



# Discriminating dominant computed tomography phenotypes in smokers without or with mild COPD

Firdaus A.A. Mohamed Hoesein <sup>a,\*</sup>, Michael Schmidt <sup>b</sup>,  
Onno M. Mets <sup>a</sup>, Hester A. Gietema <sup>a</sup>, Jan-Willem J. Lammers <sup>c</sup>,  
Pieter Zanen <sup>c</sup>, Harry J. de Koning <sup>d</sup>, Carlijn van der Aalst <sup>d</sup>,  
Matthijs Oudkerk <sup>e</sup>, Rozemarijn Vliedhart <sup>e</sup>, Ivana Isgum <sup>f</sup>,  
Mathias Prokop <sup>g</sup>, Bram van Ginneken <sup>g</sup>, Eva M. van Rikxoort <sup>g,1</sup>,  
Pim A. de Jong <sup>a,1</sup>

<sup>a</sup> Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>b</sup> Fraunhofer MEVIS, Institute for Medical Image Computing, Bremen, Germany

<sup>c</sup> Department of Respiratory Medicine, Division of Heart & Lungs, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>d</sup> Department of Public Health, Erasmus MC, Rotterdam, The Netherlands

<sup>e</sup> Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>f</sup> Image Sciences Institute, University Medical Center Utrecht, The Netherlands

<sup>g</sup> Department of Radiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

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## KEYWORDS

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## Summary

*Background:* Finding phenotypes within COPD patients may prove imperative for optimizing treatment and prognosis. We hypothesized that it would be possible to discriminate emphysematous, large airway wall thickening and small airways disease dominant phenotypes.

\* Corresponding author. Department of Radiology, University Medical Center Utrecht, PO Box 85500, HP E01.132, 3508GA Utrecht, The Netherlands. Tel.: +31 88 75556689; fax: +31 30 2581098.

*E-mail addresses:* [fmohamedhoesein@gmail.com](mailto:fmohamedhoesein@gmail.com) (F.A.A. Mohamed Hoesein), [Michael.Schmidt@mevis.fraunhofer.de](mailto:Michael.Schmidt@mevis.fraunhofer.de) (M. Schmidt), [metsonno@gmail.com](mailto:metsonno@gmail.com) (O.M. Mets), [h.gietema@umcutrecht.nl](mailto:h.gietema@umcutrecht.nl) (H.A. Gietema), [j.w.j.lammers@umcutrecht.nl](mailto:j.w.j.lammers@umcutrecht.nl) (J.-W.J. Lammers), [p.zanen@umcutrecht.nl](mailto:p.zanen@umcutrecht.nl) (P. Zanen), [h.dekoning@erasmusmc.nl](mailto:h.dekoning@erasmusmc.nl) (H.J. de Koning), [c.vanderaalst@erasmusmc.nl](mailto:c.vanderaalst@erasmusmc.nl) (C. van der Aalst), [m.oudkerk@umcg.nl](mailto:m.oudkerk@umcg.nl) (M. Oudkerk), [r.vliedhart@rad.umcg.nl](mailto:r.vliedhart@rad.umcg.nl) (R. Vliedhart), [ivana.isgum@gmail.com](mailto:ivana.isgum@gmail.com) (I. Isgum), [M.Prokop@rad.umcn.nl](mailto:M.Prokop@rad.umcn.nl) (M. Prokop), [b.vanginneken@rad.umcn.nl](mailto:b.vanginneken@rad.umcn.nl) (B. van Ginneken), [E.vanRikxoort@rad.umcn.nl](mailto:E.vanRikxoort@rad.umcn.nl) (E.M. van Rikxoort), [pimdejong@gmail.com](mailto:pimdejong@gmail.com) (P.A. de Jong).

<sup>1</sup> These authors contributed equally.

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**Methods:** Inspiratory and expiratory CTs were performed in 1140 male smokers without or with mild COPD to quantify emphysema, airway wall thickness and air trapping. Spirometry, residual volume to total lung capacity (RV/TLC) and diffusion capacity (Kco) were measured. Dominant phenotype (emphysema, airway wall thickening or air trapping dominant) was defined as one of the respective CT measure in the upper quartile, with the other measures not in the upper quartile.

