV<sub>1</sub>/VCmax (%). The differences between the optimal value of baseline and post-bronchodilator in FEV<sub>1</sub> (or FVC) were called ΔFEV<sub>1</sub>, ΔFVC. To simplify the expression, BDR results defined by the 2005 and 2021 ERS/ATS criteria were named 2005-BDR and 2021-BDR, and the positive and negative BDR were named BDR+ and BDR-, respectively. Patients who had the same 2005-BDR and 2021-BDR results were named consistent group, and those who had reversed results were named inconsistent group. Moreover, three BDR+ subgroups were defined as 2005-BDR<sub>FEV<sub>1</sub></sub>, 2005-BDR<sub>FVC</sub> and 2005-BDR<sub>Both</sub>, which met the requirement of ΔFEV<sub>1</sub>%init ≥ 12% and ΔFEV<sub>1</sub> ≥ 200mL, ΔFVC%init ≥ 12% and ΔFVC ≥ 200mL, and the both of above, respectively. 2021-BDR<sub>FEV<sub>1</sub></sub>, 2021-BDR<sub>FVC</sub> and 2021-BDR<sub>Both</sub> were defined as ΔFEV<sub>1</sub>%pred > 10%, ΔFVC%pred > 10%, and the both of above, respectively.

## Statistical Analysis

Differences were compared between asthma and COPD, between the percentages of 2005-BDR+ and 2021-BDR+, between BDR- and BDR+ groups, between inconsistent and consistent groups. The statistical analysis was performed using SPSS 23 (SPSS, Chicago, Illinois). Results are presented as mean and standard deviation or quartiles for continuous variables and frequency and percentage for categorical variables. Differences in the percentages of 2005-BDR+ and 2021-BDR+ were compared using McNemar test. Differences in baseline characteristics and lung function indices were compared between two groups using a two sample *t*-test (or Wilcoxon rank sum test, if normality was not met) for continuous variables and a Chi-square test for categorical variables. The continuous variables of three or more groups were compared by one-way analysis of variance as appropriate. The trend in the proportion of BDR+ with the level of airflow obstruction was studied using linear by linear association. The *P* value < 0.05 was considered statistically significant.

