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Significant Bronchodilator Responsiveness and "Reversibility" in a Population Sample

Heather A. Prentice (haprenti@uab.edu), **David M. Mannino** (dmmann2@email.uky.edu), **Glyn G. Caldwell**
(glyn.caldwell@uky.edu), and **Heather M. Bush** (Heather.bush@uky.edu)

University of Kentucky, College of Public Health, Lexington, Kentucky

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is defined by being "not fully reversible", most guidelines recommend measurement of lung function after the administration of a bronchodilator. The objective of this study was to compare bronchodilator responsiveness (significant improvement in the FEV_1 or FVC) to full-, partial- or "inverse"' reversibility in obstruction status in a population-based sample in Southeastern Kentucky. The study population was selected using random digit dialing of an adult population in Southeastern Kentucky as part of the Burden of Lung disease (BOLD) project. Lung function was assessed using spirometry pre- and post-bronchodilation. Subjects presence and severity of COPD was classified using modified Global Obstructive Lung Disease (GOLD) criteria. We examined the relation between changes in "obstruction" status (based on the FEV_1/ FVC of 0.7) and the presence of "significant bronchodilator responsiveness" (based on $\geq$ 12% improvement in the FEV_1 or the FVC). The final population with acceptable pre- and post-bronchodilator spirometry included 440 participants. 32/440 subjects (7.3%) changed from obstructed to unobstructed (full-reversibility), 19/440 (4.3%) changed from unobstructed to obstructed ("inverse"-reversibility), 389/440 (88.4%) had either no-change or partial-reversibility, and 65/440 (14.8%) had bronchodilator responsiveness. Among those with full-reversibility, only 9/32 (28.1%) had bronchodilator responsiveness, whereas among subjects with "inverse"-reversibility, 10/19 (52.6%) had bronchodilator responsiveness. Among all subjects with bronchodilator responsiveness, only 19/65 (29.2%) changed categories. Our findings suggest that significant bronchodilator responsiveness is not the same as "reversibility" of "obstruction", even though these terms are often used interchangeably.

BACKGROUND

COPD is a chronic disease of the lungs and is characterized by irreversible airflow limitation, and is currently the fourth-leading cause of death in the United States (1, 2). GOLD defines COPD as a preventable and treatable disease with airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (3). Both the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have, in large part, adopted this definition (4).

Response to a bronchodilator is thought to be important in COPD diagnosis and to distinguish COPD from asthma as the cause for airflow limitation, a disease that is clinically different from COPD in both pathogenesis and therapeutic response. Guidelines suggest that classification of COPD be made using spirometry performed after bronchodilator administration. One potential criterion of a significant response to a bronchodilator (i.e., the presence of "full"-reversibility) is the presence of a pre-bronchodilator ratio less than 0.7 but a post-bronchodilator ratio that is greater than or equal to 0.7, switching from "obstructed" to "unobstructed."(3). Of course, people also have the potential to switch from "unobstructed" to "obstructed" (which lacks a name but is listed as "inverse"-reversibility in this analysis).

Another potential criterion of a significant response is an improvement at or above a certain threshold in either of the components of the FEV_1/FVC ratio (bronchodilator responsiveness). Both the ATS and GOLD define this as a post-bronchodilator spirometric measurement increase $\geq$ 12% of the pre-bronchodilator measurement for the FEV_1 or the FVC, along with an increase in the FEV_1 or FVC of at least 200 mL (5). Patients who demonstrate bronchodilator responsiveness but remain obstructed, based on their FEV_1/FVC are considered to have partial-reversibility.

According to the 2008 GOLD guidelines "Spirometry should be performed after the administration of an adequate dose of an inhaled bronchodilator (e.g., 400 μg salbutamol) (5) to minimize variability. In a random population study to determine spirometry reference values, post-bronchodilator values differed markedly from pre-bronchodilator values (6). Furthermore, post-bronchodilator lung function testing in a community setting has been demonstrated to be an effective method to identify individuals with COPD." (7, 8).

The purpose of this study is to better understand how bronchodilator administration changes FEV_1 and FVC separately and how these changes affect the FEV_1/FVC. This study will determine the relation between bronchodilator responsiveness, as defined by a $\geq$ 12% increase in the FEV_1 or the FVC after administration of a bronchodilator, and either full-, partial-, or "inverse"-reversibility. We used the Burden of Lung Disease (BOLD) protocol to complete the study (9).

