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Emphysema- and airway-dominant COPD phenotypes defined by standardised quantitative computed tomography

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ABSTRACT EvA (Emphysema *versus* Airway disease) is a multicentre project to study mechanisms and identify biomarkers of emphysema and airway disease in chronic obstructive pulmonary disease (COPD). The objective of this study was to delineate objectively imaging-based emphysema-dominant and airway disease-dominant phenotypes using quantitative computed tomography (QCT) indices, standardised with a novel phantom-based approach.

441 subjects with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1–3) were assessed in terms of clinical and physiological measurements, laboratory testing and standardised QCT indices of emphysema and airway wall geometry.

QCT indices were influenced by scanner non-conformity, but standardisation significantly reduced variability ($p < 0.001$) and led to more robust phenotypes. Four imaging-derived phenotypes were identified, reflecting “emphysema-dominant”, “airway disease-dominant”, “mixed” disease and “mild” disease. The emphysema-dominant group had significantly higher lung volumes, lower gas transfer coefficient, lower oxygen (P_{O_2}) and carbon dioxide (P_{CO_2}) tensions, higher haemoglobin and higher blood leukocyte numbers than the airway disease-dominant group.

The utility of QCT for phenotyping in the setting of an international multicentre study is improved by standardisation. QCT indices of emphysema and airway disease can delineate within a population of patients with COPD, phenotypic groups that have typical clinical features known to be associated with emphysema-dominant and airway-dominant disease.



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Editorial comment in: *Eur Respir J* 2016; 48: 10–13.

This article has supplementary material available from erj.ersjournals.com

Received: Nov 11 2015 | Accepted after revision: March 17 2016 | First published online: May 26 2016

Support statement: The EvA study is an EU-funded project (#200506) under the Seventh Framework Programme (FP7). Funding information for this article has been deposited with FundRef.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterised by persistent, incompletely reversible airflow obstruction as a consequence of emphysema, airway remodelling and obliteration. To better understand the pathogenetic mechanisms of COPD, the EvA (Emphysema *versus* Airway disease) study aims at defining emphysema- and airway disease-phenotypes of the disease [1]. COPD is typically defined, diagnosed and staged using spirometric criteria [2, 3]. Whilst spirometry is convenient for use in routine clinical practice, it does not reliably differentiate the emphysema and airway disease components of COPD [4]. Quantitative computed tomography (QCT) imaging can objectively and non-invasively evaluate emphysema and airway morphology [5], and is therefore a potentially valuable tool in phenotyping studies, but its role in multi-centre phenotyping studies has not been systematically evaluated.

The quantification of emphysema *via* determination of the lung density in computed tomography (CT) images dates back more than two decades [6] and is now accepted for use as an outcome measure in studies of emphysema-modifying therapy in patients with α_1 -antitrypsin deficiency [7]. CT technologies to assess the extent of airway disease have also been developed and airway wall morphometry is used as a measure of airway remodelling in asthma [8–10]. NAKANO *et al.* [11] reported that airway wall thickness correlates with airflow obstruction in patients with COPD, and that high percent wall area and low lung density can be mutually exclusive. We therefore hypothesised that QCT could accurately subdivide COPD patients into emphysema-dominant and airways disease-dominant cases [11]. However, since EvA combines data from 10 clinical centres we sought to assess the impact of scanner differences [12–15] and to establish the potential utility of dedicated phantoms for QCT standardisation. Using this strategy we investigated whether standardised CT-defined patient subgroups have distinct clinical and laboratory features. Some of the results of these studies have been previously reported in the form of abstracts [16–19].

Material and methods

The strategy and study design for the EvA study has been described previously [1]. In summary, EvA is a multicentre study across five European countries (Germany, UK, Italy, Hungary and Poland) that involves clinical examination, CT imaging and bronchoscopic sampling, in order to identify markers specific to emphysema and airway disease in COPD. The study was approved by the relevant ethics and review boards at the participating centres and all subjects provided written informed consent.

Clinical assessment

A diagnosis of COPD was based on a post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) ratio <70%. Patients were excluded if they had very severe COPD (FEV₁ <30% predicted or <1 L), bronchodilator reversibility greater than 400 mL, had smoked within the previous 12 months, or had a primary diagnosis of bronchiectasis, asthma or any other significant respiratory diseases [1].

All subjects were assessed by clinical history, physical examination, pulmonary function testing, including plethysmography, 6-min walk distance (6MWD), quantification of dyspnoea using the modified Medical

Research Council (mMRC) scale [20] and CT. All subjects received their usual prescribed medication. Venous blood was taken for clinical chemistry including α_1 -antitrypsin and C-reactive protein. Plasma samples were frozen at -20°C and shipped on dry ice to the coordinator site (Munich, Germany) for storage at -80°C . Erythropoietin was determined in plasma samples using the e-biosciences ELISA (BMS2002CE).

CT scanning and image analysis

Detailed methods for CT acquisition and analysis are available in the online supplementary material. Patients were scanned in General Electric (Fairfield, CT, United States) or Siemens (Erlangen, Germany) CT scanners with a volumetric scan covering the whole lung for lung densitometry and a limited scan of the middle of the lung including the tracheal carina for airway morphometry of the right S1 segmental airway (table S1). Image analysis was performed using Pulmo CMS [21] and EmphyxJ [22] software packages.

The 15th percentile (Perc15) point derived from the lung density histogram was used to assess emphysema severity and the % wall area (%WA) for the right S1 segmental bronchus was used to assess airway disease. The latter may be used as a surrogate parameter for small airway disease since it has been shown that the measures of airway wall dimensions in CT predicted the dimensions of smaller airways as determined in histology [23]. Still, this study does not directly measure the dimensions of small airways nor does it compare inspiratory and expiratory scans to determine gas trapping, which is considered an indirect measure of small airway disease. For standardisation of emphysema and airway CT indices, dedicated emphysema and airway phantoms were scanned in all centres and indices were derived to generate centre-specific regression equations using a method validated in a preclinical phantom studies (figures S1 and S2 and table S2 and S3).

Statistics

COPD cases were classified into four groups using the upper 95th percentile value of the Perc15 and % WA for the normal control subjects. The four groups were termed: “emphysema dominant” (Ea), “airway disease dominant” (eA), “mixed” pathology (EA) and “mild” disease (ea). Extreme E and A phenotypes were identified by giving rank order numbers to each subject based on the product of the ranks given to Perc15 and %WA in these two groups and classifying the subjects as extreme phenotypes if they were in the half with the highest rank. Statistical analysis used the non-parametric Wilcoxon–Mann–Whitney test, Kruskal–Wallis, Chi-squared and linear, partial and multiple linear regression analyses in the R-environment. Non-parametric correlations were analysed using Spearman’s test. A p-value <0.05 was considered significant after Bonferroni–Holm correction was applied.