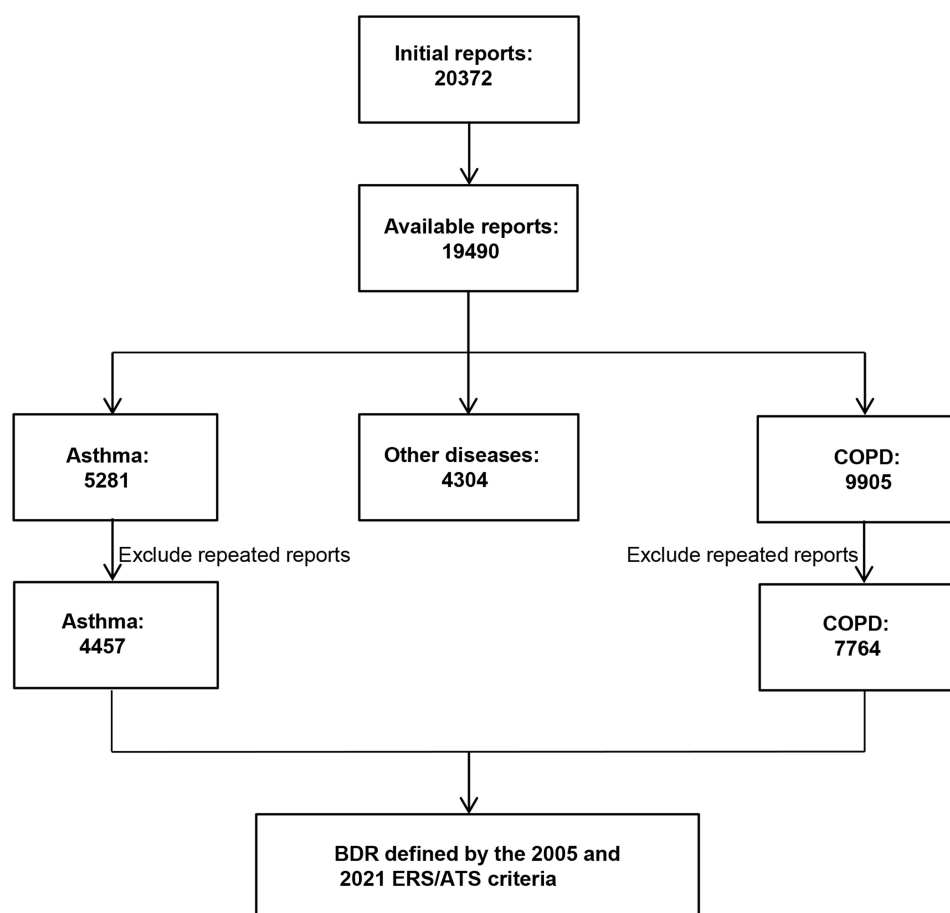
## Results

### Differences in Baseline Characteristics Between Asthma and COPD

A total of 23,072 BDR reports were initially extracted from the database. After rigorous screening, 4457 patients with asthma (male 2201; female 2256) aged 6–80 years and 7764 patients with COPD (male 6817; female 947) aged 18–80 years were included in the final analysis (Figure 1). Compared with asthma patients, COPD patients were greater in percentage of males, age, weight, height [49.4% vs 87.8%, (35, 58) (y) vs (59, 70) (y), 58.39 ± 14.92 (Kg) vs 59.67 ± 10.98 (Kg), 159.12 ± 11.59 (cm) vs 163.68 ± 7.16 (cm), all *P* < 0.05], less in FEV<sub>1</sub>, FEV<sub>1</sub>%pred, FVC%pred and FEV<sub>1</sub>/VCmax [1.57 ± 0.65 (L) vs 1.34 ± 0.66 (L), 58.85 ± 18.81 (%) vs 50.85 ± 22.25 (%), 83.29 ± 18.00 (%) vs 79.66 ± 20.44 (%), 56.03 ± 12.08 (%) vs 48.05 ± 13.00 (%), all *P* < 0.05], and no significant difference in FVC [2.68 ± 0.92 (L) vs 2.65 ± 0.83 (L), *P* = 0.127].

### Differences Between the Percentages of 2005-BDR+ and 2021-BDR+

The percentages of 2005-BDR+ and 2021-BDR+ were 63.32% (2822/4457) and 52.84% (2355/4457) for asthma, and 30.92% (2401/7764) and 22.94% (1781/7764) for COPD, respectively. Compared with 2005-BDR+, the percentage of 2021-BDR+ reduced significantly in both asthma and COPD (*P* < 0.001, Table 1). Both the percentages of 2005-BDR+ and 2021-BDR+ were higher in asthma patients than those in COPD patients (*P* < 0.001). When asthma patients were divided into children group aged 6–17 years and adult group aged 18–80 years, the percentage of 2021-BDR+ (64.6%, 306/474) was similar to that of 2005-BDR+ (63.1%, 299/474) in children but decreased in adults (51.4% vs 63.3%, *P* < 0.001, Table 2).



**Figure 1** Screening the BDR data of asthma and COPD from the database.

## Differences Between BDR- and BDR+, Between Inconsistent and Consistent Groups

As shown in Table 3, compared with 2005-BDR-group, the 2005-BDR+ group had higher percentage of males, height, FEV<sub>1</sub>pred, ΔFEV<sub>1</sub>%init, ΔFEV<sub>1</sub>%pred, FVCpred, ΔFVC%init and ΔFVC%pred but less FEV<sub>1</sub>, FEV<sub>1</sub>%pred, FVC%pred and FEV<sub>1</sub>/VCmax (all  $P < 0.05$ ). Conversely, 2021-BDR+ group had lower FEV<sub>1</sub>pred, FVCpred than 2021-BDR- group

**Table 1** The Number of BDR+ and BDR- Defined by Two Criteria in Asthma and COPD

	Asthma (n=4457)				COPD (n=7764)			
	2021-BDR+	2021-BDR-	Total	P value	2021-BDR+	2021-BDR-	Total	P value
2005-BDR+	2310	512	2822	<0.001	1685	716	2401	<0.001
2005-BDR-	45	1590	1635		96	5267	5363	
Total	2355	2102	4457		1781	5983	7764	

**Table 2** The Number of BDR+ and BDR- Defined by Two Criteria in Patients with Asthma

	Children (n=474)				Adults (n=3983)			
	2021-BDR+	2021-BDR-	Total	P value	2021-BDR+	2021-BDR-	Total	P value
2005-BDR+	284	15	299	0.324	2026	497	2523	<0.001
2005-BDR-	22	153	175		23	1437	1460	
Total	306	168	474		2049	1934	3983	

**Table 3** Differences in Pulmonary Function Indices Between 2005-BDR- and 2005-BDR+ Groups

	Asthma (n=4457)				COPD (n=7764)			
	2005-BDR- (n=1635)	2005-BDR+ (n=2822)	t or $\chi^2$ or Z	P value	2005-BDR- (n=5363)	2005-BDR+ (n=2401)	t or $\chi^2$ or Z	P value
Male, n (%)	697 (42.6)	1504 (53.3)	47.111	<0.001	4611 (86.0)	2206 (91.9)	53.914	<0.001
Female, n (%)	938 (57.4)	1318 (46.7)			752 (14.0)	195 (8.1)		
Age(year)	(33.00, 58.00)	(35.00, 59.00)	-1.661	0.097	64.24±8.39	64.78±7.74	-2.723	0.005
Weight(Kg)	57.16±14.49	59.10±14.21	-4.369	<0.001	58.59±11.05	59.87±10.85	-1.068	0.286
Height(cm)	158.07±11.92	159.73±11.35	-4.619	<0.001	163.53±7.28	164.02±6.88	-2.818	0.004
FEV <sub>1</sub> pred (L)	3.14±0.86	3.27±0.87	-4.403	<0.001	2.62±0.49	2.65±0.44	-2.540	0.011
FEV <sub>1</sub> (L)	2.61±0.71	2.71±0.71	5.743	<0.001	1.44±0.69	1.10±0.48	24.707	<0.001
FEV <sub>1</sub> %pred	62.99±21.52	56.45±16.58	10.608	<0.001	54.89±23.30	41.83±16.45	28.247	<0.001
ΔFEV <sub>1</sub> (mL)	91.53±88.65	365.18±190.33	-65.148	<0.001	77.06±77.68	226.15±129.51	-62.775	<0.001
ΔFEV <sub>1</sub> %init	6.13±6.55	26.01±15.00	-61.046	<0.001	6.01±6.12	21.55±11.31	-63.308	<0.001
ΔFEV <sub>1</sub> %pred	3.64±3.48	13.69±6.33	-68.313	<0.001	3.00±2.93	8.64±4.88	-52.545	<0.001
FVC pred (L)	3.14±0.86	3.27±0.87	-5.029	<0.001	3.32±0.61	3.37±0.55	-3.492	<0.001
FVC(L)	2.64±0.95	2.70±0.90	-2.042	0.041	2.75±0.85	2.44±0.72	16.792	<0.001
FVC%pred	84.39±19.93	82.65±16.75	2.963	0.003	82.95±20.75	72.31±17.66	23.190	<0.001
ΔFVC (mL)	57.05±121.84	332.29±242.92	-50.259	<0.001	70.19±133.77	390.91±195.48	-73.095	<0.001
ΔFVC%init	2.47±5.37	13.87±11.15	-45.964	<0.001	2.88±5.30	17.60±9.87	-68.808	<0.001
ΔFVC%pred	1.86±4.07	10.48±7.26	-50.761	<0.001	2.13±4.08	11.84±5.94	-72.744	<0.001
FEV <sub>1</sub> /VCmax (%)	59.26±13.30	54.16±10.88	13.157	<0.001	(39.01, 61.40)	(35.26, 43.71)	-19.547	<0.001

