**APPENDIX**

**Bronchodilator responsiveness as a phenotypic characteristic of established COPD**

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*Contents:*

1. *Supplemental Methods*
2. *Supplemental Tables*
3. *Supplemental Figures*

*Appendix Supplement 1.*

*Additional Methods*

Participants performed spirometry (VIASYS MasterScope™) at the same time of day, before and 15 minutes after inhaling 400 mcg salbutamol from a metered dose inhaler via a volumatic spacer. With the subject seated wearing a nose clip they performed at least three acceptable manoeuvres that met ATS/ERS criteria (s1). All traces were independently reviewed to confirm that they met the test criteria and doubtful cases were adjudicated by senior investigators, with feedback to each center to maintain between-test quality. Only data from technically acceptable traces were included in this analysis. Subjects omitted short-acting bronchodilators for at least 6 hours and long acting inhaled bronchodilators for 24 hours pre-visit. Predicted values were based on European Community Coal and Steel data (s2).

CT scanning was performed without bronchodilatation within one day of lung function testing. All CT scans were acquired using multidetector-row CT scanners (GE Healthcare, Milwaukee, Wis. or Siemens Healthcare, Erlangen, Germany) with a minimum of 4 rows at suspended full inspiration without administration of intravenous contrast. Exposure settings were 120kVp and 40mAs; images were reconstructed using 1.0mm (Siemens) or 1.25mm (GE) contiguous slices and a low spatial frequency reconstruction algorithm (GE: standard; Siemens: b35f). All CT scans were analyzed using "Pulmonary Workstation 2.0" software (VIDA Diagnostics, Iowa City, IA). Lungs were segmented from the thoracic wall, the heart and main pulmonary vessels. The extent of emphysema was estimated using the threshold technique quantifying the percent of voxels with an apparent X-ray attenuation

value below -950HU (%LAA) (s3) Emphysema was visually scored by two experienced chest radiologists, who independently scored all CT scans as follows: 0 = no emphysema, 1 = <5% (trivial), 2 = 5-25% (mild), 3 = 26-50% (moderate), 4 = 51-75% (severe) and 5 = >75% involvement of both lungs (very severe). In case of disagreement, the mean score of the two readers was used as the final score (0.5, 1.5, 2.5, 3.5 or 4.5) unless the results differed more than 1 category. For those cases consensus was reached in a separate reading session and that score was used (s4).

**References**

S1. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;**26**:319–38.

S2. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J.* 1993;**16(suppl)**:5–40.

S3. Gevenois PA, de Maertelaer V, De Vuyst P, et al. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;**152**:653-657.

S4. Gietema HA, Müller NL, Nasute Fauerbach PV, et al. Quantifying the extent of emphysema: Factors associated with radiologists' estimations and quantitative indices of emphysema severity using the ECLIPSE Cohort. *Acad Radiol.* 2011;**18**:661-71

***Appendix Table 1.*** **Demographics and Background Characteristics Stratified by History of Asthma**

| {tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2} | COPD Subjects | | | Smoker Controls | | | Non-smoker Controls | | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Yes** | **No** | **p-value** | **Yes** | **No** | **p-value** | **Yes** | **No** | **p-value** |
| N | 402 | 1429 | | 16 | 269 | | 5 | 223 | |
| Age (yrs) | 62.0 (7.5) | 63.8 (6.8) | <0.001 | 58.7 (8.6) | 55.6 (8.9) | 0.178 | 51.0 (6.0) | 54.1 (9.0) | 0.446 |
| Sex (M/F) | 223/179 | 984/445 | <0.001 | 6/10 | 159/110 | 0.090 | 1/4 | 88/135 | 0.379 |
| Pre-bronchodilator FEV1 (L) | 1.21 (0.49) | 1.26 (0.49) | 0.041 | 2.76 (0.63) | 3.23 (0.71) | 0.011 | 3.14 (0.54) | 3.25 (0.79) | 0.771 |
| Pre-bronchodilator FEV1 % Predicted | 44.4 (15.4) | 44.8 (14.8) | 0.606 | 101.0 (14.2) | 104.4 (11.9) | 0.264 | 102.5 (10.9) | 112.5 (14.0) | 0.115 |
| Chg in FEV1 Post-bronchodilator (L) | 0.13 (0.17) | 0.12 (0.14) | 0.187 | 0.15 (0.15) | 0.14 (0.15) | 0.751 | 0.20 (0.11) | 0.08 (0.14) | 0.051 |
| Reversibility (%) | 12.1 (16.4) | 10.6 (12.8) | 0.047 | 5.8 (6.1) | 4.4 (5.8) | 0.349 | 6.2 (3.2) | 2.6 (4.6) | 0.085 |

