Online Supplement

Normal Limits For Oscillometric Bronchodilator Responses and Relationships With Clinical Factors

Jetmalani, Kanika PhD[1]; Brown, Nathan J PhD[1,13]; Boustany, Chantale PhD[1,2]; Toelle, Brett G PhD[1,3], Marks, Guy B MBBS PhD[1,3,4]; Abramson, Michael J MBBS PhD[5]; Johns, David P PhD[6]; James, Alan L MBBS MD[7,8,10]; Hunter, Michael PhD[7,9]; Musk, Arthur W MBBS MD[7,8,10]; Berend, Norbert MD BS[1]; Farah, Claude S[1,11]; Chapman, David G PhD[1,12]; Thamrin, Cindy PhD[1] and King, Gregory G MBChB PhD[1,12].

[1] The Woolcock Institute of Medical Research, Faculty of Medicine and Health, The University of Sydney, NSW, Australia

[2] School of Nursing, Faculty of Medicine and Health, The University of Sydney, NSW, Australia

[3] South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

[4] Ingham Institute of Applied Medical Research, Sydney, Australia

[5] School of Population Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

[6] College of Health and Medicine, University of Tasmania, Hobart, TAS, Australia

[7] Busselton Population Medical Research Institute, Busselton, WA, Australia

[8] School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

[9] School of Population and Global Health, University of Western Australia, Perth, WA, Australia

[10] Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia

[11] Department of Thoracic Medicine, Concord Repatriation General Hospital, Sydney, Australia

[12] Department of Respiratory Medicine, Royal North Shore Hospital, Sydney, NSW, Australia

[13] Royal Brisbane and Women's Hospital, Emergency and Trauma Centre, Herston, QLD, Australia

Methods

Study population

The Sydney site was representative of the general population in Sydney based on gender distribution, age, employment status, and weekly average earnings. The Melbourne community had previously been studied as part of the European Community Respiratory Health Survey (ECRHS), and represented another Australian large city metropolitan site. Busselton is a small, coastal city that had research infrastructure from long-established general community cross-sectional and longitudinal population health studies [1]. Subjects at the Sydney and Melbourne sites were drawn from gender stratified random samples from the local divisions of the Commonwealth Electoral Roll. Subjects at the Busselton site were drawn from a random sample from the Commonwealth Electoral Roll for Busselton in the same manner as the aforementioned studies[1].

Oscillometry

A multiple-frequency oscillation (6, 11 and 19 Hz) was applied to the mouth, on one side of a flow splitter, while subjects breathed through the other side, which had a resistance mesh. Flow was measured using a 0–400 $L.min^{-1}$ pneumotachometer (Rudolph triple- screen pneumotach Series R4830B, Hans Rudolph Inc., Kansas City, MO, USA). Differential pressure was measured using a $\pm$2.5 cm H_2O solid-state pressure transducer (Sursense DC001NDC4, Honeywell Sensing and Control, Golden Valley, MN, USA) and mouth pressure was measured using a similar transducer ($\pm$12.5 cm H_2O, Sursense DC005NDC4). An antibacterial filter was used (resistance of 0.4 $cmH_2O.s.L^{-1}$ (SureGard® RJVKB2, Bird Healthcare, Port Melbourne, VIC, Australia). The pressure and flow signals were low-pass filtered at 25 Hz and then filtered using a bandwidth of 2 Hz centred around 6 Hz. All subsequent filtering and processing was performed digitally by custom software written in Matlab (The Mathworks Inc., MA, USA). Fast Fourier transforms were used to

calculate the Rrs and Xrs components of impedance from 1/6 second segments, at 0.1 second moving windows to provide 10 measurements per second. Daily impedance verifications were performed using a resistance tube of known impedance.

Subjects supported their cheeks with their hands, to minimise upper airway artefact. After verbal instruction and establishment of stable tidal breathing, a single one-minute measurement was acquired. Quality control of FOT measurements was performed after data acquisition using an automated computer algorithm based on analysis of complete breaths that has been previously described (Robinson et al., 2011). Complete breaths were considered acceptable on the basis of (1) no negative resistance points, (2) no spikes in admittance versus time that would indicate leak, (3) tidal volume within 1.5 standard deviations (SD) of the mean for all breaths, (4) expiratory flow-volume curve deviation within 1.5 SD of mean, defined in terms of sum of squared distances from the median flow value for all breaths at each volume point and (5) deviation in the Rrs-flow profile within 1.5 SD of mean, defined in terms of sum of squared distances from the median resistance value for all breaths at each flow point. A minimum of 5 acceptable breaths was used to determine average FOT parameters for each recording.