(Table 4). As shown in Table 5, in asthma, compared with inconsistent group with 2005-BDR+ and 2021-BDR- (18.14%, 512/2822), consistent group with 2005-BDR+ and 2021-BDR+ (81.86%, 2310/2822) had lower percentage of males, weight, height, FVC, FEV<sub>1</sub>pred and FVCpred, but higher FEV<sub>1</sub>%pred, FVC%pred (all  $P<0.05$ ). In COPD, compared with inconsistent group (29.82%, 716/2401), consistent group (70.18%, 1685/2401) had lower percentage of males, height, FEV<sub>1</sub>pred and FVCpred, but higher age, FEV<sub>1</sub>, FVC, FEV<sub>1</sub>%pred, FVC%pred (all  $P<0.05$ ). Additionally, of 1635 asthma patients with 2005-BDR-, 45 (2.75%) converted to 2021-BDR+; of 5363 COPD patients with 2005-BDR-, 96 (1.79%) converted to 2021-BDR+.

## The Trend in the Proportion of BDR+ with the Level of Airflow Obstruction

As shown in Figure 2, with the increasing degree of airflow obstruction, the percentage of 2005-BDR+ increased linearly in COPD ( $P<0.001$ ) but exhibited an approximate inverted U-shaped curve in asthma ( $P=0.097$ ). Similar but more flat trends were observed in 2021-BDR ( $P<0.001$ ,  $P=0.949$ ). As shown in Figure 3, in asthma, the proportion of 2005-BDR<sub>FEV1</sub> was negatively associated with the level of airflow obstruction, while 2005-BDR<sub>Both</sub> was positively associated (both  $P<0.001$ ), and the 2005-BDR<sub>Both</sub> had an increased trend but decreased at extremely severe obstruction ( $P=0.244$ ). In COPD, the proportion of 2005-BDR<sub>FEV1</sub> was negatively associated with the degree of airflow obstruction, while 2005-BDR<sub>FVC</sub> was positively associated (both  $P<0.001$ ), and the 2005-BDR<sub>Both</sub> had an increased trend but decreased at extremely severe obstruction ( $P=0.585$ ). Similar results were observed in 2021-BDR, but the percentage of 2021-BDR<sub>FEV1</sub> decreased significantly in both asthma and COPD (all  $P<0.05$ ). The component percentages of BDR+ among different levels of airflow obstruction are shown in Supplementary Figure 1 and Supplementary Table 1. The component percentage of 2005-BDR<sub>FEV1</sub>, 2005-BDR<sub>FVC</sub>, 2005-BDR<sub>Both</sub>, 2021-BDR<sub>FEV1</sub>, 2021-BDR<sub>FVC</sub> and 2021-BDR<sub>Both</sub>, were 62.1%, 11.5%, 26.4%, 42.8%, 14.8%, 42.4% for asthma, 35.5%, 42.4%, 22.0%, 15.4%, 55.3%, 29.3% for COPD, respectively. More details are found in Supplementary Figure 2 and Supplementary Table 2.