**Appendix Table 2.** Change in $FEV_1$ Lung Function after Bronchodilator in the COPD Patients as a Whole and then Separated into Current and Ex-Smoking Patients

| {tc "Report " \f C \l 1}{tc "Detailed and/or summarized report " \f C \l 2}**Mean (SD)** | **Visit (Months)** | **COPD patients** | **Current Smokers** | **Former Smokers** |
|---|---|---|---|---|
| Post-bronchodilator $FEV_1$ change (L) | 0 | 0.12 (0.15) | 0.12 (0.15) | 0.12 (0.15) |
| | 3 | 0.12 (0.14) | 0.13 (0.14) | 0.12 (0.14) |
| | 6 | 0.13 (0.15) | 0.13 (0.15) | 0.12 (0.15) |
| | 12 | 0.12 (0.14) | 0.12 (0.14) | 0.12 (0.14) |
| Post-bronchodilator FVC change (L) | 0 | 0.25 (0.34) | 0.26 (0.34) | 0.25 (0.34) |
| | 3 | 0.25 (0.32) | 0.28 (0.33) | 0.24 (0.31) |
| | 6 | 0.24 (0.32) | 0.26 (0.34) | 0.23 (0.30) |
| | 12 | 0.23 (0.31) | 0.24 (0.30) | 0.22 (0.31) |
| Post-bronchodilator $FEV_1$/FVC change | 0 | 0.29 (4.35) | 0.15 (4.48) | 0.36 (4.28) |
| | 3 | 0.35 (4.15) | 0.02 (4.02) | 0.52 (4.20) |
| | 6 | 0.61 (4.43) | 0.47 (4.36) | 0.68 (4.47) |
| | 12 | 0.71 (4.13) | 0.56 (4.22) | 0.79 (4.08) |

; A = ?????  OK here or should it be in a footnote - sme comment applies for all figure 1 parts.44444444444444444444444444444444444$FEV_1$ = forced expiratory volume in one second; FVC = forced vital capacity.

Note that continued active smoking did not influence any spirometric change after salbutamol.