METHODS

BOLD is a community-based study conducted to provide a high-quality standardized tool to measure the country-specific prevalence of COPD. The study is a simple random sample of noninstitutionalized adults (age $\geq$ 18 years) from 26 counties in Southeastern Kentucky. Initially, participants were contacted by telephone through random-digit dialing. Answers to a minimal data questionnaire were obtained, and site or home visits were scheduled for adults who were at least 40 years in age to complete questionnaires and perform pre- and post-bronchodilator spirometry. Protocol for the BOLD study has been discussed elsewhere (9). The present analysis was approved by the University of Kentucky Institutional Review Board.

Study Measures

Trained and certified technicians administered spirometry using the ndd EasyOne Spirometer. Measurements were made before and at least 15 minutes after two puffs of salbutamol (200 μg) administered via a metered dose inhaler with a spacer. Useable spirograms met ATS standards, with at least 2 acceptable and reproducible tests for both volume measurements. Adequate spirometry measurements were free from artifact, sudden stops, and back extrapolated volumes of less than 5% of FVC. Inclusion criteria for this study required subjects to have adequate pre- and post-bronchodilator spirometry. Predicted values

from the Third National Health and Nutrition Examination Survey (NHANES III) were used in the analysis (10).

Definitions

Demographic data included in this analysis were sex, age, body mass index (BMI), smoking status, and educational status (the studied population was 100% White). The study participants were classified, using the post bronchodilator lung function, into 6 lung function categories based on a modification of the GOLD criteria. Normal (no respiratory symptoms or airflow obstruction or restriction), Stage 0 (the presence of symptoms of cough, sputum, wheeze, or breathlessness without airflow obstruction or restriction), Restricted ($FEV_1/FVC \geq$ 70% and FVC < 80% of predicted), Stage 1 (FEV_1/FVC < 70% and $FEV_1 \geq$ 80% predicted), Stage 2 (FEV_1/FVC < 70% and 50% $\leq FEV_1 <$ 80% predicted), and Stage 3 or 4 (FEV_1/FVC < 70% and $FEV_1 <$ 50% predicted) (3). GOLD stage 0 is not in the most recent guidelines, but we have included this stage because previous work (11, 12) has demonstrated worse outcomes in this group of patients. We also included a "restricted" group, subjects with an $FEV_1/FVC \geq$ 70% and an FVC < 80% predicted.

Bronchodilator reversibility is defined according to how a person's obstruction classification changed between pre- and post-bronchodilator (based on the FEV_1/FVC of < 0.70) as either full-reversibility (change from obstructed to unobstructed), "inverse"-reversibility (change from unobstructed to obstructed), and no-change (no change in obstruction status). We classified subjects who were obstructed both pre- and post-bronchodilator, but also had bronchodilator responsiveness, as having "partial"-reversibility.

Significant bronchodilator responsiveness is defined as a $\geq$ 12% (from baseline) increase in either the FEV_1 or the FVC. We did not use the 200 mL increase "floor" in our classification, although 64/65 subjects we classified as having bronchodilator responsiveness had at least a 200 mL increase in their FEV_1 or FVC.

Statistical Analysis

Data analysis was completed using statistical software (Statistical Analysis Software, version 9.1; SAS Institute; Cary, NC). Descriptive statistics and frequency distributions were calculated for the eligible and the studied populations. To determine if there were any differences between the analyzed population and the eligible study cohort, χ^2 analysis was used. Additional descriptive statistics and frequency distributions were calculated for those in the study population stratified by reversibility status and bronchodilator responsiveness. Least square means were used on the data to obtain p-values.

RESULTS

A total of 15,148 different telephone numbers were dialed. In 7,073 calls, individuals refused minimal participation in the study, could not be reached, or hung up. Another 6,011

telephone numbers dialed were ineligible due to an invalid telephone number with no forwarding information, no one in the household of eligible age to participate in the study, the individuals were institutionalized, or they did not speak English. A total of 1,046 individuals were eligible and provided at least part of the minimal data but refused full participation in the study; 971 individuals responded to the minimal data questionnaire and were willing to participate in the full protocol, but 575 actually participated. Acceptable pre- and post-bronchodilator spirometry and full data were collected from 440 participants, which comprised the final study cohort.