**Table 4** Differences in Pulmonary Function Indices Between 2021-BDR- and 2021-BDR+ Groups

	Asthma (n=4457)				COPD (n=7764)			
	2021-BDR- (n=2102)	2021-BDR+ (n= 2355)	t or $\chi^2$ or Z	P value	2021-BDR- (n=5983)	2021-BDR+ (n=1781)	t or $\chi^2$ or Z	P value
Male, n (%)	1008 (48.0)	1193 (50.7)	3.248	0.071	5245 (87.7)	1572 (88.3)	0.461	0.497
Female, n (%)	1094 (52.0)	1318 (49.3)			738 (12.3)	195 (11.7)		
Age(year)	(35.00, 58.00)	(34.00, 59.00)	-1.661	0.097	64.18±8.29	65.15±7.82	-2.723	0.005
Weight(Kg)	58.69±13.70	58.11±14.89	1.341	0.180	59.66±10.98	59.73±11.00	-0.256	0.798
Height(cm)	159.92±10.75	158.41±12.25	4.388	<0.001	163.84±7.07	163.13±7.44	3.561	<0.001
FEV <sub>1</sub> pred (L)	2.72±0.68	2.64±0.74	3.884	<0.001	2.64±0.47	2.59±0.49	4.336	<0.001
FEV <sub>1</sub> (L)	1.63±0.68	1.51±0.61	5.804	<0.001	1.40±0.69	1.13±0.49	17.929	<0.001
FEV <sub>1</sub> %pred	60.09±20.53	57.74±17.06	4.113	<0.001	52.84±23.06	44.18±17.73	16.798	<0.001
ΔFEV <sub>1</sub> (mL)	124.05±104.53	390.41±196.39	-57.342	<0.001	86.73±82.77	245.56±137.94	-46.182	<0.001
ΔFEV <sub>1</sub> %init	8.27±7.38	28.04±15.49	-55.273	<0.001	7.13±6.99	23.20±12.12	-53.369	<0.001
ΔFEV <sub>1</sub> %pred	4.51±3.55	14.90±6.22	-69.427	<0.001	3.00±2.93	8.64±4.88	-49.144	<0.001
FVC pred (L)	3.27±0.83	3.18±0.91	3.626	<0.001	3.35±0.59	3.29±0.62	3.820	<0.001
FVC(L)	2.69±0.91	2.67±0.92	0.655	0.512	2.71±0.84	2.47±0.75	11.181	<0.001
FVC%pred	82.38±19.21	84.10±16.81	-3.174	0.002	80.91±20.92	75.44±18.14	10.762	<0.001
ΔFVC (mL)	88.04±133.64	359.21±252.39	-45.481	<0.001	87.45±139.91	444.58±192.73	-72.706	<0.001
ΔFVC%init	3.64±5.80	15.10±11.60	-42.359	<0.001	3.77±5.95	19.72±10.13	-63.287	<0.001
ΔFVC%pred	2.62±4.11	11.51±7.41	-50.226	<0.001	2.59±4.17	13.69±5.67	-76.695	<0.001
FEV <sub>1</sub> /VCmax (%)	59.26±13.30	54.16±10.88	13.157	<0.001	(39.01, 61.40)	(35.26, 43.71)	-19.547	<0.001

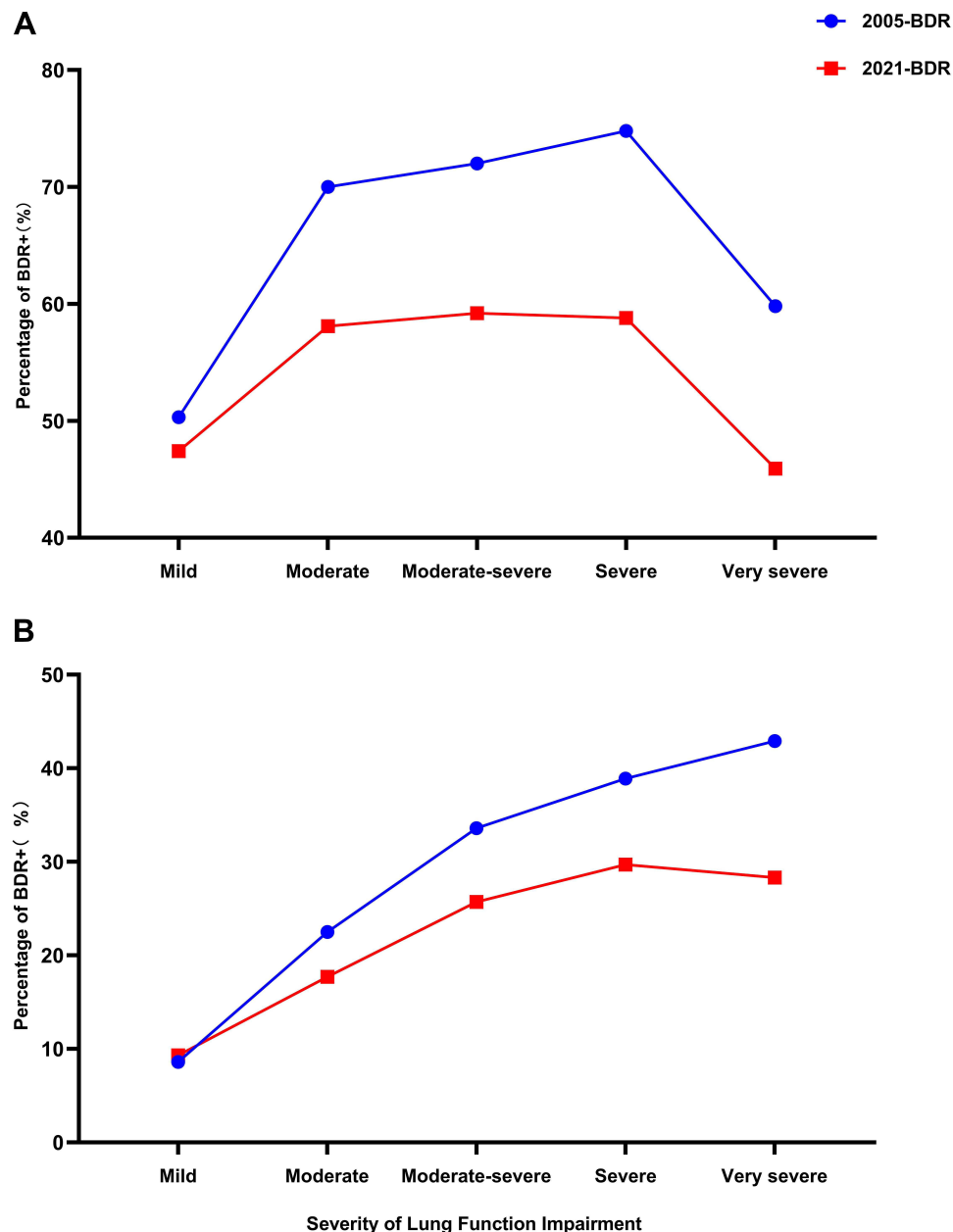
**Table 5** Differences in Pulmonary Function Indices Between Inconsistent Group and Consistent Group