**Results:** 573 subjects had any of the three CT measures in the upper quartile. Of these, 367 (64%) were in a single dominant group and 206 (36%) were in a mixed group. Airway wall thickening dominance was associated with younger age ( $p < 0.001$ ), higher body mass index ( $p < 0.001$ ), more wheezing ( $p < 0.05$ ) and lower FEV<sub>1</sub> %predicted ( $p < 0.001$ ). Emphysema dominant subjects had lower FEV<sub>1</sub>/FVC ( $p < 0.05$ ) and Kco %predicted ( $p < 0.05$ ). There was no significant difference in respiratory related hospitalizations ( $p = 0.09$ ).

**Conclusion:** CT measures can discriminate three different CT dominant groups of disease in male smokers without or with mild COPD.

**Trial registration number:** ISRCTN63545820, registered at [www.trialregister.nl](http://www.trialregister.nl).

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## Introduction

Chronic obstructive pulmonary disease (COPD) is the only chronic disease with increasing mortality rates and has a high morbidity worldwide [1]. COPD is mainly caused by inhalation of irritants found in tobacco smoke and is diagnosed when COPD is present, i.e. when the FEV<sub>1</sub>/FVC is below a predefined threshold [2,3].

Lung abnormalities associated with COPD may represent a continuum of a single disorder or may consist of multiple largely independent types. Small airways are believed to represent the principal site of obstruction in most patients with obstructive pulmonary disease [3,4]. Classical belief is that centrilobular emphysema starts with disappearance of small airways followed by emphysematous destruction. In a final stage only a few thickened large airways persist [3]. However, this sequence in the pathophysiology of centrilobular emphysema does not exclude that intrinsic small and large airway disease can independently lead to obstructive pulmonary disease without emphysematous destruction in other large groups of smokers. Nakano et al. showed that, in patients with more advanced stages of COPD, those with predominantly thickened airway walls and with predominantly emphysema (measured as low attenuation areas) could be identified on computed tomography (CT) scans [5,6]. However, there is little evidence if this is also the case in smokers without COPD or subjects only with mild COPD. Further evidence for specific independent morphologic phenotypes comes from the observation that 'emphysema-dominance' and 'airway-dominance' runs in families [7].

The search for dominant COPD phenotypes is highly relevant as large randomized controlled drug trials failed to demonstrate significant treatment effects on lung function decline [8,9]. It is however anticipated that within different COPD phenotypes specific (pharmacological) therapies might be effective [10]. Specific phenotypes might also be associated with different prognosis, comorbidities and genotypes [11]. CT imaging may be one of the tools used to phenotype COPD based on the presence of emphysema, airway wall thickening and air trapping.

We hypothesized that it would be possible to discriminate emphysematous, large airway wall thickening and small airways disease dominant phenotypes in smokers without or with mild COPD. We therefore studied differences in clinical symptoms, pulmonary function and respiratory related hospitalization in three predominant phenotypes (emphysema, airway wall thickening or air trapping) based on CT parameters.

## Methods

### Subject selection

This study was conducted as a sub-study of the Dutch and Belgium Lung Cancer Screening Trial (NELSON trial – ISRCTN63545820, registered at [www.trialregister.nl](http://www.trialregister.nl)) and only subjects from the University Medical Center Utrecht were included [12]. Details of the selection procedure have previously been described [13]. In short, subjects were 50–75 years old, current or former heavy smokers (ceased smoking  $\leq 10$  years before entering the study), with a smoking history of at least 16.5 packyears [12]. An expiratory acquisition was added to the screening protocol in the University Medical Center Utrecht, The Netherlands. Of the 1162 subjects 22 were excluded because of missing smoking history data or CT segmentation errors, resulting in 1140 subjects included. Respiratory related hospitalization rates were retrospectively ascertained through linkage with the National Registry of Hospital Discharge Diagnoses for the period 1995–2007. The lung cancer screening study was approved by the Ministry of Health of The Netherlands and the institutional ethical review board of the University Medical Center Utrecht, The Netherlands (IRB approval number 03/040). Written informed consent was obtained in all screening trial subjects.

### Clinical measurements

Detailed smoking characteristics and symptoms were obtained through a questionnaire. We asked for presence of

the following symptoms: cough, mucus production, dyspnea and wheezing, present for at least three months per year. We retrieved causes of hospital admission through the National Registry of Hospital Discharge Diagnoses. We included events that occurred between January 1995 and January 2008. All events were classified using the 9th revision of the International Classification of Diseases, and codes 460-519 were included [14,15].