Table 1 presents the frequency distributions for sex, age group, BMI, education, smoking status, respiratory symptoms, 12% increase in FEV_1, 12% increase in FVC, 12% increase in either measurement, and GOLD COPD status of the final analyzed cohort (N = 440) and the eligible population (N = 575). Comparisons of all parameters were statistically insignificant, suggesting that the two groups were similar.

Table 2 presents the demographic information for the analyzed population stratified by those with full-reversibility (N = 32, 7.3%), "inverse"-reversibility (N = 19, 4.3%), and those who did not change in obstruction status (N = 389, 88.4%). Of the 100 subjects who were obstructed at baseline, 32 (32.0%) demonstrated full reversibility, and of the 340 subjects who were unobstructed at baseline, 19 (5.6%) demonstrated "inverse"-reversibility. Overall, 65/440 (14.8%) subjects had bronchodilator responsiveness. For subjects with full-reversibility 9/32 (28.1%) had bronchodilator responsiveness, while among those with "inverse"-reversibility 10/19 (52.6%) had bronchodilator responsiveness. Out of subjects who had no change to their obstruction status and were obstructed, 28/68 (41.2%) had bronchodilator responsiveness, comprising partial-reversibility. Among the other 321 subjects with no change, 18 (5.6%) had bronchodilator responsiveness. The mean FEV_1, FVC, and FEV_1/FVC measurements before bronchodilator administration were 2.52 liters, 3.37 liters, and 0.743 respectively. The mean FEV_1, FVC, and FEV_1/FVC measurements after bronchodilator administration were 2.61 liters, 3.42 liters, and 0.760, respectively.

Figure 1 presents a bar chart of the percent change in FEV_1 from baseline for participants, stacked by bronchodilator reversibility status. The demarcation distinguishes those who had significant bronchodilator responsiveness. The figure shows that it was modest increases in FEV_1 that allowed people to change to unobstructed after bronchodilator administration. It also demonstrates that most people with bronchodilator responsiveness of the FEV_1 did not also have bronchodilator reversibility. Figure 2 presents similar data for the FVC. Again, most subjects with bronchodilator responsiveness of the FVC did not also have bronchodilator reversibility. Figure 3 presents a bar chart of GOLD stage by bronchodilator responsiveness in either the FEV_1, the FVC, or both of these measures. Among subjects with GOLD Stage 3 or 4, 12/17 (70.6%) had bronchodilator responsiveness, and 21/48 (43.8%) among those with Stage 2 disease.

Table 1. Characteristics of analyzed population versus eligible study population*

	Analyzed Population (N = 440)		Eligible Study Population (N = 575)	
	No.	%	No.	%
Sex				
Female	266	60.5	336	58.4
Male	174	39.6	239	41.6
Age Group, yrs				
40–49	124	28.2	149	25.9
50–59	164	37.3	221	38.4
60–69	112	25.5	145	25.2
70+	40	9.1	59	10.3
Missing	0	0.0	1	0.2
Body Mass Index, kg/m²				
≥ 30	202	45.9	270	47.0
< 30	238	54.1	305	53.0
Education				
> 12	205	46.6	254	44.2
≤ 12	235	53.4	321	55.8
Smoking Status				
Never	171	38.9	229	39.8
Current	118	26.8	155	27.0
Former	151	34.3	191	33.2
Respiratory Symptoms				
No	155	35.2	212	36.9
Yes	285	64.8	363	63.1
12% Increase in FEV_1				
No	394	89.5	395	68.7
Yes	46	10.5	46	8.0
Missing	0	0.0	134	23.3
12% Increase in FVC				
No	400	90.9	419	72.9
Yes	40	9.1	40	7.0
Missing	0	0.0	116	20.1
12% Increase in Either FEV_1 or FVC				
No	375	85.2	376	65.4
Yes	65	14.8	65	11.3
Missing	0	0.0	134	23.3
GOLD†				
GOLD 1, 2, 3/4	87	19.8	106	19.7
Restricted	80	18.2	90	16.8
GOLD 0	160	36.4	193	35.9
Normal	113	25.7	148	27.6
Missing	0	0.0	38	6.6

*Age, sex, body mass index, education, smoking status and respiratory symptoms parameters statistically insignificant when comparing eligible population to analyzed population.
†Modified Global Initiative on Obstructive Lung Disease Classification, as defined in methods.