	Asthma (n=2822)				COPD (n=2401)			
	Inconsistent (n=512)	Consistent (n=2310)	t or $\chi^2$ or Z	P value	Inconsistent (n=716)	Consistent (n=1685)	t or $\chi^2$ or Z	P value
Male, n (%)	330 (64.5)	1174 (50.8)	31.283	<0.001	696 (97.2)	1510 (89.6)	38.818	<0.001
Female, n (%)	182 (35.5)	1136 (49.2)			20 (2.8)	175 (10.4)		
Age(year)	(38.00, 57.50)	(35.00, 59.00)	-0.053	0.957	64.18±7.70	65.04±7.74	-3.485	0.001
Weight(Kg)	62.19±11.96	58.42±14.58	6.193	<0.001	59.93±10.86	59.85±10.84	0.623	0.533
Height(cm)	164.11±7.55	158.76±11.82	12.904	<0.001	165.50±5.82	163.39±7.19	8.713	<0.001
FEV <sub>1</sub> pred (L)	2.98±0.55	2.65±0.73	11.588	<0.001	2.75±0.36	2.60±0.47	8.295	<0.001
FEV <sub>1</sub> (L)	1.56±0.51	1.51±0.61	1.661	0.097	1.06±0.47	1.12±0.48	-2.533	0.011
FEV <sub>1</sub> %pred	52.29±14.68	57.37±16.83	-6.893	<0.001	38.54±15.55	43.22±16.63	-7.129	<0.001
ΔFEV <sub>1</sub> (mL)	232.89±73.30	394.50±195.77	-31.052	<0.001	167.08±80.04	251.24±138.09	-20.198	<0.001
ΔFEV <sub>1</sub> %init	15.58±4.93	28.32±15.49	-32.740	<0.001	16.30±6.91	23.79±12.05	-19.159	<0.001
ΔFEV <sub>1</sub> %pred	(7.17, 9.19)	(10.93, 18.14)	-29.235	<0.001	(3.85, 8.39)	(6.11, 12.17)	-18.148	<0.001
FVC pred (L)	3.62±0.67	3.20±0.90	3.626	<0.001	3.51±0.43	3.31±0.59	8.830	<0.001
FVC(L)	2.79±0.78	2.68±0.92	2.861	0.004	2.37±0.69	2.46±0.73	-2.301	0.021
FVC%pred	77.10±15.82	83.88±16.71	-8.681	<0.001	67.41±17.18	74.39±17.45	-9.437	<0.001
ΔFVC (mL)	192.87±118.38	363.19±252.44	-22.975	<0.001	24.49±10.86	45.29±19.12	-29.952	<0.001
ΔFVC%init	7.76±5.36	15.24±11.64	-22.112	<0.001	11.58±5.82	20.16±10.12	-26.094	<0.001
ΔFVC%pred	(3.07, 8.10)	(6.40, 15.49)	-19.949	<0.001	(6.19, 9.05)	(10.85, 16.57)	-31.419	<0.001
FEV <sub>1</sub> /VCmax (%)	53.64±11.23	54.27±10.80	-1.193	0.060	43.49±11.66	44.07±11.04	-1.863	0.063

## Discussion

To the best of our knowledge, there is a paucity of data exploring the differences in BDR between the 2005 and 2021 ERS/ATS criteria applied to a large sample of patients with asthma as well as COPD. The main findings of our study