Results

Patients

We recruited 534 patients with COPD and 280 controls at 10 clinical centres. CT scans of the chest were obtained from all cases and 56 controls. Quantitative indices could not be obtained in 93 patients (for the list of reasons see table S4). There were no differences in clinical parameters between those cases with or without an assessable CT or between scanner manufacturers except for a lower gas transfer in patients studied on General Electric scanners (table S5). The clinical characteristics of cases and controls are as shown table 1.

Standardisation of QCT indices

Differences in unstandardised Perc15 and %WA were associated with differences in scanner manufacturer and model (see figure 1a and b). The preclinical densitometry and airway morphometry phantom studies demonstrated that standardisation reduced variability by 84% ($p<0.001$) (mean \pm SD difference of 26.2 ± 13.4 HU in unstandardised densitometry data *versus* 4.1 ± 2.3 HU in standardised data) (table S2 and figure S3). A mean \pm SD difference of 2.9 ± 1.9 was observed in unstandardised %WA of the phantom tubes across all EvA centres. Standardisation reduced the mean difference to 0.6 ± 0.5 , representing an error reduction of 79% ($p=0.002$) (table S3 and figure S4). The mean \pm SD %WA of the phantom tubes were significantly lower on the Siemens-derived imaging compared to the General Electric-derived imaging ($62.0\pm 11.6\%$ *versus* $66.4\pm 12.0\%$; $p=0.007$).

There was a correlation between unstandardised Perc15 and %WA ($r=0.34$, $p<0.001$; figure 2a), which was reduced by adjusting lung density for lung volume ($r=0.27$, $p<0.001$; figure 2b) and further reduced following phantom standardisation ($r=0.11$, $p=0.17$; figure 2c).

Comparison of CT-defined phenotypes

QCT data from the 56 control subjects showed that the upper 95th percentile values for Perc15 was -925.6 HU and for WA was 69.3%. The COPD cases were subsequently classified into the four pre-specified groups; “emphysema-dominant” (Ea) ($n=124$), “airway disease-dominant” (eA) ($n=79$),

TABLE 1 Clinical characteristics of cases and controls

	Controls	Cases	p value
Subjects	280	441	
Age years	59 (15)	65 (9)	<0.001 [#]
Sex male %	64	68	0.23
Smoking history pack-years	22 (19) ⁺	41 (18)	<0.001 [#]
BMI kg·m⁻²	27.9 (5.7)	27.8 (6.1)	0.57
BODE index	0	1 (2)	<0.001 [#]
FEV₁/FVC LLN %	0	78	<0.001 [#]
6MWD m	545 (136)	468 (124)	<0.001 [#]
Dyspnoea score	0 (0)	1 (1)	<0.001 [#]
Spirometry			
FEV ₁ L	3.2 (1.0)	1.9 (0.8)	<0.001 [#]
FEV ₁ % predicted	109 (19)	71 (27)	<0.001 [#]
FEV ₁ /FVC %	78.8 (6.6)	56.8 (15.8)	<0.001 [#]
Bronchodilator reversibility L	0.11 (0.16)	0.13 (0.17)	<0.001 [#]
Lung mechanics			
<i>R</i> _{aw} kPa·s·L ⁻¹	0.18 (0.11)	0.3 (0.21)	<0.001 [#]
<i>sR</i> _{aw} kPa·s	0.7 (0.38)	1.4 (1.1)	<0.001 [#]
<i>R</i> _{in} kPa·s·L ⁻¹	0.15 (0.09)	0.23 (0.14)	<0.001 [#]
<i>R</i> _{ex} kPa·s·L ⁻¹	0.2 (0.14)	0.36 (0.32)	<0.001 [#]
Lung volumes			
TLC L	6.5 (1.8)	7.1 (2.0)	<0.001 [#]
TLC % predicted	107 (19)	115 (24)	<0.001 [#]
RV L	2.4 (0.8)	3.4 (1.3)	<0.001 [#]
RV % predicted	106 (30)	150 (55)	<0.001 [#]
RV/TLC % predicted	0.95	1.23	<0.001 [#]
Gas exchange			
<i>P</i> _{O₂} mmHg	78.8 (12.05)	70.9 (10.4)	<0.001 [#]
<i>P</i> _{CO₂} mmHg	38.49±3.67	38.0±3.7	0.087
<i>P</i> _{A-aO₂} mmHg	22.88 (13.0)	31.1 (12.3)	<0.001 [#]
<i>T</i> _{LCO} / <i>V</i> _A % predicted	100 (21)	79 (33)	<0.001 [#]
Blood parameters			
Leukocytes 10 ⁹ cells·L ⁻¹	6.3 (2.0)	7.1 (2.4)	<0.001 [#]
Lymphocytes 10 ⁹ cells·L ⁻¹	1.8 (0.7)	1.9 (0.8)	0.47
Neutrophils 10 ⁹ cells·L ⁻¹	3.8 (1.7)	4.3 (2.0)	<0.001 [#]
Eosinophils 10 ⁹ cells·L ⁻¹	0.12 (0.12)	0.16 (0.16)	<0.001 [#]
Haemoglobin mg·dL ⁻¹	14.3±1.2	14.5±1.2	<0.001 [#]
Haematocrit %	42 (4)	43 (5)	<0.001 [#]
Erythropoietin mIU·mL ⁻¹	8.8 (6.5)	11.5 (8.4)	<0.001 [#]
IgE kU·L ⁻¹	33 (75)	11 (8)	<0.001 [#]
CRP mg·dL ⁻¹	0.3 (0.4)	0.4 (0.3)	<0.001 [#]
AAT mg·dL ⁻¹	123 (21)	130 (30)	<0.001 [#]
CT parameters			
WA/BSA mm ² ·m ⁻²	15.6 (7.2)	15.4 (6.3)	0.94
LA/BSA mm ² ·m ⁻²	7.9 (3.7)	7.9 (5.5)	0.81
WA %	61.2 (10.8)	64.0 (9.7)	<0.001 [#]
Lung density Perc15 HU	-907 (17.4)	-919 (26)	<0.001 [#]
Emphysema distribution	-1.7 (20.2)	-3.3 (30.2)	0.48

Data are presented as median (interquartile range) or mean±sd, unless otherwise stated. BMI: body mass index; BODE: body-mass index, airflow obstruction, dyspnoea, exercise; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; 6MWD: 6-min walk distance; *R*_{aw}: airway resistance; *sR*_{aw}: specific airway resistance; *R*_{in}: inspiratory resistance; *R*_{ex}: expiratory resistance; RV: residual volume; TLC: total lung capacity; *P*_{O₂}: oxygen tension; *P*_{CO₂}: carbon dioxide tension; *P*_{A-aO₂}: alveolar-arterial oxygen tension differential; *T*_{LCO}: transfer capacity of the lung for carbon monoxide; *V*_A: alveolar volume; Ig: immunoglobulin; CRP: C-reactive protein; AAT: α₁-antitrypsin; CT: computed tomography; WA/BSA: airway wall area corrected for body surface area; LA/BSA: lumen area corrected for body surface area; WA: airway wall area; Perc15: 15th percentile point. [#]: significant after correction for multiple testing; ⁺: 47 out of 280 were never-smokers.

