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Worldwide Patterns of Bronchodilator Responsiveness: Results from the Burden of Obstructive Lung Disease (BOLD) Study

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Abstract

RATIONALE: Criteria for a clinically significant bronchodilator response (BDR) are mainly based on studies in patients with obstructive lung diseases. Little is known about the BDR in healthy general populations, and even less about the worldwide patterns.

METHODS: We evaluated 10,360 adults aged 40 years and older from 14 countries in North America, Europe, Africa and Asia who participated in the BOLD study using spirometry before and after an inhaled bronchodilator in order to determine the distribution of the BDR in population-based samples of healthy nonsmokers and individuals with airflow obstruction.

RESULTS: In 3922 healthy never smokers, the weighted pooled estimate of the 95th percentiles (95% confidence interval, CI) for bronchodilator response were 284 mL (263, 305) absolute increase in FEV1 (\(\Delta FEV1\)); 12.0% (11.2, 12.8) change in FEV1 from baseline (\(\%\Delta FEV1_i\)) and 10.0% (9.5, 10.5) change in FEV1 of predicted (\(\%\Delta FEV1_p\)). The corresponding mean changes in FVC were 322 mls (271, 373) absolute change (\(\Delta FVC\)); 10.5% (8.9, 12.0) for \(\%\Delta FVC_i\) and 9.2% (7.9, 10.5) for \(\%\Delta FVC_p\). The proportion of people who exceeded the above threshold values in the subgroup of people with spirometrically-defined GOLD stage 2 and higher (FEV1/FVC<0.7 and FEV1%predicted <80%), were 11.1%, 30.8%, 12.9% respectively for the FEV1-based thresholds and 22.6%, 28.6% and 22.1% respectively for the FVC-based thresholds.

CONCLUSIONS: The results provide reference values for bronchodilator responses worldwide that confirm guideline estimates for a clinically significant level of BDR in bronchodilator testing.
1) What is the key question?
   
   Answer: What is the distribution of bronchodilator response in healthy populations worldwide?

2) What is the bottom line?
   
   Answer: We have generated global population-based thresholds for bronchodilator reversibility testing.

3) Why read on?
   
   Answer: The article provides new insights into global bronchodilator response and reversibility.
INTRODUCTION

Airway responsiveness to a bronchodilator is widely performed in most clinical respiratory function laboratories throughout the world. Bronchodilator responsiveness (BDR) is used to predict a patient’s response to bronchodilator treatment, to establish best attainable lung function, and in clinical trials, to rule in or rule out asthma and COPD.[1-5] Although much has been learned about BDR, there continues to be confusion about its clinical usefulness [6, 7], its pathophysiologic basis, its expression[8-10] and its determinants.[11]

There is also a lack of consensus on the criteria for a significant or increased bronchodilator response.[12, 13] One obstacle is the lack of agreement on how the response should be expressed.[8-10, 12] Another is paucity of normative reference data derived from healthy general populations, as has been recommended by the American Thoracic Society (ATS)[12] and the European Respiratory Society guidelines.[13] The most common recommendation of a “cut-off” of 12% change in FEV1 from baseline for significant bronchial responsiveness has been derived from patients with obstructive lung disease.[8, 9, 14-17] It is conceivable that these cut-offs may not reflect the spectrum of responsiveness in healthy general population.[12] To date the information derived from general populations is patchy [18-20], and none comes from non-western countries. A better understanding of the worldwide distribution of BDR in health and disease would be helpful for developing global criteria for BDR for clinical use and research.
In this paper we report the bronchodilator response in terms of changes in FEV1 and in FVC, measured in population-based samples from 14 country-sites that participated in the Burden of Obstructive Lung Disease (BOLD) Study. [21, 22] The focus in this descriptive report is the distribution of BDR in healthy populations, with comparison in subpopulations with chronic airway obstruction. From these, we generated the 95th percentiles and tested for variability and consistency across countries and within the pooled sample from all countries. This study which drew participants from countries in North America, Europe, Africa, and Asia, provided the opportunity for a systematic evaluation of the reference range of airway response after bronchodilator in healthy general populations in different regions of the world.