DISCUSSION

In this study of 440 subjects with adequate pre- and post-bronchodilator lung function measurement, we found that 11.6% of participants experienced bronchodilator reversibility. Specifically, 7.3% changed from obstructed to unobstructed (full-reversibility) and 4.3% changed from unobstructed to obstructed ("inverse"-reversibility) after bronchodilator

Table 2. Characteristics of analyzed population by respiratory change status.

	Full Reversibility* (N = 32)		No Change or Partial Reversibility[†] (N = 389)		"Inverse"-Reversibility** (N = 19)		
	No.	%	No.	%	No.	%	p Value
Sex							0.440
Female	18	56.3	234	60.2	14	73.7	
Male	14	43.7	155	39.7	5	26.3	
Age Group, yrs							0.021
40–49	10	31.3	113	29.0	1	5.3	
50–59	5	15.6	151	38.8	8	42.1	
60–69	14	43.7	91	23.4	7	36.8	
70+	3	9.4	34	8.7	3	15.8	
Body Mass Index, kg/m^2							0.030
$\geq$ 30	8	25.0	187	48.1	7	36.8	
< 30	24	75.0	202	51.9	12	63.2	
Education							0.028
> 12	11	34.4	188	48.3	6	31.6	
$\leq$12	21	65.6	201	51.7	13	68.4	
Smoking Status							0.027
Never	9	28.1	158	40.6	4	21.1	
Current	15	46.9	95	24.4	8	42.1	
Former	8	25.0	136	35.0	7	36.8	
Respiratory Symptoms							0.076
No	8	25.0	144	37.0	3	15.8	
Yes	24	75.0	245	63.0	16	84.2	
12% Increase in FEV$_1$							0.002
No	23	71.9	355	91.3	16	84.2	
Yes	9	28.1	34	8.7	3	15.8	
12% Increase in FVC							<0.001
No	31	96.9	360	92.5	9	47.4	
Yes	1	3.1	29	7.5	10	52.6	
12% Increase in Either FEV$_1$ or FVC							<0.001
No	23	71.9	343	88.2	9	47.4	
Yes	9	28.1	46	11.8	10	52.6	
GOLD[††]							<0.001
GOLD 1, 2, 3 / 4	0	0.0	68	17.5	19	100.0	
Restricted	8	25.0	72	18.5	0	0.0	
GOLD 0	17	53.1	143	36.8	0	0.0	
Normal	7	21.9	106	27.2	0	0.0	

*Defined by a pre-bronchodilator FEV$_1$/ FVC ratio <0.7 and post-bronchodilator ratio $\geq$0.7.
[†] 28/68 (41.2%) obstructed subjects had at least a 12% increase in their FEV$_1$ or FVC yet remained obstructed, comprising "partial-reversibility".
**Defined by a pre-bronchodilator FEV$_1$/ FVC ratio $\geq$0.7 and post-bronchodilator ratio <0.7.
[††] Modified Global Initiative on Obstructive Lung Disease Classification, as defined in methods.

administration. An additional 28/440 (6.4%) had evidence of bronchodilator responsiveness but remained obstructed, comprising partial-reversibility. Ironically, only 9/32 (28.1%) of subjects with full-reversibility met criteria for bronchodilator responsiveness, whereas 10/19 (52.6%) of subjects with "inverse"-reversibility met these criteria. By definition, 100% of subjects with partial-reversibility met criteria for bronchodilator responsiveness, although this comprised 28/68 (41.2%) of subjects who remained obstructed following a bronchodilator. Overall, 46/343 (11.8%) of subjects who did not change "obstruction" categories met criteria for bronchodilator responsiveness.