Predictors of bronchodilator response in healthy subjects

Anthropometric predictors of bronchodilator responsiveness measured by spirometry and by oscillometry were examined in the $Healthy_{Asym}$ group. The candidate anthropometric predictors that were examined were age, sex, height, weight, BMI. In addition, baseline FEV1 Z-scores and FEV1/FVC Z-scores, baseline Rrs_6 and Xrs_6, also expressed as their Z-scores, were included as predictors for spirometry bronchodilator responses.

Sex was found to be a significant predictor and so correlations were examined separately for females and males. Table E4 and E5 show univariate correlations for females and males, respectively. In females BMI was weakly, positively associated with the bronchodilator responses in EFLi only. In males, BMI was associated with the bronchodilator responses in Rrs_6 expressed as absolute and percentage change, and Rrs_6(insp), only. All Rrs_6, Xrs_6 and spirometry indices predicted the bronchodilator responses in each other. As expected, the relationships were strongest for baseline parameters predicting their own change with bronchodilator.

In summary, anthropometric factors have weak and limited influence bronchodilator responsiveness, whereas baseline lung function consistently and in some cases, strongly predict bronchodilator responses, in both females and males.

Proportion of abnormal oscillometry parameters in each of the 5 clinical groups

The proportions of subjects who had abnormal pre-bronchodilator Rrs_6, Xrs_6, EFLi, FEV_1 and FEV_1/FVC ratio within each of the clinical groups, are shown in Table E7. Note that both smokers groups were defined by having normal post-bronchodilator FEV_1/FVC Z-scores according to the GLI equations[2]. Table E7 shows however, that there was a small percentage who had abnormal FEV_1/FVC Z-scores.

References

1. Musk AW, Knuiman M, Hunter M, Hui J, Palmer LJ, Beilby J, Divitini M, Mulrennan S, James A. Patterns of airway disease and the clinical diagnosis of asthma in the Busselton population. *European Respiratory Journal* 2011: 38(5): 1053-1059.
2. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Stocks J, the ERSGLfI. Multi-Ethnic Reference Values For Spirometry For The 3-95 Year Age Range: The Global Lung Function 2012 Equations: Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. *The European respiratory journal* 2012: 40(6): 1324-1343.

3. Dellaca RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklem PT, Pedotti A, Calverley PMA. Detection of expiratory flow limitation in COPD using the forced oscillation technique. *European Respiratory Journal* 2004: 23(2): 232-240.

Figure E1. Rrs6 and Xrs6 pre- and post- bronchodilator inhalation, for the 6 clinical groups. Clear boxes are pre-bronchodilator and shaded boxes are post-bronchodilator values.

Table E1. Pre-bronchodilator and post-bronchodilator spirometry and impedance.

	Pre-BD	**Post-BD**	**p**
FEV1 (L)*	2.93 ±0.83	3.00 ±0.84	<0.0001
FVC (L)*	3.82 ±1.02	3.79 ±1.01	<0.0001
FEV1/FVC*	0.77 ±0.06	0.79 ±0.06	<0.0001
Rrs ($cmH_2O/L/s$)	3.10 (2.53 – 3.78)	2.86 (2.33 – 3.52)	<0.0001
Xrs ($cmH_2O/L/s$)	-0.39 (-0.66 – -0.18)	-0.32 (-0.32 – -0.14)	<0.0001
Rrs_{insp} ($cmH_2O/L/s$)	2.92 (2.43 – 3.56)	2.61 (1.28 – 3.15)	<0.0001
Xrs_{insp} ($cmH_2O/L/s$)	-0.48 (-0.77 – -0.25)	-0.37 (-0.59 – -0.19)	<0.0001
EFLi ($cmH_2O/L/s$)	-0.15 (-0.27, -0.02)	-0.12 (-0.22 – -0.03)	0.001

* Mean ±SD. The remainder or median (interquartile range). p is significance value for paired T-tests.