METHODS

Subject design and participants

The target population included women and men aged 40 years and older in random population samples from 14 countries in North America, Europe, Africa, and Asia. A detailed description of the study design and rationale, and initial results of the BOLD Study, have been published elsewhere.[21, 22] Population-based sampling plans were used to recruit participants who were then invited to complete interviewer-administered standardized questionnaires on respiratory health and symptoms, smoking history, quality of life, use of health care services, cardiovascular comorbidities and other respiratory diseases. Pre-bronchodilator and post-bronchodilator spirometry testing was done for all eligible participants.
**Spirometric Testing and Quality Assurance Review**

Lung function was obtained at all BOLD sites with the use of a portable spirometer (EasyOne, ndd Medical Technologies, Andover, USA) to collect data on forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) with forced expiratory time (FET) standardized at > 6 seconds or a plateau in the last second of expiration. With the rare exception in which spirometry was contraindicated[21, 22], all sites attempted to collect pre- and post-bronchodilator measurements from all participants. Lung function was measured before and 15 mins after administering 2 doses of 100 ug of salbutamol (albuterol) via a spacer. All spirograms were reviewed by the BOLD Pulmonary Function Reading Center and assigned a quality score based on acceptability and repeatability criteria from the American Thoracic Society.[23] Data for FEV1 and FVC were deemed usable and included in this analysis if they fully met ATS acceptability criteria and were repeatable to within 200 mL.

**Definition of COPD**

As in all BOLD publications, we used the Global Initiative for Chronic Obstructive Lung Disease (GOLD) lung function criteria for defining and staging COPD,[21, 24] and the prediction equations for Caucasian derived from the third US National Health and Nutrition Examination Survey[25] to compute percentage predicted FEV1 and FVC. COPD is defined as GOLD stage 2 and greater for subgroups computation.
**Statistical Analysis**

*Indices of BDR*

We generated six measures of bronchodilator response, 3 each for the forced expiratory volume in first second (FEV1) and in forced vital capacity (FVC), using indices recommended by the ATS[12] and the ERS[10]: Absolute change from baseline values [ΔFEV1 and ΔFVC] [10, 12] percentage change relative to initial value [%ΔFEV1, and %ΔFVC] [10, 12]; percentage change relative to predicted value [%ΔFEV1_p and %ΔFVC_p].[8, 9, 13, 18]

*Establishment of the upper normal limit of BDR*

The ‘normal’ range of BDR was determined from its distribution among healthy never-smoking participants, defined as never smokers who did not report current asthma, chronic bronchitis, doctor diagnosis of emphysema, COPD or tuberculosis, which is the standard definition used in developing prediction equations for lung function.[Hankinson 1999] The upper limit of normality of the BDR was defined as the observed upper 95^{th} percentile [18] calculated separately for each site. These estimates and their associated 95\% confidence intervals were then used to generate forest plots and accompanying weighted estimates of the 95^{th} percentiles that are pooled across sites along with tests for heterogeneity across sites. Individual sites are weighted according to the precision of the estimate at that site and these weights are reflected in the forest plots. We used simple un-weighted statistics to summarize various statistics in tabular form for the cohort overall and for subgroups. All analyses were done using Stata, version 10.0 [Stata Corp, College station, TX, USA], and the forest plot analyses used the metan procedure.
RESULTS

Of a total of 10,712 subjects, 10,360 [97%] had either acceptable pre- and post-bronchodilator FEV1 data [n=10,217] or acceptable pre-and post-bronchodilator FVC data [n=9,546] and are included in this analysis.