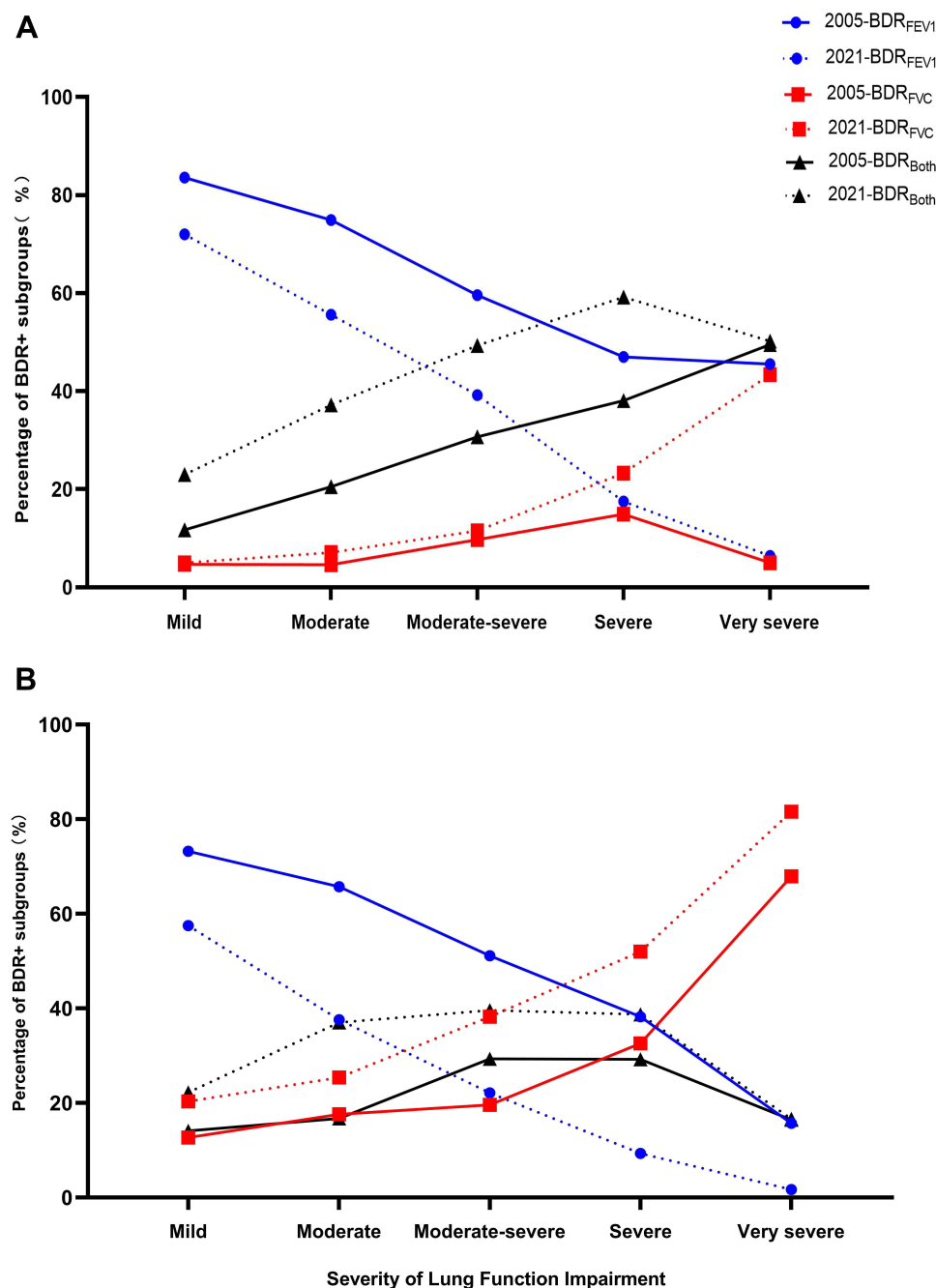




**Figure 2** The trend in the proportion of BDR+ with the increased degree of airflow obstruction in asthma (A) and COPD (B).

were the decreased proportion of 2021-BDR+ in asthma and COPD and the similar trends in the proportion of BDR+ with the level of airflow obstruction.

The present study showed the percentage of 2021-BDR+ reduced by 10.48% and 7.98% in asthma and COPD, respectively, being lower than a previous study in which the percentage of responders reduced by about 50% when BDR expressed as a percentage of the predicted value or a change in  $z$  score.<sup>11</sup> On the contrary, Bhatt reported the prevalence of BDR+ in COPD increased from 32.5% (2005-BDR+) to 44.6% (2021-BDR+).<sup>19</sup> The different results may be partly due to the heterogeneity in subjects. Interestingly, we found that the percentage of BDR+ increased slightly in children with asthma, which may be attributed to the lower predicted FEV<sub>1</sub> or FVC in children. As we know, BDR+ is often misinterpreted as a hallmark of asthma. Herein, approximately 20–30% and 50–60% of BDR+ occurred in COPD and asthma, respectively. As reported previously, 39% of COPD patients had a  $\geq 10\%$  absolute increase in percent predicted FEV<sub>1</sub> values;<sup>20</sup> 52.7% COPD patients exhibited BDR.<sup>21</sup> Undoubtedly, it is quite difficult to distinguish asthma from



**Figure 3** The trend in the proportion of BDR+ subgroups with the increased degree of airflow obstruction in asthma (A) and COPD (B).

COPD based merely on BDR test in clinical practice. In addition, in our study, whichever criterion was adopted, BDR+ group had lower FEV<sub>1</sub>, FVC, FEV<sub>1</sub>%pred, FVC%pred than BDR-group. In contrast, patients with consistent BDR+ had higher initial FEV<sub>1</sub>%pred, FVC%pred, indicating that consistent BDR+ was associated with better lung function. Notably, some patients changed from 2005-BDR- to 2021-BDR+, and their characteristics need further exploration.