“mixed” pathology (EA) (n=34) and “mild” disease (ea) (n=204) (figure 3a). There was no difference for age, sex and smoking history among the four phenotypes (table 2). When comparing the E-dominant versus A-dominant cases in that table then the E-dominant cases (Ea) had, for instance, a lower body mass

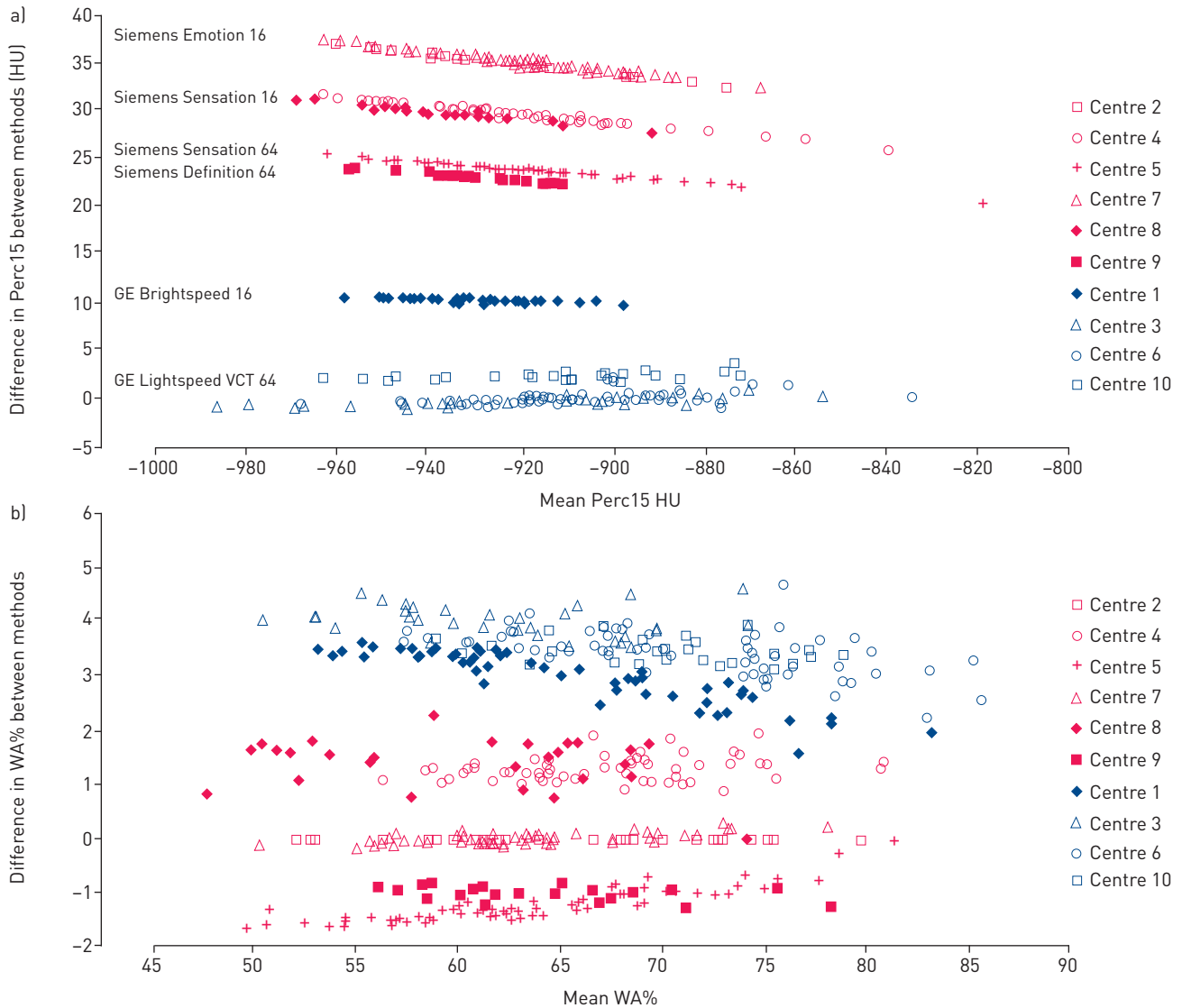


FIGURE 1 Bland-Altman plots for unstandardised versus standardised 15th percentile point (Perc15) and wall area (WA). a) Bland-Altman plot comparing unstandardised Perc15 (corrected for blood and air with Pulmo CMS software) with Perc15 standardised against the densitometry reference scanner (prior to volume correction). b) Bland-Altman plot comparing unstandardised WA (%) against WA (%) standardised against the airway reference scanner. n=441.

index (BMI) of 25.9 kg·m⁻² than the A-dominant cases (eA) with a BMI of 30.1 kg·m⁻². In the last column, “1” indicates that in a pairwise comparison this Ea versus eA difference is significant and “[¶]” indicates that it is also significant after correction for multiple testing. The table furthermore shows that the E-dominant cases had more obstructive spirometry, increased lung volumes, reduced gas transfer, higher haemoglobin, lower PO₂ and PCO₂ and more were prescribed long-acting muscarinic antagonists. The group with mixed pathology had upper lobe predominant emphysema but no clear distinguishing features when compared to the “emphysema-dominant” and “airway disease-dominant” groups. Patients with mild disease had better spirometric measures than the other phenotypes. The proportion of subjects in each CT-phenotype was significantly different between centres (table S6) and scanner type (table S7) (p<0.001).