Table E2. Predicted values for impedance at 6Hz derived from the healthy, asymptomatic group (n=587).

Respiratory system resistance (Rrs_6) parameters		**RSD**	**Adusted R^2, p value**
Males	$Ln(Rrs_6) = 0.011 * Weight – 0.016 * Height + 2.912$	0.245	0.22, p<0.001
	$Ln(Rrs_6(insp)) = 0.010 * Weight – 0.016 * Height + 2.874$	0.242	0.21, p<0.001
Females	$Ln(Rrs_6) = 0.009 * Weight – 0.013 * Height + 2.714$	0.265	0.15, p<0.001
	$Ln(Rrs_6(insp)) = 0.009 * Weight – 0.013 * Height + 2.616$	0.258	0.15, p<0.001
Respiratory system reactance (Xrs_6) parameters			
Males	$Exp(Xrs_6) = 0.010 * Height – 0.018 * BMI – 0.002 * age – 0.283$	0.202	0.19, p<0.001
	$Exp(Xrs_6(insp)) = 0.010 * Height – 0.011 * BMI – 0.002 * age – 0.554$	0.191	0.14, p<0.001
	$EFLi = 0.009 * Weight – 0.009 * Height + 0.821$	0.329	0.08, p<0.001
Females	$Exp(Xrs_6) = 0.003 * Height – 0.012 * BMI – 0.004 * age + 0.660$	0.196	0.16, p<0.001
	$Exp(Xrs_6(insp)) = 0.005 * Height – 0.009 * BMI – 0.003 * age + 0.213$	0.181	0.13, p<0.001
	$EFLi = 0.006 * age + 0.006 * Weight – 0.898$	0.352	0.06, p<0.001

Age in years, Weight in Kg, Height in cm, BMI in kg/m^2, Ln: natural logarithm, Exp: raised to the exponent e, RSD standard deviation of residuals.

Table E3. Univariate correlations between anthropometric characteristics, symptoms, asthma diagnosis, smoking history, baseline lung function, and; bronchodilator responses in oscillometry and spirometry parameters. Analysis involves the entire cohort (n=1145).

	Age	Height	BMI	Asthma diagnosis	Symptoms [#]	Smoking	FEV1 Z-score	FEV1/FVC Z-score	Rrs_6 Z-score	Xrs_6 Z-score
ΔRrs_6 (abs)	0.07 (0.10)	-0.12 (0.66)	**-0.10 (0.001)**	**0.13 (0.003)**	**0.14 (0.001)**	**-0.11 (0.001)**	**0.23 (<0.001)**	**0.25 (<0.001)**	**-0.50 (<0.001)**	**0.26 (<0.001)**
ΔRrs_6 (%)	0.08 (0.10)	-0.08 (0.07)	-0.04 (0.24)	**0.10 (0.001)**	**0.13 (0.002)**	**-0.09 (0.002)**	**0.19 (<0.001)**	**0.24 (<0.001)**	**-0.40 (<0.001)**	**0.20 (<0.001)**
ΔRrs_6 (Z-score)	-0.05 (0.12)	-0.03 (0.25)	-0.04 (0.20)	**0.10 (0.001)**	**0.13 (<0.001)**	**-0.09 (0.001)**	**0.19 (<0.001)**	**0.23 (<0.001)**	**-0.40 (<0.001)**	**0.21 (<0.001)**
ΔRrs_6(insp) (abs)	0.07 (0.09)	-0.02 (0.65)	**-0.11 (<0.001)**	**0.13 (<0.001)**	**0.15 (<0.001)**	**-0.08 (0.004)**	**0.26 (<0.001)**	**0.27 (<0.001)**	**-0.51 (<0.001)**	**0.27 (<0.001)**
ΔRrs_6(insp) (%)	0.08 (0.06)	-0.08 (0.07)	-0.04 (0.24)	**0.10 (0.001)**	**0.13 (0.002)**	**-0.09 (0.002)**	**0.19 (<0.001)**	**0.24 (<0.001)**	**-0.40 (<0.001)**	**0.20 (<0.001)**
ΔXrs_6 (abs)	0.07 (0.12)	0.02 (0.72)	**0.16 (<0.001)**	**-0.17 (<0.001)**	**0.15 (<0.001)**	**0.15 (<0.001)**	**-0.29 (<0.001)**	**-0.21 (<0.001)**	**0.39 (<0.001)**	**-0.51 (<0.001)**
ΔXrs_6 (Z-score)	-0.02 (0.65)	**0.12 (0.004)**	**0.11 (<0.001)**	**-0.11 (<0.001)**	**0.11 (0.008)**	**0.12 (<0.001)**	**-0.22 (<0.001)**	**-0.17 (<0.001)**	**0.30 (<0.001)**	**-0.40 (<0.001)**
ΔXrs_6(insp) (abs)	0.00 (0.99)	0.05 (0.22)	**0.12 (<0.001)**	**-0.17 (<0.001)**	**-0.16 (<0.001)**	**-0.08 (0.008)**	**-0.28 (<0.001)**	**-0.20 (<0.001)**	**0.38 (<0.001)**	**-0.45 (<0.001)**
$\Delta EFLi$ (abs)	**-0.14 (0.01)**	0.01 (0.78)	**-0.11 (<0.001)**	0.03 (0.29)	**0.09 (0.03)**	**-0.14 (<0.001)**	**0.10 0.002**	**0.07 0.01**	**-0.10 0.001**	**0.20 (<0.001)**
$\Delta FEV1$ (%)	0.06 (0.15)	0.00 (0.98)	-0.01 (0.71)	**-0.22 (<0.001)**	**-0.25 (<0.001)**	**-0.07 (0.01)**	**-0.41 (<0.001)**	**-0.37 (<0.001)**	**0.21 (<0.001)**	**-0.18 (<0.001)**
ΔFVC (%)	**0.15 (<0.001)**	0.01 (0.86)	**0.10 (0.01)**	**-0.13 (0.001)**	**-0.22 (<0.001)**	**0.12 (<0.001)**	**-0.30 (<0.001)**	-0.06 0.05	**0.17 (<0.001)**	**-0.20 (<0.001)**