With the deterioration of respiratory function, the percentage of BDR+ increased linearly in COPD, but exhibited an approximate inverted U-shaped curve in asthma. This reveals that patients with severe asthma patients may respond poorly to bronchodilator. As reported previously, severity of asthma had a significant influence on BDR and more severe asthma predicted a smaller BDR.<sup>22</sup> An explanation account for the above observations might be the irreversible airflow limitation in severe asthma, which was associated with airway inflammation, airway wall thickening, smooth muscle



hypertrophy, and hyperinflation.<sup>23,24</sup> We also found that in COPD patients, the proportion of  $BDR_{FEV_1}$  was negatively associated with the degree of airflow obstruction while  $BDR_{FVC}$  was positively associated, indicating  $BDR_{FEV_1}$  occurred more frequently in mild COPD while  $BDR_{FVC}$  occurred more often in advanced COPD. This finding was consistent with that previously reported by Barjaktarevic et al.<sup>21</sup> Previous studies showed that  $BDR_{FVC}$  rather than  $BDR_{FEV_1}$  better reflected the physiological processes of air trapping<sup>25–28</sup> and  $BDR_{FVC}$  was demonstrated to be more prevalent in subjects with greater emphysema and gas trapping.<sup>21,29</sup> As is known, in advanced COPD, emphysema with loss of alveolar attachments, distal airway remodeling and mucus hypersecretion may lead to air trapping and dynamic hyperinflation. Bronchodilator administration can partly reduce lung hyperinflation, resulting in a more significant impact on the change in FVC in comparison to that in  $FEV_1$ . Meanwhile, we noted that  $BDR_{Both}$  had a quite component percentage among three BDR+ subgroups, but its clinical significance was not fully understood. Fortis and coworkers reported that  $BDR_{Both}$  was associated with less emphysema and indicated a COPD phenotype with asthma-like characteristics.<sup>30</sup>

In the present study, we mainly addressed the differences in baseline pulmonary indices, the proportion of BDR+ and the trend with respiratory impairment, but did not include other indices associated with clinical outcomes such as dyspnea, exercise capacity, radiological airway measures, exacerbations and mortality. However, an ideal criterion for BDR should be integrated with clinical data to estimate prognosis. Patients with  $BDR_{FEV_1} > 8\%$  of predicted were reported to have an optimal survival advantage compared with those with  $BDR_{FEV_1} \leq 8\%$  of predicted.<sup>10</sup> In another study, neither the 2005 nor the 2021 BDR criterion predicted exacerbations or mortality in COPD when adjusted for the severity of lung disease.<sup>19</sup> Furthermore, whether an acute response can predict long-term outcomes other than survival remains unclear.<sup>20,31,32</sup> On the other side, some researchers argued that reversibility of airway obstruction in response to a bronchodilator was not a dichotomous trait but a continuous variable, so any cut-off level of a positive BDR might be arbitrary.<sup>9</sup> In addition to binary BDR categorization, a novel classification with five distinct categories was put forward, including negative, minimal, mild, moderate or marked, which was based on the changes in  $FEV_1$  relative to the predicted values with the following intervals  $\leq 0\%$ , 0–2%, 2–4%, 4–8% and  $> 8\%$ .<sup>33</sup>

The strengths of our study include the stringent quality control of data processing and a large dataset, but it has several limitations. First, as mentioned earlier, whether 2021-BDR outweighs 2005-BDR deserves further study and could not be judged from the available results. Second, the presence of BDR was reported to be variable at follow-up visits,<sup>20</sup> and the results from a single BDR test in this retrospective study should be interpreted with caution. Third, BDR results may be influenced by a variety of factors, such as smoking index, disease phenotype, comorbidities and the administration protocol of bronchodilators, more relevant factors should be considered in our future analysis.

## Conclusions

When BDR was defined by the 2021 ERS/ATS criterion, the proportion of BDR+, especially  $BDR_{FEV_1}$  decreased in asthma patients and COPD patients. The proportion of BDR+ had an upward linear trend with the increased degree of airflow obstruction in COPD but exhibited an approximate inverted U-shaped curve in asthma. Patients with consistent BDR+ have higher initial  $FEV_1\%$ pred and  $FVC\%$ pred. However, the clinical significance of the new criterion in the evaluation of obstructive lung diseases warrants for further study.

## Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by grants from the National Key Research and Development Program of China (No. 2018YFC1311900) and Medical Scientific Research Foundation of Guangdong Province (C2021073).