Analysis of the extreme CT-defined phenotypes

The distribution of the Perc15 versus %WA for the COPD cases and controls are as shown in figure 3a with the extreme emphysema-dominant (E_{ex}) and extreme airway disease-dominant (A_{ex}) shown in figure 3b. Comparison between the extreme emphysema-dominant (E_{ex}) (n=62) and extreme airways-disease dominant (A_{ex}) (n=40) groups demonstrated that the pattern of several clinical and laboratory characteristics were more pronounced with a greater difference in lung function parameters, blood gases, haemoglobin and leukocytes (table S8).

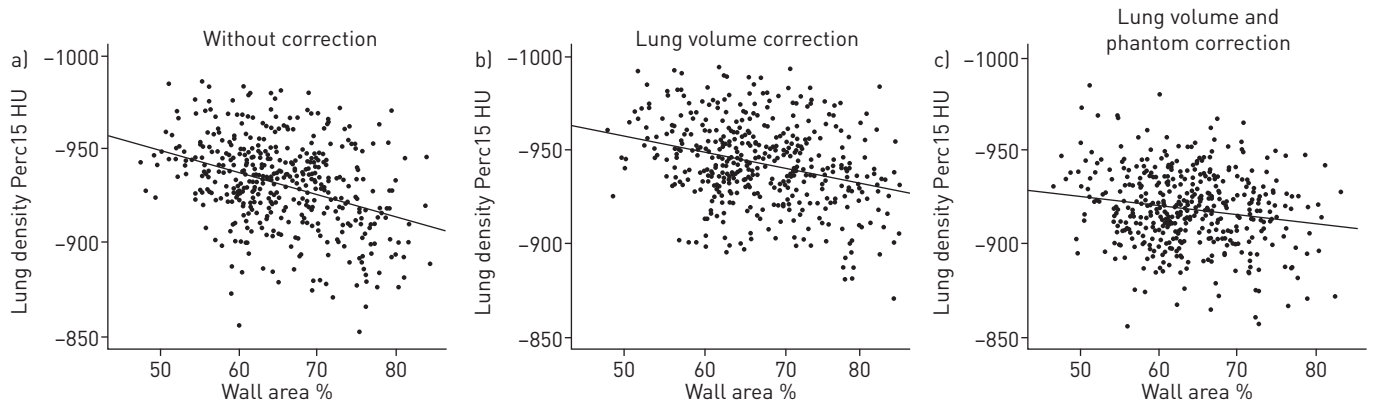


FIGURE 2 Impact of volume and phantom correction on patterns of wall area versus lung density in the Emphysema versus Airway disease chronic obstructive pulmonary disease cases. a) without correction, b), with correction of lung density for volume, c) following phantom-derived standardisation methodology and volume correction. n=441. Spearman's Rho is 0.336, 0.271 and 0.113 for a, b, and c, respectively.

Correlation and multiple linear regression analyses

Univariate analyses were undertaken between the clinical, physiological and laboratory indices and both Perc15 and %WA (table 3). Lung density was positively correlated with FEV1% predicted, BMI, PO_2 , PCO_2 , and gas transfer factor, and negatively with lung volumes, haemoglobin and total leukocyte counts. Partial correlation of lung density adjusting for %WA revealed that the associations with these parameters were independent of %WA (table 3). %WA was positively correlated with BMI, PO_2 , PCO_2 and negatively correlated with lung volumes and there was an association with small airways resistance parameters. Partial correlation of %WA adjusting for lung density demonstrated that the association of %WA with PO_2 and PCO_2 was independent of lung density. The correlation between %WA and small airways resistance (R_{aw}) was more pronounced following adjustment for lung density with a p-value of 2.1×10^{-8} before and of 1×10^{-9} after adjustment. Multiple linear regression analysis revealed that BMI, FEV1, total lung capacity

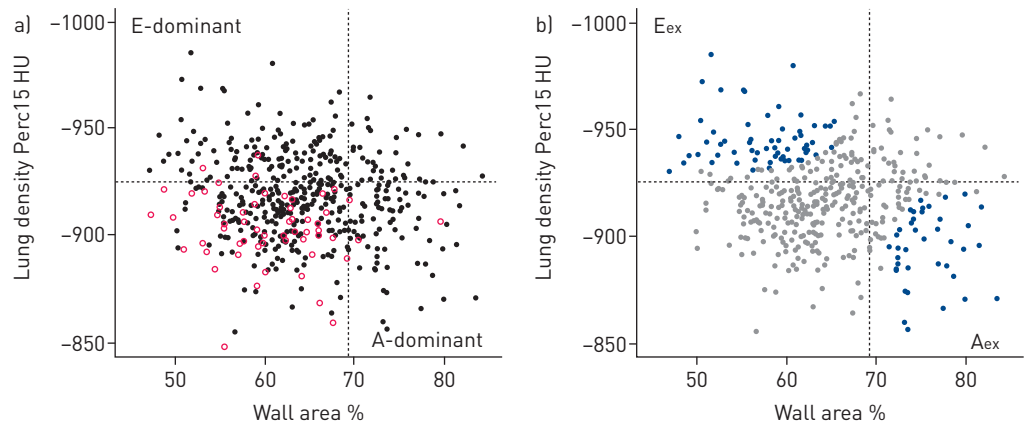


FIGURE 3 Definition of emphysema-dominant, airway disease dominant and extreme phenotypes based on computed tomography (CT). a) wall area (WA) and lung density in the Emphysema versus Airway disease (EvA) chronic obstructive pulmonary disease (COPD) cases (n=441, filled circles) and controls (n=56, open circles) are given in this wall area versus lung density plot. The upper limit of normal (ULN) for wall area (69.3%) and lower limit of normal (LLN) for emphysema (-925.6 HU) are given as vertical and horizontal dotted lines, respectively. b) wall area and lung density in the EvA COPD cases: extreme phenotypes. Rank orders were determined in that all WA% values in the upper left quadrant were given rank numbers, with highest wall area ranked as 1. Also all 15th percentile [Perc15] values in the upper left quadrant were given a rank number, with the highest lung density ranked as 1. The two rank numbers for each individual were multiplied and individuals were ordered according to the product size. Individuals in the upper half of this rank product list were classified as extreme emphysema dominant (E_{ex}). For extreme airway disease dominant (A_{ex}) in the lower right corner, the procedure was applied accordingly. Cases with this extreme CT-phenotype are indicated by coloured dots on the background of the grey dots for the remainder of patients. E-extreme in the upper left (n=62) and A-extreme in the lower right (n=40). The ULN for wall area (69.3%) and LLN for emphysema (-925.6 HU) are given as vertical and horizontal dotted lines, respectively.