**Appendix Figure 1. Frequency distribution of the change in FEV$_1$ post–bronchodilator in all COPD patients, smoker controls and non-smoker controls (panels A to C) and in the COPD group divided by GOLD stage II to IV respectively (panels D to F).**
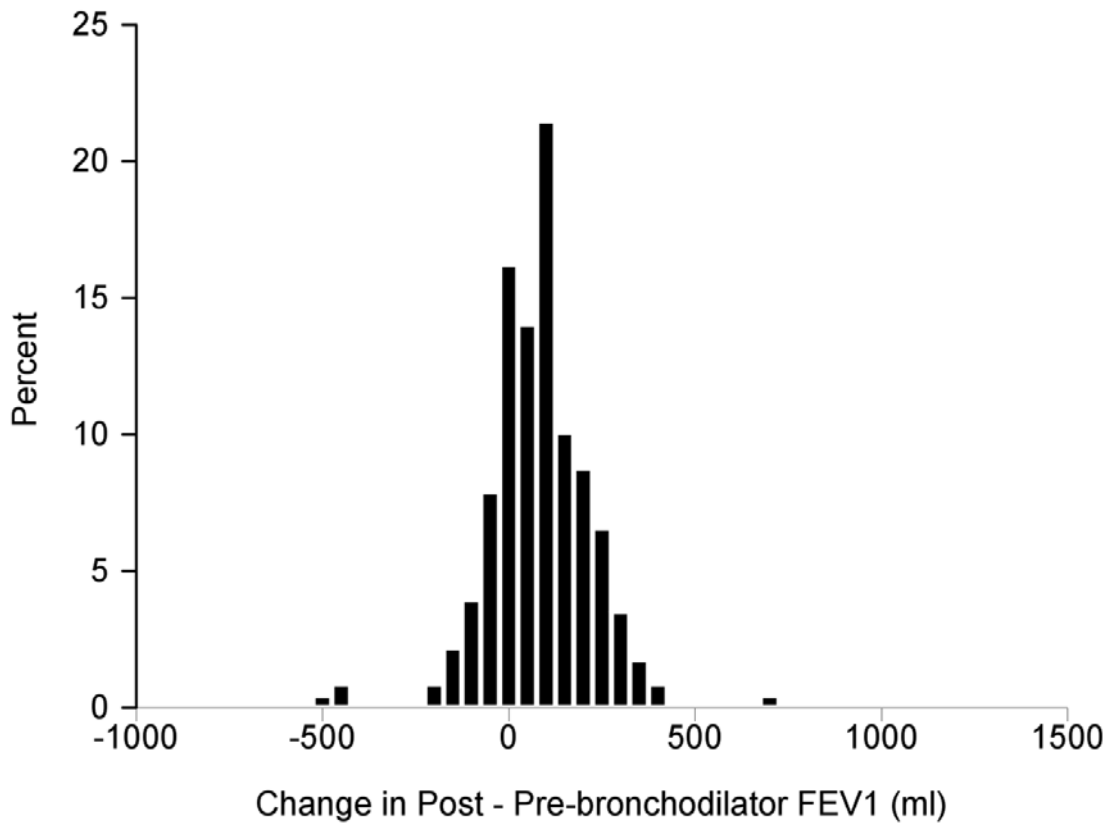
*Appendix Figure 1A - All COPD:* **Skewness – Test statistic (SE) = 0.88 (0.06), *P* < 0.001; Kurtosis – Test statistic (SE) = 4.34 (0.11), *P* < 0.001; Kolmogorov-Smirnov – Test statistic = 0.07, *P* < 0.010.**