Table 1 shows the demographics and baseline characteristics of the analyzed cohort for each site. The mean ages and standard deviation (sd) ranged from 52.3 years (10.3) in the Philippines to 60.1 (12.8) years in Norway. Patterns of current cigarette smoking varied widely across sites: the lowest smoking rate was 14% in Canada; the highest smoking rate was 46% in South Africa. The intensity of tobacco exposure for smokers expressed as mean(sd) pack-years ranged from 18.5(19.8) in the Philippines to 38.6(28.9) in Kentucky, USA.
<table>
<thead>
<tr>
<th>Site</th>
<th>Australia</th>
<th>Austria</th>
<th>Canada</th>
<th>China</th>
<th>Germany</th>
<th>Iceland</th>
<th>Kentucky</th>
<th>Norway</th>
<th>Philippines</th>
<th>Poland</th>
<th>South Africa</th>
<th>Sweden</th>
<th>Turkey</th>
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<tr>
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<td>1349</td>
<td>856</td>
<td>602</td>
<td>713</td>
<td>760</td>
<td>563</td>
<td>707</td>
<td>918</td>
<td>603</td>
<td>896</td>
<td>588</td>
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<td>697</td>
</tr>
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<td>Men (%)</td>
<td>50%</td>
<td>55%</td>
<td>42%</td>
<td>48%</td>
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<td>53%</td>
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<td>52%</td>
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<tr>
<td>Men &amp; women</td>
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<td>1298</td>
<td>845</td>
<td>572</td>
<td>574</td>
<td>600</td>
<td>517</td>
<td>676</td>
<td>916</td>
<td>562</td>
<td>865</td>
<td>553</td>
<td>846</td>
<td>688</td>
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<td>Age in yrs</td>
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<td>54.0</td>
<td>58.2</td>
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<td>56.7</td>
<td>60.1</td>
<td>52.3</td>
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<td>(12.4)</td>
<td>(11.6)</td>
<td>(11.9)</td>
<td>(10.9)</td>
<td>(11.0)</td>
<td>(11.8)</td>
<td>(9.9)</td>
<td>(12.8)</td>
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<td>(11.6)</td>
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<td>(10.6)</td>
<td>(11.5)</td>
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<td>Current Smoker %</td>
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<td>19.2</td>
<td>13.5</td>
<td>28.2</td>
<td>20.6</td>
<td>26.3</td>
<td>26.0</td>
<td>32.4</td>
<td>28.8</td>
<td>45.9</td>
<td>14.7</td>
<td>33.7</td>
<td>21.1</td>
<td>20.6</td>
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<tr>
<td>PackYears (Cohort)</td>
<td>12.4</td>
<td>13.2</td>
<td>11.9</td>
<td>11.1</td>
<td>15.1</td>
<td>12.8</td>
<td>23.4</td>
<td>12.7</td>
<td>9.7</td>
<td>16.1</td>
<td>11.5</td>
<td>10.5</td>
<td>16.0</td>
<td>16.3</td>
</tr>
<tr>
<td>PackYears (Smoker)</td>
<td>12.4</td>
<td>13.2</td>
<td>11.9</td>
<td>11.1</td>
<td>15.1</td>
<td>12.8</td>
<td>23.4</td>
<td>12.7</td>
<td>9.7</td>
<td>16.1</td>
<td>11.5</td>
<td>10.5</td>
<td>16.0</td>
<td>16.3</td>
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<td>Pre-BD FEV1 % pred</td>
<td>93.3</td>
<td>92.8</td>
<td>95.6</td>
<td>84.8</td>
<td>95.2</td>
<td>89.8</td>
<td>83.4</td>
<td>92.3</td>
<td>74.7</td>
<td>92.2</td>
<td>76.8</td>
<td>93.0</td>
<td>89.0</td>
<td>87.6</td>
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<tr>
<td>Post-BD FEV1 % pred</td>
<td>95.9</td>
<td>95.5</td>
<td>99.2</td>
<td>86.5</td>
<td>97.5</td>
<td>93.0</td>
<td>86.7</td>
<td>94.7</td>
<td>77.0</td>
<td>94.9</td>
<td>79.4</td>
<td>95.8</td>
<td>92.3</td>
<td>90.7</td>
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<tr>
<td>GOLD stages†</td>
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<tr>
<td>Stage I</td>
<td>8.3</td>
<td>14.8</td>
<td>10.2</td>
<td>4.3</td>
<td>8.1</td>
<td>8.6</td>
<td>5.4</td>
<td>11.9</td>
<td>1.2</td>
<td>11.6</td>
<td>4.0</td>
<td>9.6</td>
<td>8.6</td>
<td>11.0</td>
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<td>Stage II</td>
<td>9.3</td>
<td>8.3</td>
<td>6.3</td>
<td>5.6</td>
<td>5.6</td>
<td>6.7</td>
<td>10.7</td>
<td>7.7</td>
<td>7.1</td>
<td>8.6</td>
<td>13.0</td>
<td>4.7</td>
<td>9.1</td>
<td>9.3</td>
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<td>Stage III</td>
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<td>1.1</td>
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<td>3.7</td>
<td>0.9</td>
<td>3.7</td>
<td>1.8</td>
<td>5.8</td>
<td>1.5</td>
<td>1.1</td>
<td>2.1</td>
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<td>Stage IV</td>
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<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.5</td>
<td>0.7</td>
<td>0.0</td>
<td>0.6</td>
<td>0.0</td>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
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<tr>
<td>Any respiratory Medication (%)</td>
<td>23.0</td>
<td>6.4</td>
<td>32.4</td>
<td>2.6</td>
<td>19.7</td>
<td>30.0</td>
<td>44.0</td>
<td>26.5</td>
<td>8.6</td>
<td>9.8</td>
<td>41.6</td>
<td>6.0</td>
<td>22.5</td>
<td></td>
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<tr>
<td>Asthma Ever (%)</td>
<td>17.2</td>
<td>7.1</td>
<td>14.3</td>
<td>3.2</td>
<td>9.7</td>
<td>16.7</td>
<td>22.1</td>
<td>17.3</td>
<td>6.6</td>
<td>7.3</td>
<td>14.7</td>
<td>14.5</td>
<td>6.4</td>
<td>19.5</td>
</tr>
</tbody>
</table>