TABLE 2 Characteristics of the CT-derived phenotypes

	E-dominant (Ea)	A-dominant (eA)	Mixed (EA)	Mild (ea)	p-value	Pairwise comparisons p<0.05 [#]
Subjects	124	79	34	204		
Age years	66 [8]	66 [9]	65 [7]	65 (10)	0.72	
Sex male %	68	68	65	69	0.96	
Smoking history pack-years	41 (18)	42 (19)	40 (17)	42 (18)	0.99	
BMI kg·m⁻²	25.9 (5.6)	30.1 (6.9)	27.8 (5.4)	28.2 (5.7)	<0.001 [¶]	1 [¶] ,2,3 [¶]
BODE index	2 (2)	1 (2)	1 (2)	1 (2)	<0.001	3 [¶]
FEV₁/FVC LLN %	97	70	91	68	<0.001 [¶]	1 [¶] ,3 [¶] ,6 [¶]
6MWD m	452 (105)	439 (147)	475 (104)	483 (133)	0.01	5
Dyspnoea score	1.0 (1.0)	1.0 (1.8)	1.0(1.0)	1.0 (1.0)	0.32	
Spirometry						
FEV ₁ L	1.67 (0.62)	1.88 (0.77)	1.71 (0.99)	2.11 (0.83)	<0.001 [¶]	1,3 [¶] ,5,6 [¶]
FEV ₁ % predicted	64 (22)	68 (21)	67 (30)	76 (28)	<0.001 [¶]	1,3 [¶] ,5,6 [¶]
FEV ₁ /FVC %	50 (16)	59 (14)	49 (18)	62 (13)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
Bronchodilator reversibility L	0.12 (0.15)	0.17 (0.17)	0.13 (0.14)	0.13 (0.18)	0.33	
Lung mechanics						
R _{aw} kPa·s·L ⁻¹	0.33 (0.22)	0.35 (0.26)	0.39 (0.25)	0.26 (0.19)	<0.001 [¶]	3 [¶] ,5 [¶] ,6 [¶]
sR _{aw} kPa·s	1.61 (1.25)	1.43 (1.26)	1.88 (1.67)	1.13 (0.82)	<0.001 [¶]	3 [¶] ,4,5,6 [¶]
R _{in} kPa·s·L ⁻¹	0.25 (0.13)	0.27 (0.13)	0.26 (0.11)	0.20 (0.14)	<0.001 [¶]	3 [¶] ,5 [¶] ,6 [¶]
R _{ex} kPa·s·L ⁻¹	0.41 (0.36)	0.44 (0.46)	0.47 (0.54)	0.29 (0.29)	<0.001 [¶]	3 [¶] ,5 [¶] ,6 [¶]
Lung volumes						
TLC L	7.9 (2.3)	6.2 (1.5)	7.6 (1.4)	6.8 (1.6)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
TLC % predicted	128 (20)	107 (21)	126 (18)	110 (19)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
RV L	4.1 (1.3)	3.2 (1.0)	4.0 (1.5)	3.1 (1.1)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
RV % predicted	178 (58)	140 (38)	177 (60)	136 (49)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
RV/TLC % predicted	1.31 (0.31)	1.25 (0.30)	1.34 (0.29)	1.15(0.30)	<0.001 [¶]	1,3 [¶] ,5,6
Gas exchange						
P _{O₂} mmHg	68 (10)	73 (10)	74 (9)	71 (11)	<0.001	1 [¶] ,2,3,5,
P _{CO₂} mmHg	37±4	40±3	38±3	38±4	<0.001 [¶]	1 [¶] ,3,5,
P _{A-aO₂} mmHg	35 (13)	28 (11)	30 (11)	31 (12)	<0.001 [¶]	1 [¶] ,2,3 [¶] ,5 [¶] ,
T _{LCO} /V _A % predicted	66 (21)	89 (31)	66 (30)	85 (35)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
Blood parameters						
Leukocytes 10 ⁹ cells·L ⁻¹	7.5 (2.7)	6.8 (2.0)	7.2 (2.2)	6.8 (2.3)	0.02	1,3
Lymphocytes 10 ⁹ cells·L ⁻¹	1.9 (0.7)	2.0 (0.7)	1.8 (0.7)	1.8 (0.9)	0.52	
Neutrophils 10 ⁹ cells·L ⁻¹	4.7 (2.6)	4.0 (1.9)	4.4 (1.6)	4.3 (1.9)	0.02	1,3
Eosinophils 10 ⁹ cells·L ⁻¹	0.15 (0.15)	0.15 (0.19)	0.16 (0.12)	0.16 (0.17)	0.85	
Haemoglobin mg·dL ⁻¹	14.8±1.2	14.1±1.4	15.0±1.2	14.5±1.3	<0.001 [¶]	1 [¶] ,3,4 [¶] ,5,6
Haematocrit %	44 (4)	42 (4)	45 (5)	43 (5)	<0.001 [¶]	1 [¶] ,3,4 [¶] ,6
Erythropoetin mIU·mL ⁻¹	11.6 (10.4)	11.5 (4.8)	not done	6.4 (9.2)	0.65	
IgE kU·L ⁻¹	37 (69)	42 (128)	51 (158)	54 (114)	0.13	3
CRP mg·dL ⁻¹	0.4 (0.4)	0.4 (0.3)	0.4 (0.3)	0.5 (0.4)	0.09	6
AAT mg·dL ⁻¹	132 (32)	130 (29)	128 (20)	130 (27)	0.67	
CT parameters						
WA/BSA mm ² ·m ⁻²	17.3 (7.1)	14.3 (5.0)	14.0 (6.0)	15.1 (5.4)	<0.001 [¶]	1 [¶] ,2,3,
LA/BSA mm ² ·m ⁻²	9.9 (5.9)	4.9 (2.8)	4.2 (1.95)	9.0 (4.4)	<0.001 [¶]	1 [¶] ,2 [¶] ,5 [¶] ,6 [¶]
WA %	61.7 (8.5)	73.5 (3.7)	72.6 (4.0)	62.1 (5.6)	<0.001 [¶]	1 [¶] ,2 [¶] ,5 [¶] ,6 [¶]
Lung density Perc15 HU	-937 (13)	-908 (22)	-934 (18)	-911 (18)	<0.001 [¶]	1 [¶] ,3 [¶] ,4 [¶] ,6 [¶]
Emphysema distribution	3.0 (28)	-4.9 (28)	10.2 (74)	-5.8 (24.1)	<0.001	1,3,4

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. BMI: body mass index; BODE: body-mass index, airflow obstruction, dyspnoea, exercise; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; 6MWD: 6-min walk distance; R_{aw}: airway resistance; sR_{aw}: specific airway resistance; R_{in}: inspiratory resistance; R_{ex}: expiratory resistance; RV: residual volume; TLC: total lung capacity; P_{O₂}: oxygen tension; P_{CO₂}: carbon dioxide tension; P_{A-aO₂}: alveolar-arterial oxygen tension differential; T_{LCO}: transfer capacity of the lung for carbon monoxide; V_A: alveolar volume; Ig: immunoglobulin; CRP: C-reactive protein; AAT: α₁-antitrypsin; CT: computed tomography; WA/BSA: airway wall area corrected for body surface area; LA/BSA: lumen area corrected for body surface area; WA: airway wall area; Perc15: 15th percentile point. [#]: 1: Ea versus eA; 2: Ea versus EA; 3: Ea versus ea; 4: eA versus EA; 5: eA versus ea; 6: EA versus ea. [¶]: significant after correction for multiple testing.