Values are Spearman correlations and (p vales).
[#]highest Rho for any symptoms.
Bold values indicate $p<0.05$.

Table E4. Univariate Spearman correlations between bronchodilator responses (measured by spirometry and oscillometry) and; anthropometric features and baseline lung function, in females from the Healthy$_{Asym}$ group (n=333). The significant correlations (p<0.05) are in bold.

FEMALE	Age	Height	BMI	Rrs_6 (Z-score)	Xrs_6 (Z-score)	EFLi	FEV1 (Z-score	FEV1/FVC Z-score
ΔRrs_6 (abs)	0.04 (0.53)	0.02 (0.66)	-0.08 (0.14)	**-0.46 (<0.001)**	**0.25 (<0.001)**	-0.07 (0.23)	**0.18 (<0.001)**	**0.19 (<0.001)**
ΔRrs_6 (%)	0.05 (0.34)	-0.019 (0.73)	-0.01 (0.89)	**-0.35 (<0.001)**	**0.17 (<0.001)**	-0.02 (0.67)	**0.14 (0.01)**	**0.19 (<0.001)**
ΔRrs_6 (Z-score)	0.05 (0.34)	-0.019 (0.73)	-0.01 (0.89)	**-0.35 (<0.001)**	**0.17 0.002**	-0.02 (0.67)	**0.14 (0.01)**	**0.19 (0.001)**
ΔRrs_6(insp) (abs)	0.10 (0.07)	-0.04 (0.44)	-0.07 (0.20)	**-0.50 (<0.001)**	**0.28 (<0.001)**	-0.03 (0.54)	**0.21 (<0.001)**	**0.23 (<0.001)**
ΔRrs_6(insp) (%)	0.05 (0.34)	-0.02 (0.73)	-0.01 (0.89)	**-0.35 (<0.001)**	**0.17 0.002**	-0.02 (0.67)	**0.14 (0.01)**	**0.19 (0.001)**
ΔXrs_6 (abs)	-0.11 (0.05)	0.03 (0.59)	0.07 (0.20)	**0.31 (<0.001)**	**-0.41 (<0.001)**	0.03 (0.59)	**-0.11 (0.04)**	-0.07 (0.21)
ΔXrs_6 (Z-score)	**0.14 (0.01)**	0.063 (0.25)	0.03 (0.58)	**0.26 (<0.001**	**-0.34 <0.001**	0.00 (0.98)	-0.1 (0.08)	-0.09 (0.12)
ΔXrs_6(insp) (abs)	-0.10 (0.06)	0.06 (0.27)	0.04 (0.47)	**0.36 (<0.001)**	**-0.39 (<0.001)**	**-0.16 (0.003)**	**-0.13 0.02)**	-0.06 (0.28)
ΔEFLi (abs)	-0.04 (0.44)	0.089 (0.11)	**-0.12 (0.03)**	0.04 0.51	0.05 0.35	**-0.41 (<0.001)**	0.04 (0.48)	0.03 (0.63)
ΔFEV1 (%)	0.07 (0.19)	0.04 (0.53)	0.05 (0.40)	**0.20 (<0.001)**	-0.05 0.38	0.10 (0.07)	**-0.37 (<0.001)**	**-0.3 (<0.001)**
ΔFVC (%)	0.14 (0.01)	0.01 (0.89)	0.06 (0.26)	**-0.12 0.03**	-0.04 0.52	0.09 (0.12)	**-0.21 (<0.001)**	0.07 (0.20)