These findings challenge some of the underlying assumptions about pre- and post-bronchodilator measurements and their use-fulness in classifying COPD or in separating COPD (as not fully reversible) and asthma (as fully reversible). The 2008 GOLD guidelines acknowledge that "while post-bronchodilator FEV$_1$/ FVC and FEV$_1$ measurements are recommended for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g., FEV$_1$ after bronchodilator or glucocorticosteroids) is no longer recommended for diagnosis, differential diagnosis with asthma, or predicting the response to long-term treatment with bronchodilators or glucocorticosteroids"(8). Our analysis shows that most people who were "fully reversible" met this definition on the basis of relatively small changes in their FEV$_1$ and FVC, thus, they have "reversibility of obstruction" in the absence of having bronchodilator responsiveness.
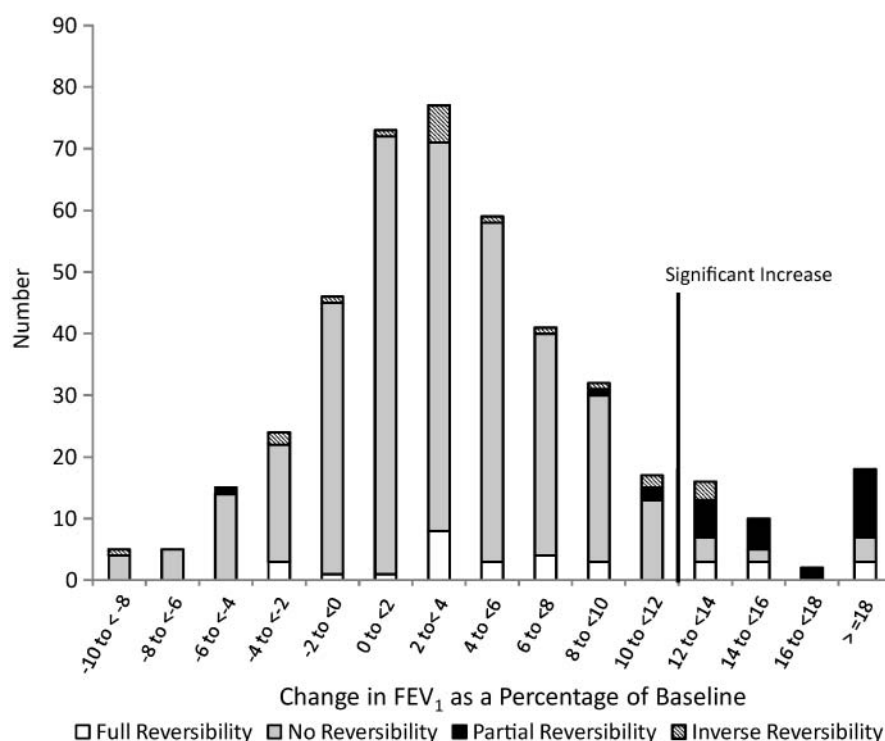
Figure 1. The increase in the forced expiratory volume in one second (FEV_1) following administration of 200 μg of salbutamol, and the presence of full-reversibility (change from obstructed to unobstructed based on the FEV_1/ forced vital capacity (FVC) ratio of < 0.70), partial reversibility ($> = 12\%$ increase in the FEV_1 or the FVC but no change in obstructive status), inverse reversibility (change from unobstructed to obstructed based on the FEV_1/ FVC ratio of < 0.70), and no reversibility (not in any of the above categories).

Conversely, subjects with "inverse"-reversibility (a category which is not, to our knowledge, acknowledged in any guidance document) had the largest proportion of people demonstrating bronchodilator responsiveness because of a large FVC response. Prior to bronchodilator administration, 9 (47.4%) of the subjects with "inverse"-reversibility were classified as restricted, 8 of whom experienced bronchodilator responsiveness; while 2 of the 10 subjects classified as normal experienced bronchodilator responsiveness.

Others have shown that the presence of "reversibility" in patients with COPD is common and can vary in individuals over short periods of time. For example, Calverley et al. demonstrated that in baseline data from subjects enrolled in a clinical COPD trial, over a 2-month period, 52.1% of subjects changed their bronchodilator responsiveness status. They concluded that "classifying patients as 'responders' and 'non-responders' can be misleading and does not predict disease progression" (13). Similarly, in the baseline data from another larger clinical trial, Tashkin et al. found that over 65% of subjects with documented COPD had at least a 15% increase in their FEV_1 after bronchodilator administration (400 μg of salbutamol and 80 μg of ipratropium) (14). This finding is similar to ours in Stage 3 or 4 subjects, where 70% had a 12% increase in either their FEV_1 or their FVC following 200 μg of salbutamol.

Prior studies have noted individual changes in FEV_1 and FVC after bronchodilator administration. Both Perez-Padilla et al. and Johannessen et al. found a greater increase in FEV_1 compared to FVC for patients who had a significant increase in FEV_1/ FVC after bronchodilator administration (7,15). In both studies for those with partial-reversibility, a consistent increase in FVC was seen, explaining why FEV_1/ FVC levels remained decreased after bronchodilator administration.