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720–735. doi:10.1183/09031936.05.00034905
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805
- Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948–968. doi:10.1183/09031936.05.00035205
- Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J*. 2005;26(3):511–522. doi:10.1183/09031936.05.00035005
- Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society Technical Statement. *Am J Respir Crit Care Med*. 2017;196(11):1463–1472. doi:10.1164/rccm.201710-1981ST
- Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49(1):1600016. doi:10.1183/13993003.00016-2016
- Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med*. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
- Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma strategy 2021: executive summary and rationale for key changes. *Eur Respir J*. 2022;59(1):2102730. doi:10.1183/13993003.02730-2021
- Brand PL, Quanjer PH, Postma DS, et al. Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. *Thorax*. 1992;47(6):429–436. doi:10.1136/thx.47.6.429
- Ward H, Cooper BG, Miller MR. Improved criterion for assessing lung function reversibility. *Chest*. 2015;148(4):877–886. doi:10.1378/chest.14-2413
- Quanjer PH, Ruppel GL, Langhammer A, et al. Bronchodilator response in FVC is larger and more relevant than in FEV(1) in severe airflow obstruction. *Chest*. 2017;151(5):1088–1098. doi:10.1016/j.chest.2016.12.017
- Tan WC, Vollmer WM, Lamprecht B, et al. Worldwide patterns of bronchodilator responsiveness: results from the burden of obstructive lung disease study. *Thorax*. 2012;67(8):718–726. doi:10.1136/thoraxjnl-2011-201445
- Burity EF, Pereira CA, Jones MH, Sayão LB, Andrade AD, Britto MC. Bronchodilator response cut-off points and FEV 0.75 reference values for spirometry in preschoolers. *J brasileiro de pneumologia*. 2016;42(5):326–332. doi:10.1590/s1806-37562015000000216
- Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60(1). doi:10.1183/13993003.01499-2021
- Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med*. 2017;195(5):557–582. doi:10.1164/rccm.201701-0218PP
- Gao Y, Han J, Jiang L, et al. Guidelines for pulmonary function tests (Part IV) -bronchodilator reversibility testing. *Chin J Tuberc Respir Dis*. 2014;37(09):655–658.
- Pulmonary Function Group RDSocMA. Guidelines for pulmonary function tests (Part II)- spirometer examination. *Chin J Tuberc Respir Dis*. 2014;37(07):481–486.
- Pulmonary Function Group RDSocMA. Guidelines for Pulmonary Function Tests (Part I) - Overview and general requirements. *Chin J Tuberc Respir Dis*. 2014;37(06):402–405.
- Bhatt SP, Fortis S, Bodduluri S. New guidelines for bronchodilator responsiveness in COPD: a test in search of a use. *Am J Respir Crit Care Med*. 2022. doi:10.1164/rccm.202203-0458LE
- Hanania NA, Sharafkhaneh A, Celli B, et al. Acute bronchodilator responsiveness and health outcomes in COPD patients in the UPLIFT trial. *Respir Res*. 2011;12(1):6. doi:10.1186/1465-9921-12-6
- Barjaktarevic IZ, Buhr RG, Wang X, et al. Clinical significance of bronchodilator responsiveness evaluated by forced vital capacity in COPD: SPIROMICS cohort analysis. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2927–2938. doi:10.2147/copd.S220164
- Koga T, Kamimura T, Oshita Y, et al. Determinants of bronchodilator responsiveness in patients with controlled asthma. *J Asthma*. 2006;43(1):71–74. doi:10.1080/02770900500448662
- Ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med*. 2001;164(5):744–748. doi:10.1164/ajrcm.164.5.2011026
- Little SA, Sproule MW, Cowan MD, et al. High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. *Thorax*. 2002;57(3):247–253. doi:10.1136/thorax.57.3.247
- Han MK, Wise R, Mumford J, et al. Prevalence and clinical correlates of bronchoreversibility in severe emphysema. *Eur Respir J*. 2010;35(5):1048–1056. doi:10.1183/09031936.00052509
- Chen C, Jian W, Gao Y, Xie Y, Song Y, Zheng J. Early COPD patients with lung hyperinflation associated with poorer lung function but better bronchodilator responsiveness. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2519–2526. doi:10.2147/copd.S110021
- Walker PP, Calverley PM. The volumetric response to bronchodilators in stable chronic obstructive pulmonary disease. *Copd*. 2008;5(3):147–152. doi:10.1080/15412550802092928
- Lee JS, Huh JW, Chae EJ, et al. Response patterns to bronchodilator and quantitative computed tomography in chronic obstructive pulmonary disease. *Clin Physiol Funct Imaging*. 2012;32(1):12–18. doi:10.1111/j.1475-097X.2011.01046.x

29. Hansen JE, Dilektasli AG, Porszasz J, et al. A new bronchodilator response grading strategy identifies distinct patient populations. *Ann Am Thorac Soc.* **2019**;16(12):1504–1517. doi:10.1513/AnnalsATS.201901-030OC
30. Fortis S, Comellas A, Make BJ, et al. Combined forced expiratory volume in 1 second and forced vital capacity bronchodilator response, exacerbations, and mortality in chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* **2019**;16(7):826–835. doi:10.1513/AnnalsATS.201809-601OC
31. Ferrer Galván M, Javier Alvarez Gutiérrez F, Romero Falcón A, Romero B, Sáez A, Medina Gallardo JF. Is the bronchodilator test an useful tool to measure asthma control? *Respir Med.* **2017**;126:26–31. doi:10.1016/j.rmed.2017.03.008
32. Janson C, Malinovschi A, Amaral AFS, et al. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. *Eur Respir J.* **2019**;54(3):1900561. doi:10.1183/13993003.00561-2019
33. Ioachimescu OC, Ramos JA, Hoffman M, McCarthy K, Stoller JK. Assessing bronchodilator response by changes in per cent predicted forced expiratory volume in one second. *J Investig Med.* **2021**;69(5):1027–1034. doi:10.1136/jim-2020-001663

## International Journal of Chronic Obstructive Pulmonary Disease

Dovepress

### Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols. This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>