Values are Spearman correlations and (p vales).

Bold values indicate p<0.05.

Table E5. Univariate Spearman correlations between bronchodilator responses (measured by spirometry and oscillometry) and; anthropometric features and baseline lung function, in males from the Healthy$_{Asym}$ group (n=244). The significant correlations (p<0.05) are in bold.

Male	Age	Height	BMI	Rrs_6 (Z-score)	Xrs_6 (Z-score)	EFLi	FEV1 (Z-score	FEV1/FVC Z-score
ΔRrs_6 (abs)	-0.01 (0.90)	0.03 (0.68)	**-0.16 (0.02)**	**-0.34 (<0.001)**	**-0.34 (<0.001)**	0.06 (0.33)	0.07 (0.28)	**0.15 (0.02)**
ΔRrs_6 (%)	-0.02 (0.74)	0.03 (0.69)	**-0.17 (0.01)**	**-0.28 (<0.001)**	**-0.28 (<0.001)**	0.09 (0.16)	0.06 (0.34)	**-0.16 (0.01)**
ΔRrs_6 (Z-score)	0.05 (0.34)	-0.02 (0.73)	-0.01 (0.89)	**-0.35 (<0.001)**	**-0.35 (<0.001)**	0.09 (0.16)	0.06 (0.34)	**0.19 (0.01)**
ΔRrs_6(insp) (abs)	-0.04 (0.57)	0.04 (0.53)	**-0.17 (0.01)**	**-0.43 (<0.001)**	**0.18 (0.003)**	0.04 (0.54)	**0.17 (0.008)**	**0.20 (0.002)**
ΔRrs_6(insp) (%)	-0.02 (0.74)	0.03 (0.69)	-0.07 (0.30)	**-0.30 (<0.001)**	0.11 (0.09)	0.09 (0.16)	0.06 (0.34)	**0.16 (0.01)**
ΔXrs_6 (abs)	0.04 (0.51)	-0.1 (0.11)	0.02 (0.82)	**0.26 (<0.001)**	**0.26 (<0.001)**	-0.06 (0.35)	-0.09 (0.15)	-0.1 (0.11)
ΔXrs_6 (Z-score)	0.04 (0.51)	-0.1 (0.13)	0.01 (0.85)	**0.23 (<0.001)**	**0.23 (<0.001)**	-0.07 (0.28)	-0.09 (0.18)	-0.11 (0.09)
ΔXrs_6(insp) (abs)	0.06 (0.35)	-0.11 (0.10)	0.11 (0.09)	**0.32 (<0.001)**	**-0.44 (<0.001)**	**-0.21 (0.001)**	**-0.19 (0.003)**	-0.07 (0.27)
ΔEFLi (abs)	0.04 (0.57)	0.24 (0.71)	0.01 (0.86)	-0.02 (0.74)	-0.02 (0.74)	**-0.41 (<0.001)**	-0.08 (0.20)	0.07 (0.29)
ΔFEV1 (%)	0.04 (0.52)	-0.04 (0.51)	0.08 (0.22)	0.00 (0.96)	-0.003 (0.96)	0.00 (0.95)	**-0.25 (<0.001)**	**-0.27 (<0.001)**
ΔFVC (%)	0.09 (0.16)	0.00 (0.98)	-0.04 (0.54)	-0.05 (0.45)	0.01 (0.90)	0.09 (0.14)	-0.09 (0.18)	0.06 (0.37)