Our group of subjects with "inverse"-reversibility had the highest proportion of those who experienced a 12% increase in either FEV_1 and/or FVC (52.6%). This is contrary to what bronchodilator reversibility testing is hoping to capture and therefore has important implications for public health and clinically. For example, the NHANES 2007–2008 spirometry protocol states for bronchodilator administration "Only participants with abnormal baseline spirometry values showing airflow obstruction defined as FEV_1/ FVC% equal to or less than the lower limit of normal (LLN), or an observed FEV_1/ FVC% equal to or less than 70% will be selected for bronchodilator reversibility testing" (16). This important group of people would be missed entirely since they are not obstructed at baseline.

This study also showed that the majority of subjects who did experience bronchodilator responsiveness, defined by a 12% increase in the FEV_1 or the FVC were still classified as obstructed according to GOLD criteria. These findings support the
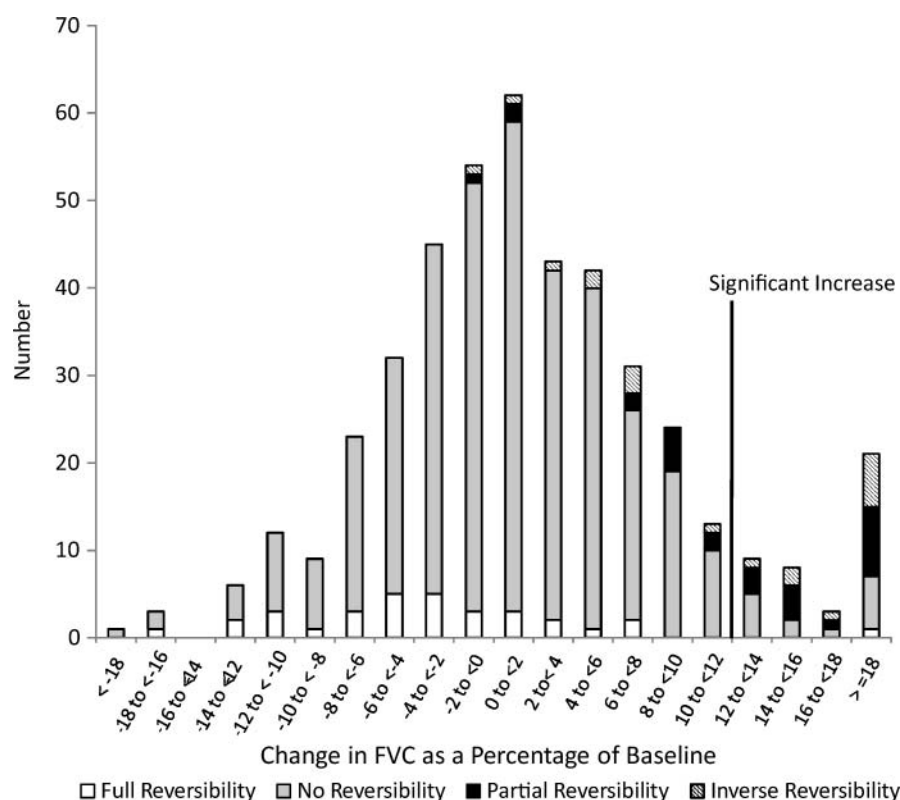
Figure 2. The increase in the forced vital capacity (FVC) following administration of 200 μg of salbutamol, and the presence of full-reversibility (change from obstructed to unobstructed based on the forced expiratory volume in 1 second (FEV$_1$) / FVC ratio of $<$ 0.70), partial reversibility ($> =$ 12% increase in the FEV$_1$ or the FVC but no change in obstructive status), inverse reversibility (change from unobstructed to obstructed based on the FEV$_1$/ FVC ratio of $<$ 0.70), and no reversibility (not in any of the above categories).

conclusions from Cazzola et al. that bronchodilator therapy should not be considered only for those who become unobstructed after bronchodilator administration (17). This analysis shows that patients who are classified as having COPD according to GOLD criteria can have significant bronchodilator responsiveness, potentially highlighting the overlap of COPD and asthma (14,18,19).