Total = 10712, analyzed cohort = 10360 [96.7%]; BMI=body mass index; FEV1=forced expiratory volume in one second; Pre-BD FEV1% pred.: pre-bronchodilator FEV1 % predicted; Pre-BD FEV1% pred.: post-bronchodilator FEV1 % predicted. * Data presented as percentage of the population or mean (SD) unless otherwise stated. † GOLD stage I: FEV1/FVC<70% and FEV1≥80% predicted; GOLD stage II: FEV1/FVC<70% and 50%<FEV1<80% predicted; GOLD stage III: FEV1/FVC<70% and 30%<FEV1<50% predicted; GOLD stage IV: FEV1/FVC<70% and FEV1<30% predicted.
All indices of bronchodilator responses in FEV1 and FVC displayed normal or near-normal distribution for the whole study population. **Table 2** shows the simple unweighted estimates of the mean change and standard deviation (SD) of BDR. For the healthy subgroup, these averages were several-fold smaller than the mean values for the subgroup with COPD. **Table 3** shows the simple unweighted estimates of the upper 95th percentiles (and associated 95% confidence intervals) for the whole study population and for selected subgroups. BDR, when expressed as an absolute change, was larger in men than in women. However the opposite pattern was seen when BDR was expressed as a percentage change. In addition, percent change when expressed relative to initial value, was always greater (sometimes markedly so) when expressed relative to initial rather than predicted value. Finally, the 95th percentiles were consistently larger for individuals with COPD (regardless of co-morbid asthma status) than for healthy lifetime never smokers.
Table 2. Mean and standard deviation (SD) [unweighted values] for Bronchodilator responses for whole study population, healthy and COPD subgroups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Population</th>
<th>Healthy Subgroup</th>
<th>COPD GS2+</th>
<th>COPD GS2+ (without asthma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Male &amp; Female</td>
<td>Male &amp; Female</td>
<td>Male &amp; Female</td>
</tr>
<tr>
<td>FEV1-based measures</td>
<td>N1=10217</td>
<td>N1=4826</td>
<td>N1=5391</td>
<td>N1=3922</td>
</tr>
<tr>
<td>∆FEV1(ml)</td>
<td>82(139)</td>
<td>95(156)</td>
<td>70(120)</td>
<td>72(130)</td>
</tr>
<tr>
<td>∆FEV1i(%)</td>
<td>3.7(6.9)</td>
<td>3.6(6.5)</td>
<td>3.8(7.3)</td>
<td>3.1(6.0)</td>
</tr>
<tr>
<td>∆FEV1p(%)</td>
<td>2.8(4.8)</td>
<td>2.7(4.6)</td>
<td>2.8(5.0)</td>
<td>2.6(4.8)</td>
</tr>
<tr>
<td>FVC-based measures</td>
<td>N2=9546</td>
<td>N2=4560</td>
<td>N2=4986</td>
<td>N2=3593</td>
</tr>
<tr>
<td>∆FVC(ml)</td>
<td>0(237)</td>
<td>4(257)</td>
<td>-4(217)</td>
<td>-21(219)</td>
</tr>
<tr>
<td>∆FVCi(%)</td>
<td>0.5(7.9)</td>
<td>0.5(6.9)</td>
<td>0.5(8.7)</td>
<td>-0.3(7.4)</td>
</tr>
<tr>
<td>∆FVCp(%)</td>
<td>0.1(6.6)</td>
<td>0.2(5.9)</td>
<td>0(7.3)</td>
<td>-0.5(6.7)</td>
</tr>
</tbody>
</table>
ΔFEV1(ml) and ΔFVC(ml) are absolute change after bronchodilator; ΔFEV1i and ΔFVCi are change as a percent of initial value; ΔFEV1p and ΔFVCp are change as percent of predicted value. N1 is number with nonmissing FEV1s and N2 is number with nonmissing FVCs. COPD GS2+ = FEV1/FVC< 0.7 and FEV1% predicted<80%; COPD GS2+ (without asthma) = post bronchodilator spirometrically-defined COPD excluding those with self-reported asthma.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Population</th>
<th>Healthy Subgroup</th>
<th>COPD GS2+</th>
<th>COPD GS2+ (without asthma)</th>
</tr>
</thead>
</table>