Change in Post - Pre-bronchodilator FEV1 (ml)
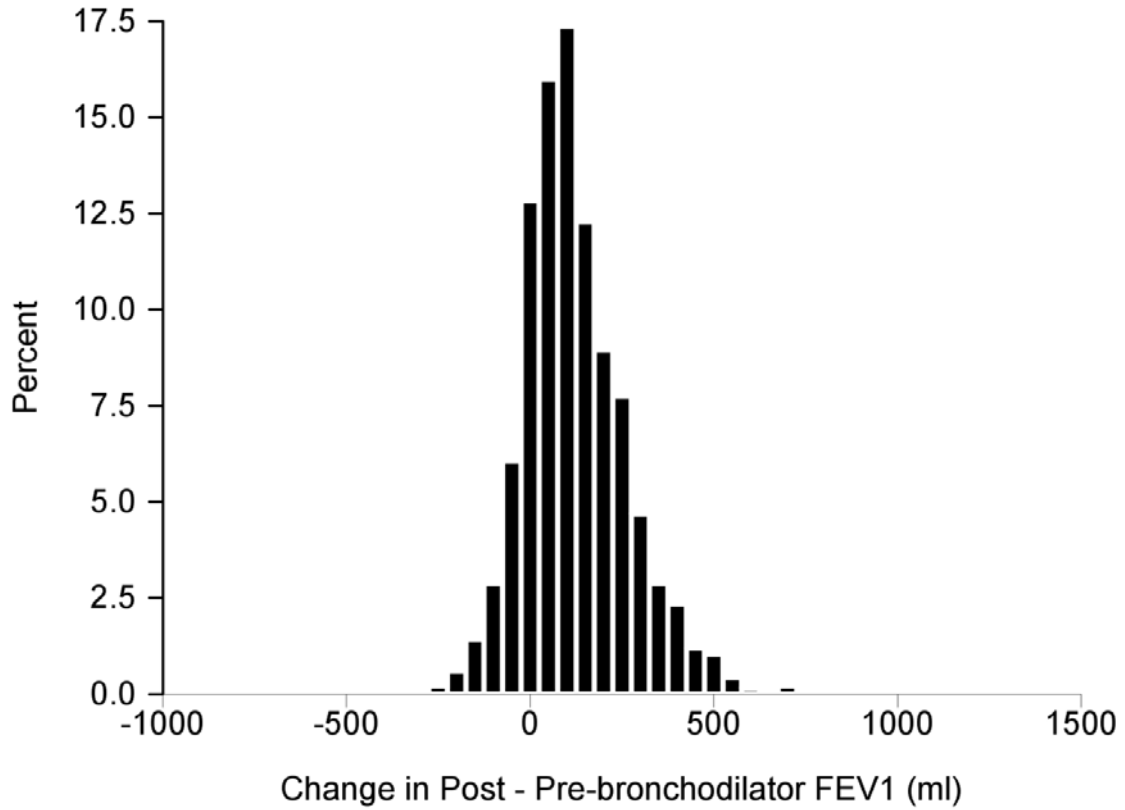
**Appendix Figure 1B - Smoker Controls:** Skewness – Test statistic (SE) = 2.05 (0.15), *P* < 0.001; Kurtosis – Test statistic (SE) = 11.65 (0.29), *P* < 0.001; Kolmogorov-Smirnov – Test statistic = 0.08, *P* < 0.010.
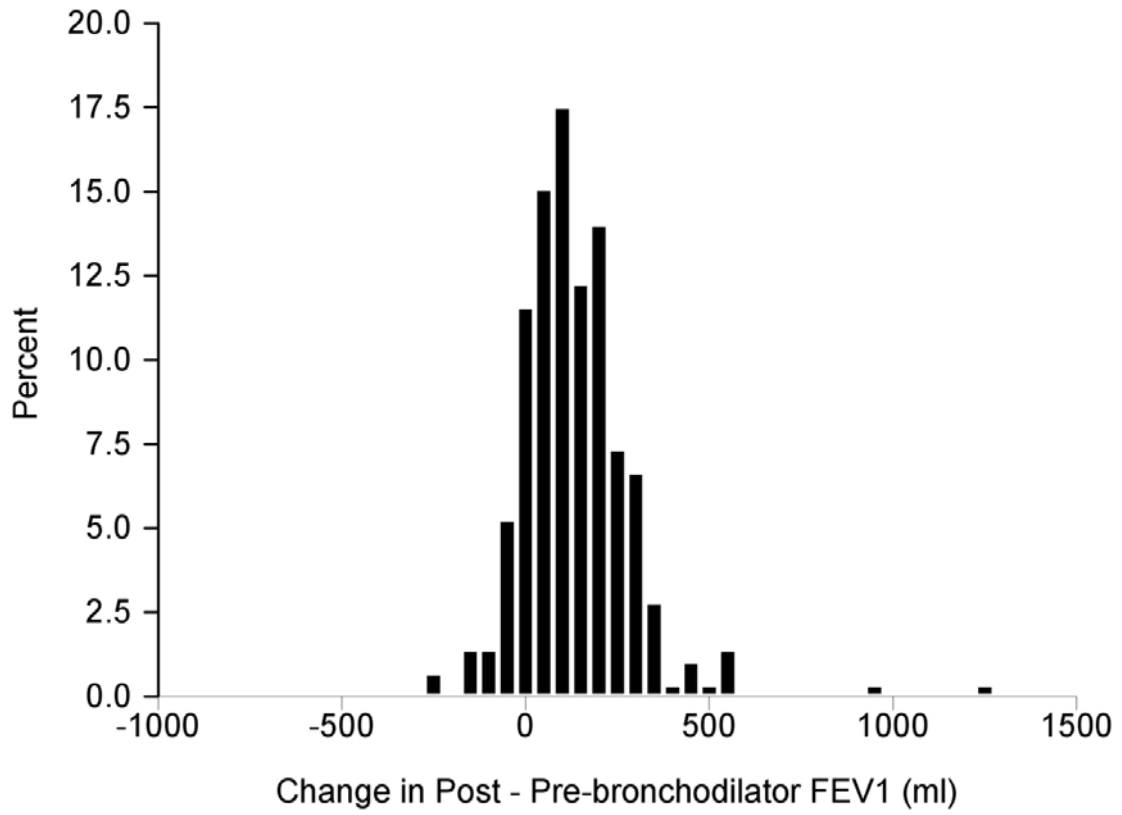
**Appendix Figure 1C - Non-Smoker Controls:** Skewness – Test statistic (SE) = –0.27 (0.16), *P* = 0.100; Kurtosis – Test statistic (SE) = 3.92 (0.32), *P* = 0.005; Kolmogorov-Smirnov – Test statistic = 0.06, *P* = 0.022.
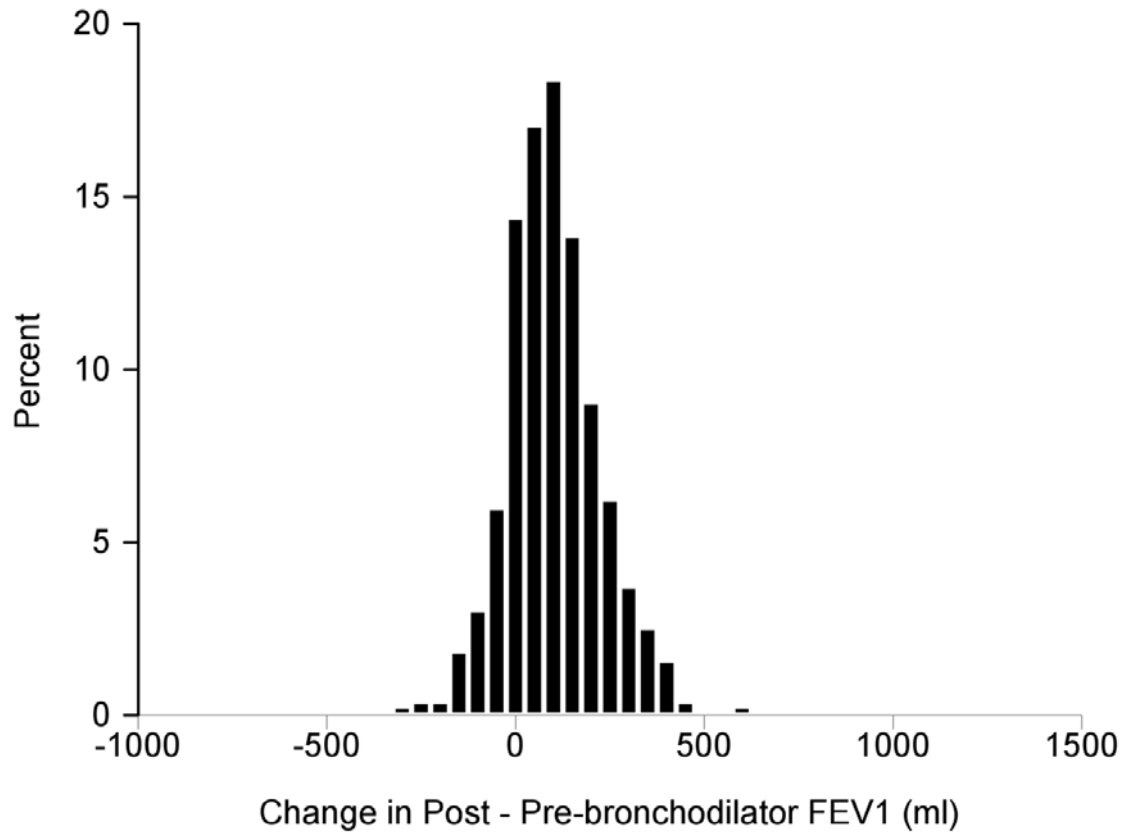
**Appendix Figure 1D – GOLD II:** Skewness – Test statistic (SE) = 0.90 (0.08), *P* < 0.001; Kurtosis – Test statistic (SE) = 4.16 (0.17), *P* < 0.001; Kolmogorov-Smirnov – Test statistic = 0.06, *P* < 0.010
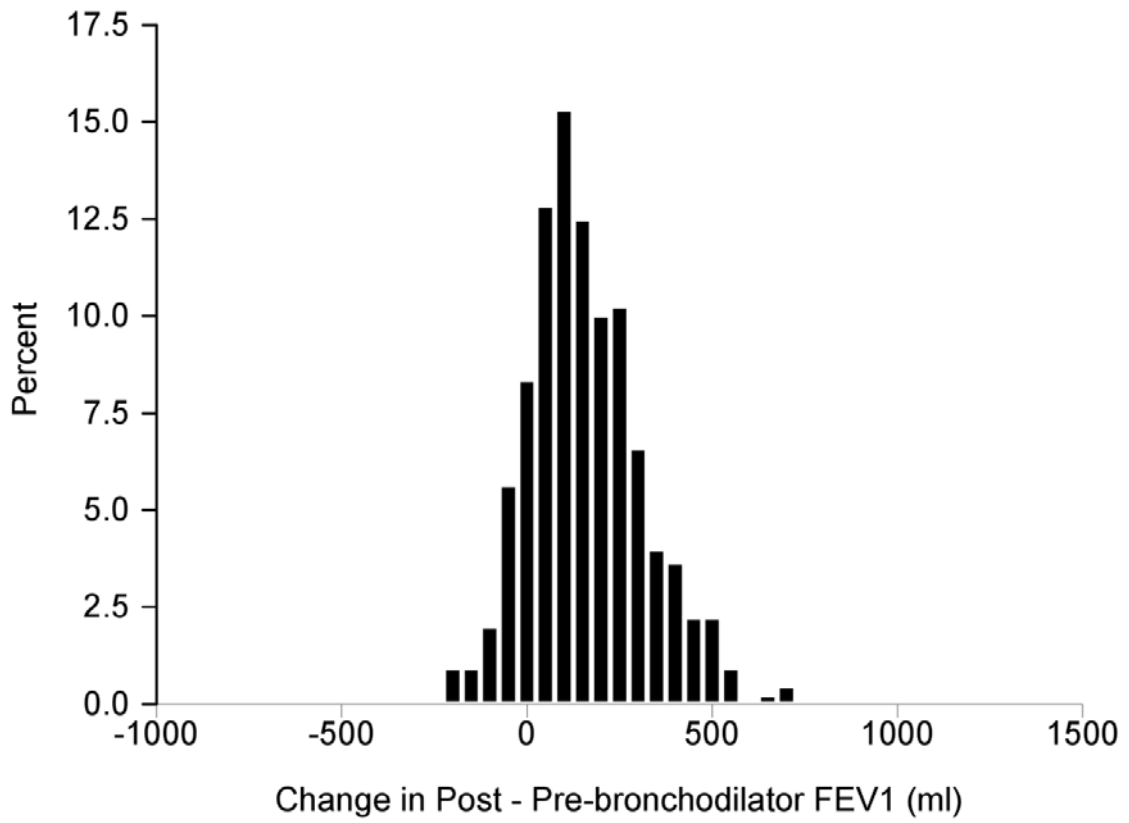
**Appendix Figure 1E – GOLD III:** Skewness – Test statistic (SE) = 0.07 (0.09), *P* = 0.445; Kurtosis – Test statistic (SE) = 1.65 (0.18), *P* < 0.001; Kolmogorov-Smirnov – Test statistic = 0.05, *P* < 0.010.

**Appendix Figure 1F – GOLD IV:** Skewness – Test statistic (SE) = 0.36 (0.16), *P* = 0.024; Kurtosis – Test statistic (SE) = 0.26 (0.32), *P* < 0.001; Kolmogorov-Smirnov – Test statistic = 0.06, *P* = 0.042.