### Pulmonary function testing

Information of the pulmonary function tests, including spirometry and body plethysmography, has been reported elsewhere [16]. Data was obtained according to European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines and was performed with ZAN equipment (ZAN Messgeräte GmbH, Germany) [17,18]. Measurements included forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC), mid expiratory flow at 50% of FVC (MEF<sub>50</sub>), residual volume (RV), total lung capacity (TLC) and the transfer coefficient for carbon monoxide (Kco) as measure of lung diffusion capacity. The FEV<sub>1</sub>/FVC and residual volume to total lung capacity (RV/TLC) were expressed as percentage. The Kco was used as a measure of lung diffusion capacity.

### CT scanning

The CT protocol has been described in detail before [13,19]. All CTs were performed without intravenous contrast injection, and obtained with 16 × 0.75 mm collimation on the same scanner (Brilliance 16P, Philips Medical Systems, USA). Volumetric inspiratory and end-expiratory CT scans were obtained after standardized breathing instructions in all subjects. The expiratory CT scan was obtained directly after the inspiratory one during the same session. Axial images were reconstructed from lung bases to lung apices at a slice thickness of 1.0 mm at 0.7 mm increment, using a smoothed reconstruction filter (B-filter, Philips).

### Quantitative CT assessment of the lung parenchyma

All quantifications were performed with CIRRUS Lung 12.03 (<http://cirrus.diagnijmegen.nl>, Diagnostic Image Analysis Group Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany). As previously described, the lungs were automatically segmented from the chest wall, airways and mediastinum using dedicated software [20,21]. We defined CT emphysema as the percentage of voxels below Hounsfield Unit (HU) –950 and CT air-trapping as the expiratory mean lung density in HU divided by the inspiratory mean lung density expressed as percentage [13,22,23].

### Quantitative CT assessment of large airways

The airway lumen was automatically segmented. Airway cross-sections are defined perpendicular to the local airway direction at a spacing of 1 mm across all airway centerlines. Inner and outer airway wall borders are segmented for each of these cross-sections based on an intensity-integration

based analysis of 72 rays pointing radially from the centerpoint outwards [24]. Cross-sections obtained from the trachea, main bronchi, branching regions as well as cross-sections where the airway wall segmentation failed were automatically discarded from further analysis. The airway lumen was automatically segmented, airways up until the 11th generation were included for analysis. The square root of wall area for a theoretical airway with 10 mm lumen perimeter (=Pi10) was calculated and was used as measurement of airway wall thickening (=AWT) [7,24,25]. For each CT scan a random selection of cross-sections of the detected airway walls borders was visually inspected to assess if the automatic wall segmentation was correct.

### Definition of dominant CT groups

Dominant emphysema, AWT dominant and dominant air trapping were defined as the respective CT measure in the upper quartile, with the other measures outside the upper quartile.

### Data analysis

As no established thresholds exist, we arbitrarily used the upper quartile (values above the 75th percentile) for presence of significant CT emphysema, CT AWT and CT air trapping. Since CT density has been reported to be dependent on smoking status, the 75th percentile for emphysema was calculated for former and current smokers separately. No significant disease was defined as all measures were outside the upper quartile. Mixed disease was defined as multiple CT measures were in the upper quartile. Descriptive statistics are presented as mean (standard deviation (SD)) for normally distributed variables, and as median and inter-quartile range (IQR) for non-normally distributed variables. Differences between groups are illustrated using box plots. Statistical significance was tested only between the 3 dominant groups using analysis of variance and post-hoc Bonferroni tests for normally distributed variables, and using Kruskal–Wallis and post-hoc Mann–Whitney-*U* tests for non-normally distributed values. *P* < 0.05 was considered statistically significant. All statistical analyses were performed via SPSS 16 (SPSS, Chicago, USA).

## Results

### Subjects

The 1140 included males were slightly over 60 years old and smoked on average 41 packyears. Approximately 50% were current smokers. In this population 61.7% did not reach the Global initiative on Obstructive Lung Disease (GOLD) criteria for COPD. The majority of COPD subjects (86%) were in GOLD stage 1, 14% had GOLD stage 2 or 3. About a quarter of the population reported the presence of all four recorded respiratory symptoms. In total 62 (5.2%) subjects were hospitalized at least once for a respiratory disease between 1995 and 2007. More detailed characteristics are presented in Table 1.