Table 3. Upper 95th percentiles with 95% confidence interval (C.I.) [ unweighted values] for Bronchodilator responses for whole study population, healthy and COPD subgroups.
\( \Delta FEV1(\text{ml}) \) and \( \Delta FVC(\text{ml}) \) are absolute change after bronchodilator; \( \Delta FEV1i \) and \( \Delta FVCi \) are change as a percent of initial value; \( \Delta FEV1p \) and \( \Delta FVCp \) are change as percent of predicted value. N1 is number with nonmissing FEV1s and N2 is number with nonmissing FVCs.

COPD GS2+ = FEV1/FVC< 0.7 and FEV1% predicted<80%; COPD GS2+, without asthma = COPD GS2+ but with no self-reported diagnosis of asthma.

In the COPD subgroups, the confidence intervals for individual sites were large due to small sample size[<50].

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>Male &amp; Female</th>
<th>Male &amp; Female</th>
<th>Male &amp; Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV1-based measures</strong></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>( \Delta FEV1(\text{ml}) )</td>
<td>N1=10217</td>
<td>314 (306,324)</td>
<td>354 (340,368)</td>
<td>265 (257,278)</td>
<td>291 (279,309)</td>
<td>371 (343,402)</td>
</tr>
<tr>
<td>( \Delta FEV1(% ) )</td>
<td>14.6 (14.1,15.3)</td>
<td>14.0 (13.2,14.6)</td>
<td>15.4 (14.5,16.0)</td>
<td>12.5 (11.9,13.2)</td>
<td>30.9 (27.8,33.8)</td>
<td>27.7 (21.6,30.9)</td>
</tr>
<tr>
<td>( \Delta FEV1(\text{p}% ) )</td>
<td>10.6 (10.3,10.9)</td>
<td>10.2 (9.9,10.6)</td>
<td>10.9 (10.5,11.3)</td>
<td>10.1 (9.7,10.7)</td>
<td>13.1 (12.3,14.6)</td>
<td>12.3 (11.6,13.5)</td>
</tr>
<tr>
<td><strong>FVC-based measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta FVC(\text{ml}) )</td>
<td>N2=9546</td>
<td>395 (381,414)</td>
<td>454 (419,486)</td>
<td>347 (328,374)</td>
<td>337 (317,358)</td>
<td>635 (591,678)</td>
</tr>
<tr>
<td>( \Delta FVC(% ) )</td>
<td>13.3 (12.7,13.9)</td>
<td>12.6 (11.8,13.4)</td>
<td>14.1 (13.2, 15.1)</td>
<td>11.2 (10.5,12.2)</td>
<td>29.4 (26.6,31.6)</td>
<td>26.7 (24.4,30.6)</td>
</tr>
<tr>
<td>( \Delta FVC(\text{p}% ) )</td>
<td>10.8 (10.4,11.4)</td>
<td>10.4 (9.7,10.8)</td>
<td>11.6 (10.7,12.5)</td>
<td>9.6 (9.1,10.3)</td>
<td>18.0 (17.0,19.7)</td>
<td>17.3 (15.7,18.8)</td>
</tr>
</tbody>
</table>
Figures 1 to 6 show the forest plots of the upper 95\textsuperscript{th} percentile for the 6 measures of BDR for the subset of healthy never smokers. More precise estimates received greater weight, as shown in the figures, when calculating the pooled estimates, and hence the pooled estimates here differ somewhat from the un-weighted estimates of 95\textsuperscript{th} percentiles for all subjects shown in table 3, although they are qualitatively similar. In healthy lifetime non-smokers, pooled weighted estimate of the threshold for absolute change $\Delta$FEV1 is 284 mL, with significant cross-site heterogeneity in estimates, that is 54% of overall variation in estimate comes from site to site variability. [Fig1]. The pooled weighted estimate for $\%\Delta$FEV1\textsubscript{p} [Fig3] is smaller than for $\%\Delta$FEV1\textsubscript{i} [Fig2], with no cross-site heterogeneity in both cases. In contrast, the estimates for the FVC-based thresholds [Figs.4-6] all demonstrated marked cross-site heterogeneity, ranging from 66-80%.