(TLC), and transfer capacity of the lung for carbon monoxide (T_{LCO})/alveolar volume (V_A) % predicted and Hb were strongly associated with lung density, while %WA was associated with BMI, 6MWD, P_{O₂} and P_{CO₂} (table 4).

TABLE 3 Linear and partial regression

	Lung density		Lung density adjusted for % wall area		Wall area %		Wall area % adjusted for lung density	
	p	r	p	r	p	r	p	r
Age years	0.82	-0.01	0.90	-0.01	0.35	-0.04	0.36	-0.04
BODE index	0.001 [†]	-0.15	<0.001 [†]	-0.16	0.27	0.05	0.14	0.07
BMI kg·m⁻²	<0.001 [†]	0.31	<0.001 [†]	0.30	<0.001 [†]	0.21	<0.001 [†]	0.18
6MWD m	0.99	0.00	0.78	0.01	<0.001 [†]	-0.16	<0.001 [†]	-0.16
Spirometry								
FEV ₁ L	<0.001 [†]	0.27	<0.001 [†]	0.29	0.04	-0.10	0.004	-0.14
FEV ₁ % predicted	<0.001 [†]	0.25	<0.001 [†]	0.27	0.08	-0.08	0.01	-0.12
FEV ₁ /FVC %	<0.001 [†]	0.54	<0.001 [†]	0.54	0.78	0.01	0.23	-0.06
Lung mechanics								
R _{aw} kPa·s·L ⁻¹	0.013	-0.12	0.001 [†]	-0.16	<0.001 [†]	0.27	<0.001 [†]	0.28
sR _{aw} kPa·s	<0.001 [†]	-0.30	<0.001 [†]	-0.32	<0.001 [†]	0.17	<0.001 [†]	0.22
R _{in} kPa·s·L ⁻¹	0.02	-0.11	0.004 [†]	-0.14	<0.001 [†]	0.23	<0.001 [†]	0.25
R _{ex} kPa·s·L ⁻¹	0.005	-0.13	<0.001 [†]	-0.17	<0.001 [†]	0.25	<0.001 [†]	0.27
Lung volumes								
TLC L	<0.001 [†]	-0.44	<0.001 [†]	-0.43	0.006	-0.13	0.054	-0.09
TLC % predicted	<0.001 [†]	-0.64	<0.001 [†]	-0.64	0.043	-0.10	0.52	-0.03
RV L	<0.001 [†]	-0.52	<0.001 [†]	-0.51	0.28	-0.05	0.86	0.01
RV % predicted	<0.001 [†]	-0.56	<0.001 [†]	-0.56	0.58	-0.03	0.35	0.04
RV/TLC	<0.001 [†]	-0.30	<0.001 [†]	-0.32	0.08	0.08	0.01	0.13
Gas exchange								
P _{O₂} mmHg	<0.001 [†]	0.20	<0.001 [†]	0.18	<0.001 [†]	0.17	0.001 [†]	0.15
P _{CO₂} mmHg	<0.001 [†]	0.17	0.001 [†]	0.15	<0.001 [†]	0.19	<0.001 [†]	0.17
P _{A-aO₂} mmHg	<0.001 [†]	-0.25	<0.001 [†]	-0.24	<0.001 [†]	-0.23	<0.001 [†]	-0.21
T _{LCO} /V _A % predicted	<0.001 [†]	0.54	<0.001 [†]	0.53	0.02	0.11	0.19	0.06
Blood parameters								
Leukocytes 10 ⁹ cells·L ⁻¹	0.001 [†]	-0.16	<0.001 [†]	-0.16	0.45	-0.04	0.70	-0.02
Haemoglobin mg·dL ⁻¹	<0.001 [†]	-0.19	<0.001 [†]	-0.19	0.10	-0.08	0.22	-0.06
Haematocrit %	<0.001 [†]	-0.21	<0.001 [†]	-0.21	0.28	-0.05	0.56	-0.03
CT parameters								
WA %	0.017	0.11			0	1.00		
Lung density Perc15 HU	0	1			0.02	0.11		

BODE: body-mass index, airflow obstruction, dyspnoea, exercise; BMI: body mass index; 6MWD: 6-min walk distance; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; R_{aw}: airway resistance; sR_{aw}: specific airway resistance; R_{in}: inspiratory resistance; R_{ex}: expiratory resistance; TLC: total lung capacity; RV: residual volume; P_{O₂}: oxygen tension; P_{CO₂}: carbon dioxide tension; P_{A-aO₂}: alveolar–arterial oxygen tension differential; T_{LCO}: transfer capacity of the lung for carbon monoxide; V_A: alveolar volume; CT: computed tomography; WA: airway wall area; Perc15: 15th percentile point. [†]: significant after correction for multiple testing.

Discussion

The current study has demonstrated that emphysema-dominant and airways disease-dominant phenotypic groups may be delineated within a heterogeneous COPD population with mild-to-moderate airflow obstruction using standardised QCT. In addition, groups with mixed disease and mild disease were identified that had comparable smoking history to the other groups. We also showed that QCT indices obtained from different sites were significantly influenced by scanner make and model, and that the use of dedicated standardisation phantoms was of critical importance in improving comparability between centres. Standardisation of CT measures is not relevant to clinical practice at this point in time but it is important in multicentre trials for proper classification of patients with COPD. This has been noted earlier in the COPDGene study [24].