There are some limitations to this study analysis. Of the 2,017 subjects potentially eligible for inclusion in this study, only 575 participated and 440 were ultimately included in this analysis. Studies with low participation rates are more subject to bias. Individuals who refused to participate or who did not meet the strict eligibility criteria for this study, having adequate lung function measurements for both pre- and post-bronchodilator spirometry, may be different from those who were included. Our study design, however, which compares the same individuals before and after a bronchodilator administration, should limit the bias that low participation introduces.

This study may not be generalizable to populations outside rural Kentucky. Further, the study sample sizes for both the full-reversibility and the "inverse"-reversibility cohorts were small. The small sample sizes for both the fully reversible and "inverse" reversible groups limited further analysis such as regres-

sion analysis of factors that may affect disease severity such as age and BMI. Finally, the dose of salbutamol used in this study (200 μg) was less than what was recommended for clinical testing of reversibility (400 μg). Even with these important limitations, the findings in this project present important new knowledge in understanding FEV$_1$ and FVC in COPD reversibility after bronchodilator administration.

In conclusion, little overlap was found between the presence of bronchodilator responsiveness as indicated by a 12% increase in the FEV$_1$ or FVC and the presence of full-, partial-, and "inverse"-reversibility as indicated by a status change in the FEV$_1$/ FVC following administration of a bronchodilator. Only a minority of subjects with full-reversibility demonstrated bronchodilator responsiveness, and most subjects with significant bronchodilator responsiveness did not change obstruction categories. We believe these findings question the rationale for using post-bronchodilator lung function measurements alone to classify and categorize COPD. This also challenges the wisdom of not doing bronchodilator testing in people with "non-obstructed" lung function, in that a percentage of the population will have an improvement in their FVC that renders them "obstructed" following testing.
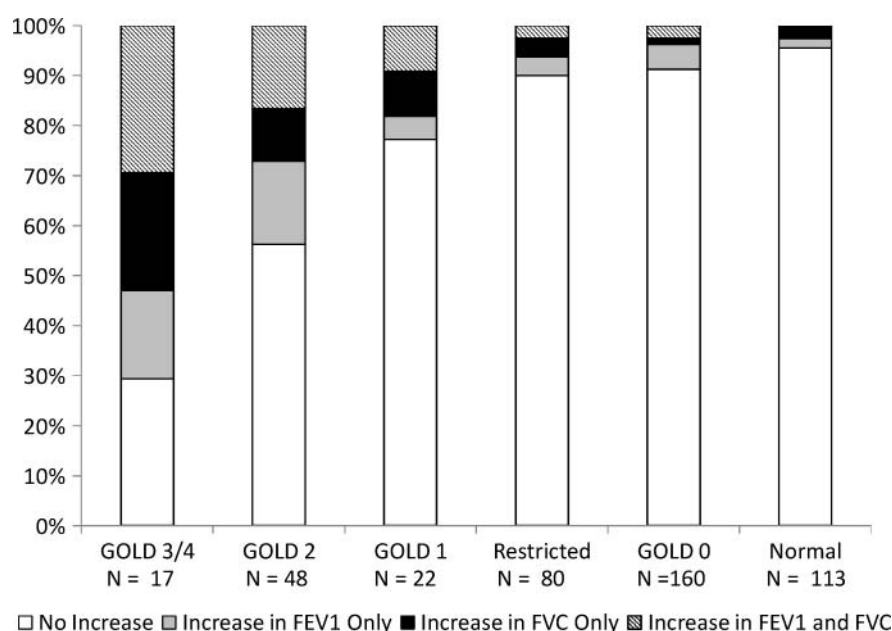
Figure 3. The post-bronchodilator lung function classification using the modified Global Initiative on Obstructive Lung Disease (GOLD) scheme as described in the methods, and the presence of bronchodilator responsiveness as indicated by a 12% or great increase in the forced expiratory volume in 1 second (FEV_1), the forced vital capacity (FVC), or both. Those in GOLD stages 1, 2, 3 and 4 with bronchodilator responsiveness comprise "partial reversibility".

This may be particularly true among patients being evaluated for respiratory complaints. The finding that values following a bronchodilator are different does not mean they are better in classifying disease or predicting outcomes. Appropriate longitudinal studies using both pre- and post-bronchodilator lung function measurements are necessary to identify long-term outcomes for patients who experience bronchodilator reversibility and/or responsiveness and to determine which measurement is more useful prognostically.

Declaration of interest

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