Using the weighted thresholds from figures 1-6, we then calculated the simple, unweighted proportion of individuals who exceeded these thresholds for various subgroups (Table 4). The proportion of people without airway obstruction who exceeded the threshold was consistently lower than that for people with airway obstruction for both the FEV1-based and FVC-based thresholds. The proportion people in the COPD subgroups who exceeded the FEV1-based thresholds( except for $\Delta$FEV1\textsubscript{i}) decreased with increasing severity of COPD as defined by GOLD stages.[24] On the contrary, the proportion of people in the COPD subgroups who exceeded the FVC-based thresholds showed a tendency to increase with severity.
Table 4. The proportion of people in excess of thresholds for overall cohort, for subgroups of normal, GOLD stage1, GOLD stage2 and GOLD stage 3-4

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>Normal</th>
<th>GOLD stage 1</th>
<th>GOLD stage2</th>
<th>GOLD stage 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1-based thresholds</td>
<td>N1=10217</td>
<td>N1=7931</td>
<td>N1=846</td>
<td>N1=790</td>
<td>N1=219</td>
</tr>
<tr>
<td>∆FEV1(&gt;284 ml)</td>
<td>6.7%</td>
<td>5.6%</td>
<td>11.5%</td>
<td>12.2%</td>
<td>7.3%</td>
</tr>
<tr>
<td>∆FEV1i(&gt;12%)</td>
<td>7.8%</td>
<td>4.4%</td>
<td>11.6%</td>
<td>27.3%</td>
<td>43.4%</td>
</tr>
<tr>
<td>∆FEV1p(&gt;10%)</td>
<td>6.0%</td>
<td>4.3%</td>
<td>12.3%</td>
<td>13.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>FVC-based thresholds</td>
<td>N2=9546</td>
<td>N2=7697</td>
<td>N2=819</td>
<td>N2=764</td>
<td>N2=212</td>
</tr>
<tr>
<td>∆FVC(&gt;322ml)</td>
<td>7.5%</td>
<td>4.0%</td>
<td>21.2%</td>
<td>20.7%</td>
<td>29.7%</td>
</tr>
<tr>
<td>∆FVCi(&gt;10.5%)</td>
<td>7.5%</td>
<td>3.8%</td>
<td>17.0%</td>
<td>24.7%</td>
<td>42.5%</td>
</tr>
<tr>
<td>∆FVCp(&gt;9.2%)</td>
<td>6.8%</td>
<td>3.2%</td>
<td>21.6%</td>
<td>20.5%</td>
<td>27.8%</td>
</tr>
</tbody>
</table>

V1(ml) and ∆FVC(ml) are absolute change after bronchodilator; ∆FEV1i and ∆FVCi are change as a percent of initial value; ∆FEV1p and ∆FVCp are change as percent of predicted value. N1 is number with nonmissing FEVs and N2 is number with nonmissing FVCs. Normal = not classified as any GOLD stage; GOLD stage1 = FEV1/FVC<0.7 and FEV1%predicted >80%; GOLD stage 2 = FEV1/FVC<0.7 and FEV1% predicted<80%, GOLD stage 3-4 = FEV1/FVC<0.7 and FEV1%predicted<50%.
DISCUSSION

We have measured the bronchodilator response in general population samples, aged 40 and older, from sites in 14 countries spanning four continents. The main findings indicated that the thresholds or upper limit of normality for the percent change in FEV1 relative to initial level is 12% and for the FEV1 relative to predicted FEV1 is 10% without heterogeneity across populations. These values agree well with current ATS guideline cut-offs for defining a significant bronchodilator response and strengthen the applicability of these measures for global interpretation in bronchodilator testing. We further validated these thresholds in obstructed and non-obstructed people and confirmed that a higher proportion of people with obstruction of all stages of severity had BDR compared with non-obstructed people, findings that are consistent with previous studies in healthy individuals and people with airway obstruction using ATS–ERS thresholds.[10]