The “emphysema-dominant” and “airway disease-dominant” phenotypes delineated in our COPD population had clinical characteristics that are recognisable in the historical descriptions of the “pink puffer” and the “blue bloater” [25, 26], respectively. Furthermore, these two groups are similar to those described in previous phenotyping studies using cluster analysis [27–29]. In our study, subjects in the “emphysema-dominant” group had more obstructive spirometry, increased lung volumes, lower BMI, greater impairment of gas exchange, and higher TLC and residual volume (RV) in comparison with the “airways disease-dominant” group. The finding that these two groups were comparable with respect to age, disease severity, smoking exposure and inflammatory markers supports the contention that genetic susceptibility to the development of emphysema may be distinct from susceptibility to the development of airways disease. The clinical features of

TABLE 4 Multiple linear regression

	Linear regression		Multiple linear regression			
	p	r	β	SE	p-value	R ²
Lung density					<2.20×10 ⁻¹⁶	0.569
BMI kg·m ⁻²	<0.001	0.31	0.90	0.18	<0.001	
6MWD m	0.99	0.00	0.003	0.01	0.70	
FEV ₁ % predicted	<0.001	0.25	19.81	6.59	0.003	
sR _{aw} kPa·s	<0.001	-0.30	-0.53	1.05	0.62	
TLC % predicted	<0.001	-0.64	-59.04	8.85	<0.001	
RV % predicted	<0.001	-0.56	3.25	3.84	0.40	
P _{O₂} mmHg	<0.001	0.20	-0.09	0.10	0.35	
P _{CO₂} mmHg	<0.001	0.17	0.39	0.22	0.076	
T _{LCO} /V _A % predicted	<0.001	0.54	20.44	3.40	<0.001	
Leukocytes 10 ⁹ cells·L ⁻¹	<0.001	-0.16	-1.27	1.06	0.23	
Lymphocytes 10 ⁹ cells·L ⁻¹	0.42	-0.04	1.94	1.32	0.14	
Neutrophils 10 ⁹ cells·L ⁻¹	0.008	-0.13	0.87	1.15	0.45	
Haemoglobin mg·dL ⁻¹	<0.001	-0.19	-3.04	0.60	<0.001	
IgE kU·L ⁻¹	0.055	0.09	0.002	0.002	0.42	
CRP mg·dL ⁻¹	0.009	0.12	0.14	0.70	0.84	
AAT mg·dL ⁻¹	0.06	-0.09	0.02	0.03	0.46	
Lung density Perc15 HU percentage WA %	0.017	0.11	0.08	0.11	0.463	
Wall area					0.017	0.185
BMI kg·m ⁻²	<0.001	0.21	0.27	0.09	0.002	
6MWD m	<0.001	-0.16	-0.01	0.004	0.002	
FEV ₁ % predicted	0.080	-0.08	-3.69	3.14	0.24	
sR _{aw} kPa·s	<0.001	0.17	0.58	0.50	0.24	
TLC % predicted	0.043	-0.10	4.88	4.43	0.27	
RV % predicted	0.58	-0.03	-1.43	1.81	0.43	
P _{O₂} mmHg	<0.001	0.17	0.17	0.05	<0.001	
P _{CO₂} mmHg	<0.001	0.19	0.25	0.10	0.013	
T _{LCO} /V _A % predicted	0.017	0.11	1.08	1.68	0.52	
Leukocytes 10 ⁹ cells·L ⁻¹	0.45	-0.04	0.25	0.50	0.62	
Lymphocytes 10 ⁹ cells·L ⁻¹	0.032	0.10	-0.12	0.62	0.84	
Neutrophils 10 ⁹ cells·L ⁻¹	0.081	-0.08	-0.75	0.54	0.17	
Haemoglobin mg·dL ⁻¹	0.096	-0.08	0.002	0.29	1.00	
IgE kU·L ⁻¹	0.51	0.03	0.001	0.001	0.32	
CRP mg·dL ⁻¹	0.52	0.03	0.13	0.33	0.69	
AAT mg·dL ⁻¹	0.45	-0.04	-0.01	0.01	0.62	
Lung density Perc15 HU percentage WA %	0.017	0.11	0.02	0.03	0.46	

BMI: body mass index; 6MWD: 6-min walk distance; FEV₁: forced expiratory volume in 1 s; sR_{aw}: specific airway resistance; TLC: total lung capacity; RV: residual volume; P_{O₂}: oxygen tension; P_{CO₂}: carbon dioxide tension; T_{LCO}: transfer capacity of the lung for carbon monoxide; V_A: alveolar volume; Ig: immunoglobulin; CRP: C-reactive protein; AAT: α_1 -antitrypsin; WA: airway wall area.

these two groups were more pronounced when the extreme subphenotypes were compared. The definition of extreme phenotypes (Ex and Aex) is based on CT measures only but we could show that these phenotypes go along with more extreme clinical laboratory values like FEV₁ and P_{O₂} (see table S8). This concept has been developed for this specific study and needs to be validated in independent cohorts.

As shown in previous studies [30–32], we found a negative correlation between the indices of emphysema severity and airway wall thickening. Whilst this inverse relationship appears to suggest that these two disease characteristics are relatively independent, we demonstrated that it was at least partially accounted for by the influence of inspiratory volume during scan acquisition and scanner non-conformity. Consequently, we hypothesise that because a greater inspiratory level during imaging would cause a reduction in lung density and an increase in airway distension, this would produce apparent worsening in emphysema indices whilst simultaneously reducing apparent airway wall thickness; the reverse changes would be seen with a lower inspiratory volume during imaging. Therefore correction for lung volume is an important part of the standardisation exercise.

The mixed group phenotype, which was observed in only 7.7% of our COPD population, was comprised of patients with upper lobe predominant emphysema and airway wall thickening. This is similar to the recently described cluster which CASTALDI *et al.* [27] described as “mild upper zone-predominant emphysema and airflow obstruction”. In their study, this cluster accounted for 15% of their population and was shown to be more likely to experience an exacerbation and more likely to have used the emergency room or been admitted to the hospital for a respiratory issue compared to patients with “relatively resistant” disease. In our study, patients in the “mixed” group did not exhibit greater functional impairment arising from a summative effect of both components when compared to those with emphysema or airways disease alone. Consequently, this combination of features may have a sparing effect on functional impairment; however, further studies are needed to clarify this finding.

The majority of patients in our study were in the group classified as having a “mild” COPD phenotype. They demonstrated relative preservation of FEV₁ and gas transfer with QCT indices consistent with minimal emphysematous change and airway wall thickening, despite comparable age and smoking history to the other groups. It is uncertain whether this phenotypic group represents a truly mild form of COPD or consists of a sub-group of subjects on the cusp of abnormality, who have been “misclassified” as a consequence of the current, commonly employed definition of COPD. To address this question we re-analysed our dataset and replaced the fixed FEV₁/FVC ratio of 0.7 as the cut-off value with the use of a lower limit of normal (LLN) [33]; only 68% in the “mild” group were still classified as having airflow obstruction, which suggests that almost one-third of subjects in this “mild” group may not have COPD. When comparing mild cases above and below LLN then those above LLN had TLC and TLCO/Va values similar to controls while airway resistance was significantly increased (see table S9). This issue may be resolved following the collection of longitudinal data to identify any progressive change, or by clarification of the current uncertainty relating to the definition of airflow obstruction in COPD.