Table E6: Anthropometric data of the clinical groups

	$Healthy_{Asymp}$	$Healthy_{Symp}$	$Smokers_{Asym}$	$Smokers_{Sym}$	Asthma	COPD
n (male%)	577 (42%)	126 (52%)	159 (65%)	115 (65%)	122 (43%)	46 (63%)
Age (years)	60.7 ±12.6	62.0 ±12.8	62.4 ±12.3	62.2 ±11.5	60.4 ±12.5	65.8 ±11.4
Height (cm)	167 ±0.09	168 ±10.2	170.1 ±9.1	169.8 ±9.2	168.2 ±9.1	169.8 ±8.3
BMI ($kg.m^{-2}$)	26.9 ±4.0	29.1 ±5.3*	28.1 ±4.5*	29.9 ±4.6*#	28.4 ±5.2	27.0 ±3.9
Smoking (pack/years)	1.1 ±2.2	1.1 ±2.3	24.7 ±15.1	30.6 ±19.7	1.3 ±2.5	40.6 ±31.8
Rrs_6 ($cmH_2O.s.L^{-1}$)	3.12 (2.54,3.85)	3.53* (2.84,4.43)	3.16 (2.47,3.96)	3.62* (3.00,4.61)	3.73* (3.11,4.61)	4.67* (4.67,6.18)
Rrs_6 (z-score)	-0.1 (-0.7,0.6)	-0.1 (-0.5,0.9)	0.0 (-0.7,0.9)	0.4* (-0.5,1.1)	0.5* (-0.2,1.3)	1.7* (0.8,2.4)
Xrs_6 ($cmH_2O.s.L^{-1}$)	-0.39 (-0.67,-0.19)	-0.53* (-0.91,-0.23)	-0.41 (-0.77,-0.18)	-0.64* (-1.13,-0.29)	-0.64* (-1.21,-0.36)	-1.53* (-2.89,-0.81)
Xrs_6 (z-score)	0.4 (-0.2,1.1)	0.2 (-0.8,0.9)	-0.2 (-0.8,1.0)	-0.3* (-1.3,0.7)	-0.3* (-1.4,0.6)	-2.0* (-2.8,-0.4)
FEV1 (Litres)	2.92 ±0.83	2.75 ±0.85*	2.97 ±0.75	2.74 ±0.80*	2.58 ±0.84*	1.95 ±0.66*
FEV1 (z-score)	0.1 ±0.9	-0.4 ±1.0*	-0.1 ±0.8*	-0.6 ±0.9*	-0.7 ±1.2*	-2.0 ±1.0*
FVC (Litres)	3.8 ±1.02	3.61 ±1.03	3.92 ±0.93	3.70 ±1.02	3.57 ±0.99*	3.43 ±0.95*
FVC (z-score)	0.2 ±0.9	-0.2 ±0.9*	0.0 ±0.8*	-0.3 ±1.0*	-0.3 ±1.0*	-0.5 ±1.2*
FEV_1/FVC	0.77 ±0.06	0.76 ±0.07	0.77 ±0.06	0.74 ±0.06*	0.71 ±0.10*	0.56 ±0.08*
FEV_1/FVC (z-score)	-0.3 ±0.8	-0.3 ±0.9	-0.3 ±0.7	-0.5 ±0.7*	-0.8 ±1.2*	-2.5 ±0.7*

Mean ±SD or median (IQR).

* significant differences compared with the Non-Smokers group (Kruskal-Wallis $p<0.05$, with Bonferroni correction).

$Smokers_{Symp}$ have BMIs greater than the asthma and COPD groups.

Differences in smoking history was not tested.

Table E7. Bronchodilator responses for the 5 clinical groups.