There were two secondary findings. First, the BDR threshold for people with chronic airflow obstruction was lower when asthma was excluded, but there was considerable overlap between the two groups with and without exclusion of asthma, consistent with previous studies.[1, 26, 27] Also, there were differences between the FEV1-based and the FVC-based thresholds in their association with severity of airflow obstruction. The proportion with reversibility measured by changes in FEV1 generally decreased as COPD severity increased while that with reversibility measured by changes in FVC increased with increasing COPD severity, findings which are consistent with the findings reported in clinical trials of COPD patients, using ATS reversibility criteria.[4] These findings
support the use of lung volume-based measures of reversibility in addition to FEV1-based measures in patients with more severe COPD.[26]

In this analysis the thresholds for BDR for healthy people were derived from random samples of adults aged 40 years and over in the general population. According to the ERS guidelines, an ambiguous bronchodilator response should exceed spontaneous variability and the response observed in healthy individuals.[13] Yet, evidence for the different published criteria had largely been based on data of selected patients with airflow limitation.[8, 9, 14-17, 28] Existing data on the upper limit of the bronchodilator response in the healthy population are few and dated[18, 29] although a recent study of unselected urban population in Iceland reported a 95\textsuperscript{th} percentile of 9% for increase in FEV1 from baseline [ %\Delta FEV1i].[19] Therefore, the results from this study add to reference values from smaller population studies from single countries[18-20] and provided global reference values for the interpretation of bronchodilator testing.

Two separate approaches have been used to derive reference values for a bronchodilator response. The first method was to assume that values greater than the 95\textsuperscript{th} percentile in distribution of healthy subjects was abnormal.[18] The second method was to measure the short term spontaneous variation or placebo-induced changes in FEV1 in patients.[15-17] The first method was used in this study. The joint ATS-ERS guidelines[10] recommendation of 12% percentage change from baseline and 200 mL absolute changes in FEV1 and /or FVC in an individual subject to identify a positive/ significant bronchodilator response was derived using the second approach, but recognized the need
to obtain references in healthy populations based on the first method. Thus, the results from this study provided new data relevant to this gap in information.

The ‘cut-off’ values in our analysis differ somewhat compared with that from single site population studies of healthy subjects. For defining a positive response, these studies had suggested 95th percentile thresholds of 130 mL[18] or 240 mL[19] for absolute change in FEV1; 9%[18] or 5.9%[19] for % change in FEV1 from initial value [%ΔFEV1i] and 9%[8, 18] for change in FEV1 relative to predicted value [%ΔFEV1p]. In our study, the derived cut-offs for %ΔFEV1i and %ΔFEV1p are higher but stable as evidenced by the lack of site heterogeneity. Also, these threshold values complied with the caution to exceed the measurement variability of at least 8% change within individuals for defining an unambiguous response.[8, 30, 31] The FVC thresholds were included as the ATS/ERS recommendation included these[10] to accommodate both flow responder as well as volume responders to inhaled bronchodilators.[32, 33]

Comparison of our healthy population-based thresholds with the thresholds of guidelines based on patient studies provided insight into the short-term variability of BDR measurements. In this global study, the 95th percentile cut-offs of bronchodilator response in healthy never-smokers of 12% for ΔFEV1i was identical to the cut-offs of 12% change in FEV1 or FVC for a positive response required by international guidelines[10] while 10% for ΔFEV1p was similar to 9% found by one study in patients.[8] The guideline recommendation for a positive BDR had been based on observations in selected patients with asthma and COPD, and on the fact that there was a short term intrasubject variability
of 200 mL in flow volume indices.[34] Although the long term variability in lung function in patients is larger than in the healthy subjects, the short term variability in patients in a stable condition is very similar to normal subjects, with an observed 95% confidence interval of change in FEV1 of 190 mL and 12.3%.[15, 16] This could be a potential explanation for the similarity between thresholds values in our study and the guideline recommendations.[10]

There is no consensus on how bronchodilator response is best expressed: in absolute terms or as % of initial value[10, 12], or as % of predicted value.[13] Of the six indices of bronchodilator response in this global study, we showed that the % change in FEV1 relative to either baseline or predicted were the most stable across sites, while there was significant site-to-site variability in all FVC estimates and in absolute FEV1 change. Overall, this population-based evidence supports the use of 10 % increase relative to predicted FEV1 to determine BD reversibility, as this feature is stable across sites, is independent of sex and stable across GOLD stages - yet discriminates healthy subjects from obstructive individuals. Nevertheless in practice, it would be prudent to couple any % threshold with a qualifying volume threshold .[10]