The partial regression analysis provides further evidence of the association between QCT measures of lung structure and clinical parameters. In keeping with the findings of MARTINEZ *et al.* [32] we observed a strong correlation between standardised emphysema measurement (adjusted for %WA) and the BODE (body-mass index, airflow obstruction, dyspnoea, exercise) index. The association was mainly due to the strong correlation between emphysema measurement and FEV₁ and BMI; however, in this study we did not observe an association with 6MWD. Furthermore, in keeping with previous studies, there was an association between standardised airway wall measurements (adjusted for Perc15) and 6MWD [32], BMI [34, 35] but not the BODE index [32]. Both indices correlated with measures of gas exchange, however only emphysema measurement negatively correlated with haemoglobin concentration and leukocyte count. This association cannot be explained by hypoxia alone and warrants further investigation in future studies.

While in early studies, increased haemoglobin concentrations had been reported in COPD [36], more recent studies reported on lower levels along the lines of anaemia of chronic disease [37]. Our data now show that increases of haemoglobin can be detected in COPD, when the appropriate sub-phenotypes are being analysed. Of note, the finding of increased blood haemoglobin and increased blood leukocytes in the emphysema-dominant patients but not in airway disease dominant patients points towards fundamental differences in the pathophysiology of these two sub-phenotypes, which is already apparent in early stage patients studied herein.

The clearly defined clinical features of the emphysema and airways disease groups that were delineated in the current study confirm the clinical relevance and, thereby, imply the validity of the phenotyping methodology that was utilised. We demonstrated, using lung phantoms, that there is significant non-conformity between scanners of different make and model, even when comparable image acquisition protocols are used. Using our standardisation methodology we identified the cut-off between “normal” and emphysema as -925.6 HU and for airways disease as 69.3% WA. Further studies are required to establish normal values using a larger population of controls, with comparable age and smoking history. Furthermore, the approach used for standardisation is currently too cumbersome for use in routine clinical practice and will require refinement and further development before it can be applied to routine clinical practice.

There are a number of limitations to this cross-sectional study. Firstly, we did not recruit patients with very severe airflow obstruction, because tolerance of bronchoscopy was essential for participation in the EvA study [1]. Therefore the majority of cases in this study represent GOLD stages 1 and 2. Hence, the findings reported herein do not apply the full spectrum of COPD cases but are predominantly relevant to the mild to moderate COPD group. It is of interest that even in these cases with only mild to moderate disease, the emphysema-dominant and airway disease-dominant cases can be clearly identified.

Secondly, it is likely that the phenotypic groups that were defined in the current study could be further divided if we had included additional clinical parameters (*e.g.* emphysema subtypes) and utilised cluster

analysis. However, our approach was determined *a priori* and this degree of detailed phenotyping was not required for the primary purpose of the EvA study, which is to identify candidate susceptibility genes in emphysema- and airways-dominant phenotypes. Nevertheless, application of the methodology described here to a larger dataset may enable further phenotypic delineation.

Thirdly, data from 93 patients were excluded primarily due to lack of appropriate imaging data; notwithstanding this limiting factor, sub-analysis on this group did not find any significant clinical differences with the patients included in this study.

Fourthly, our study only included CT imaging obtained on General Electric and Siemens scanners, and it remains unclear whether QCT standardisation methods described in our study are applicable to imaging on CT scanners produced by other manufacturers.

Lastly, the COPD phenotypes presented in this study were determined based on whole lung densitometry and airway morphometry of a single proximal airway. Various studies have demonstrated that, despite heterogeneity, the right upper lobe segmental airway is a good surrogate of proximal airway remodelling in the remainder of the lung [9, 38]. However, it is uncertain whether similar changes will be seen in the small airways [10]. Small airway assessment using inspiratory and expiratory scans to determine gas-trapping, which is considered an indirect measure of small airway disease, may help in future studies to validate the COPD phenotypes as described herein.

In conclusion, the current study demonstrates the utility of QCT in phenotyping of COPD, specifically for the delineation of emphysema and airway disease sub-groups. Standardisation of QCT was shown to be of critical importance when imaging is acquired from scanners of different make and model, as frequently occurs in multicentre studies. It is anticipated that the methodology employed in the current study will facilitate future studies in these two distinct COPD phenotypes. Furthermore, it is desirable that these phenotypic groups, and the methodology, are further validated through the collection of longitudinal data and the demonstration of an association with biomarkers and genotype; this may be provided in due course by the results of the EvA project. Also, it will be important to determine in future studies as to whether the different phenotypes will show a different outcome with respect to exacerbations, antibiotic use, lung function decline and mortality.

Acknowledgements

We are indebted to the European Respiratory Society for their support in launching the project. We would like to thank Dr. Greg Gibbons, Adam Land and Professor Ken Young from the Warwick Manufacturing Groups for constructing the Warwick Densitometry Phantom.

Author contributions: conception, hypotheses delineation and design of the study: L. Ziegler-Heitbrock, C. Brightling, I. Gut, K. Haeussinger, D. Singh, D.G. Parr; acquisition of the data or the analysis and interpretation of such information: D.R. Subramanian, S. Gupta, D. Burggraf, S.J. vom Silberberg, I. Heimbeck, M.S. Heiss-Neumann, K. Haeussinger, C. Newby, B. Hargadon, V. Raj, D. Singh, U. Kolsum, T.P. Hofer, K. Al-shair, N. Luetzen, A. Prasse, J. Müller-Quernheim, G. Benea, S. Leprotti, P. Boschetto, D. Gorecka, A. Nowinski, K. Oniszh, W. zu Castell, M. Hagen, I. Barta, B. Döme, J. Strausz, T. Greulich, C. Vogelmeier, A.R. Koczulla, I. Gut, J. Hohlfeld, T. Welte, M. Lavae-Mokhtari, L. Ziegler-Heitbrock, C. Brightling, D.G. Parr; Writing the article or substantial involvement in its revision prior to submission: L. Ziegler-Heitbrock, D. Singh, S. Gupta, D. Burggraf, C. Brightling, D.G. Parr.

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