	$Healthy_{Symp}$ N=126	$Smokers_{Asym}$ N=159	$Smokers_{Sym}$ N=115	Asthma N=122	COPD N=46
ΔRrs_6 ($cmH_2O.s.L^{-1}$)	-0.28 (-0.79 – 0.08) (4.0%)	-0.32 (-0.67 – 0.02) (8.2%)	-0.32 (-0.79 – 0.07) (7.8%)	-0.51 (-0.99 – -0.09) (12.3%)	-0.71 (-1.21 – -0.23) (17.4%)
ΔRrs_6 (%)	-8.5 (-18.6 – 3.2) (6.3%)	-10.6 (-18.6 – 0.78) (8.8%)	-9.2 (-19.5 – 1.4) (11.3%)	-13.4 (-22.9 – -3.4) (13.9%)	-14.5 (-25.3 – -5.9) (10.9%)
ΔRrs_6 (z-score)	-1.1 (-2.1 – -0.2) (6.3%)	-1.2 (-2.2 – -0.5) (9.4%)	-1.6 (-3.1 – -0.5) (12.2%)	-0.9 (-2.3 – -0.2) (13.1%)	-1.3 (-2.4 – -0.56) (10.9%)
ΔRrs_6(insp) ($cmH_2O.s.L^{-1}$)	-0.41 (-0.73 – 0.01) (7.1%)	-0.32 (-0.72 – -0.08) (8.2%)	0.37 (-0.82 – -0.13) (9.6%)	-0.59 (-2.3 – -0.1) (15.6%)	-0.71 (-1.28 – -0.16) (21.7%)
ΔRrs_6(insp) %	-9.3 (-22.9 – 3.1) (6.3%)	-11.9 (-22.9 – 0.7) (8.8%)	-10.1 (-24.2 – 1.4) (11.3%)	-15.5 (-29.7 – -3.5) (13.9%)	-16.9 (-33.8 – -6.3) (10.9%)
ΔXrs_6 ($cmH2O.s.L^{-1}$)	0.15 ±0.49 (7.9%)	0.19 ±0.39 (11.9%)	0.27 ±0.52 (17.4%)	0.18 (0.02 – 0.43) (19.7%)	0.48 (0.06 – 1.34) (47.8%)
ΔXrs_6 (z-score)	0.29 ±0.69 (6.3%)	0.42 ±0.71 (7.5%)	0.51 ±0.86 (17.4%)	0.4 (0.1 – 0.9) (14.8%)	0.5 (0.1 – 1.4) (26.1%)
ΔXrs_6(insp) ($cmH_2O.s.L^{-1}$)	0.14 ±0.28 (7.9%)	0.12 ±0.29 (7.5%)	0.19 ±0.41 (20.0%)	0.24 (0.06 – 0.43) (18.9%)	0.41 (0.13 – 0.99) (37.0%)
ΔEFLi ($cmH_2O.s.L^{-1}$)	-0.017 ±0.641 (9.5%)	-0.033 (-0.17 – 0.105) (13.2%)	-0.142 ±0.536 (19.1%)	0.046 (-0.131 – 0.202) (13.9%)	-0.255 (-0.682 – 0.074) (45.7%)

Mean ±SD for normally distributed data, otherwise median (IQR).
Numbers in brackets are % with positive bronchodilator responses as defined in Table 2.

Table E8. Percentage of abnormal oscillometry parameters and spirometry, as defined by their Z-scores, for each of the clinical groups.

	$Healthy_{Asym}$ N=577	$Healthy_{Symp}$ N=126	$Smokers_{Asym}$ N=159	$Smokers_{Sym}$ N=115	Asthma N=122	COPD N=46
Rrs_6	5.4	7.1	7.5	13.0	18.0	52.0
Xrs_6	8.8	15.9	16.4	29.6	27.9	63.0
$EFLi^{\#}$	0	1.6	1.3	2.6	2.5	10.9
FEV_1	1.4	12.7	2.5	14.8	20.5	69.6
FEV_1/FVC	4.7	4.8	1.9	7.8	26.2	100

The Z-scores for oscillometry were calculated from the equations in Table E1 above. $^{\#}$For EFLi, a value of >2.8 $cmH_2O.s.L^{-1}$ was used to define the presence of expiratory flow limitation, as defined by Dellaca et al[3]. Note that the 95th percentile for EFLi in the $Healthy_{Asym}$ group was 2.00 $cmH_2O.s.L^{-1}$. For spirometry, abnormality was define by the GLI equations[2].