This is the first study to compare BDR in population-based samples from a large number of sites on several continents. This information adds to the growing body of data on lung function that will help us to understand the range of normality and what may influence this. Other strengths of the study include the careful attention to standardization and quality control used across all sites in the BOLD study[21, 22] and the well-recognized
technique of the defining the 95th percentile in the healthy population for deriving the reference for bronchodilator response thresholds.[18, 19]

A potential limitation of the study is that our definition of healthy never smokers relies on self report of doctor diagnosed lung disorders rather than objectively defined obstructive lung disease, since both diagnostic practices and access to care might vary across our widely dispersed sites. Nonetheless this is standard practice for developing reference equations for lung function [ Hankinson et al; PLATINO et al ] . Also, we would note that only 4% of our healthy never smokers met criteria for GOLD stage 2 or higher COPD, suggesting that the results would be unlikely to change much by excluding these individuals, and indeed we confirmed this for tables 2 and 3 (data not shown).

Second, because the distribution of bronchodilator responses are continuous and unimodal as had been shown in clinical studies[8, 9, 15] and population studies.[18-20] Hence, the cut-off value for a ‘positive’ response in all studies including ours, remained somewhat arbitrary.[35] Third, we used 200 µg of salbutamol/albuterol instead of higher doses as an extra precaution because it was a field study and involved home visits in many sites. While GOLD guidelines recommended 400 µg, many published clinical studies have used different types and doses of drugs as summarized in the recent paper on bronchodilator reversibility by Hanania et al.[26] Lastly, we had demonstrated the effect of acute reversibility due to bronchodilator in one setting but not its reproducibility on repeated testing and also not the long term reversibility due to anti-inflammatory drugs. Hence, a lack of a response to bronchodilator testing in one setting may not preclude a clinical response to bronchodilating or anti-inflammatory therapy.[10, 24]
In conclusion, the results from this study add new worldwide data on the distribution of bronchodilator response and airway reversibility. The reference values derived from healthy individuals addressed the reference gap in BDR. The values agreed well with the current guideline cut-offs for a significant bronchodilator response, were discriminative for different subpopulations and strengthen the applicability of these measures for global interpretation in bronchodilator testing.

REFERENCES


LEGENDS

Figure 1: Absolute Change in FEV1 in mls. after bronchodilator [ΔFEV1] expressed as 95\textsuperscript{th} percentile with 95\% confidence interval [CI] in healthy non-smokers. Those sites whose estimates are most stable get greater weight (right hand column) in constructing the pooled estimate of 284ml. We observed significant heterogeneity across sites (p=0.008), with 54\% of the overall variability in the data attributable to site-site variability.

Figure 2: Percentage Change in FEV1 relative to initial baseline, after bronchodilator [BDR FEV1\textsubscript{i}] expressed as 95\textsuperscript{th} percentile with 95\% confidence interval [CI], in healthy non-smokers. The pooled estimate is 12\% with no evidence of cross-site heterogeneity.

Figure 3: Percentage Change in FEV1 relative to predicted FEV1, after bronchodilator [%ΔFEV1\textsubscript{p}] expressed as 95\textsuperscript{th} percentile with 95\% confidence interval [CI], in healthy non-smokers. The pooled estimate is 10\% with no evidence of cross-site heterogeneity.

Figure 4: Absolute Change in FVC after bronchodilator [BDRFVC mls] expressed as 95\textsuperscript{th} percentile with 95\% confidence interval [CI] in healthy non-smokers. Those sites whose estimates are most stable get greater weight (right hand column) in constructing the pooled estimate of 322ml. We observed significant heterogeneity across sites (p<0.0001), with 75\% of the overall variability in the data attributable to site-site variability.
Figure 5: Percentage Change in FVC relative to initial baseline, after bronchodilator [BDR FVC1i] expressed as 95th percentile with 95% confidence interval [CI] , in healthy non-smokers. Those sites whose estimates are most stable get greater weight (right hand column) in constructing the pooled estimate of 11%. We observed significant heterogeneity across sites (p<0.0001), with 66% of the overall variability in the data attributable to site-site variability.

Figure 6: Percentage Change in FVC relative to predicted FVC, after bronchodilator [BDR FVCp] expressed as 95th percentile with 95% confidence interval [CI] , in healthy non-smokers. Those sites whose estimates are most stable get greater weight (right hand column) in constructing the pooled estimate of 9%. We observed significant heterogeneity across sites (p<0.0001), with 80% of the overall variability in the data attributable to site-site variability.