**Table 1** Characteristics of the included 1140 male subjects.

| Characteristic  | N    | Value           |
|---|------|-----------------|
| Age (yrs) mean $\pm$ SD   | 1140 | 62.5 $\pm$ 5.2  |
| Smoking (packyears) mean $\pm$ SD   | 1140 | 41.0 $\pm$ 18.0 |
| Current smoker (Number, %)  | 1140 | 609, 53.4%      |
| BMI (kg/m <sup>2</sup> )  | 1140 | 27.1 $\pm$ 3.6  |
| GOLD stage  |      |                 |
| 0 (Number, %)   |      | 703, 61.7%      |
| 1 (Number, %)   |      | 277, 24.3%      |
| 2–3 (Number, %)   |      | 160, 14.0%      |
| FEV <sub>1</sub> (%pred) mean $\pm$ SD  | 1140 | 94.8 $\pm$ 17.6 |
| FEV <sub>1</sub> /FVC (%) mean $\pm$ SD   | 1140 | 70.9 $\pm$ 9.3  |
| MEF <sub>50</sub> (%pred) mean $\pm$ SD   | 1140 | 68.8 $\pm$ 29.3 |
| RV/TLC (%) mean $\pm$ SD  | 418  | 35.9 $\pm$ 8.4  |
| Kco (%pred) mean $\pm$ SD   | 420  | 87.7 $\pm$ 17.4 |
| Cough (Number, %)   | 1037 | 327, 28.7%      |
| Mucus (Number, %)   | 1120 | 300, 26.3%      |
| Dyspnea (Number, %)   | 1035 | 288, 25.3%      |
| Wheezing (Number, %)  | 1017 | 216, 18.9%      |
| Subjects with respiratory related hospitalization   | 1140 | 62, 5.4%        |
| CT emphysema % voxels < -950HU median, IQR  | 1140 | 0.75, 0.40-1.46 |
| CT airway wall thickness at lumen perimeter 10-mm mean $\pm$ SD                                 | 1120 | 2.4 $\pm$ 0.51  |
| CT air trapping (mean lung density expiration/mean lung density inspiration*100%) mean $\pm$ SD | 1140 | 83.8 $\pm$ 6.2  |

SD = standard deviation, BMI = body mass index, GOLD = Global Initiative on Obstructive Lung Disease, FEV<sub>1</sub> = forced expiratory volume in one second, FVC = forced vital capacity, MEF = mid expiratory flow, RV = residual volume, TLC = total lung capacity, Kco = transfer coefficient for carbon monoxide, IQR = inter-quartile range, CT = computed tomography, HU = Hounsfield unit.

## Parenchyma and airway disease on CT

The 75th percentile for CT emphysema was 1.23% and 1.72% for current and former smokers, respectively. The 75th percentile for CT air-trapping was 87.8% and the 75th percentile for CT airway wall thickening was 2.74 mm. A number of 547 (49%) subjects had all three CT measures below the 75th percentile. Of the 573 subjects with any of the three CT measure in the upper quartile, 367 (64%) were in a single dominant group, and 206 (36%) were in a mixed group. Of all included subjects 143 (13%) subjects were emphysema dominant, 91 (8%) air trapping dominant and 133 (12%) AWT dominant. Fig. 1 illustrates CT images of subjects with GOLD stage 2 in each of the dominant groups.

## Differences between dominant groups

Fig. 2 and Table 2 illustrate and present the differences between the dominance groups based on imaging parameters for clinical, and lung function characteristics. AWT dominant subjects were on average significantly younger

compared to the emphysema ( $p = 0.002$ ) and air trapping ( $p = 0.048$ ) dominant subjects. The three groups had smoked a similar number of packyears ( $p = 0.14$ ) and smoking status did not differ between the groups ( $p = 0.13$ ). AWT dominant subjects had on average a higher BMI compared to the emphysema ( $p < 0.001$ ) and air trapping dominant subjects ( $p < 0.001$ ).

For lung function measures, the AWT dominant group had a significantly worse FEV<sub>1</sub> %predicted compared to the emphysema ( $p < 0.001$ ) and air trapping ( $p = 0.001$ ) dominant groups. Emphysema dominant subjects had a significantly worse FEV<sub>1</sub>/FVC% compared to the air trapping ( $p < 0.001$ ) and AWT ( $p = 0.02$ ) dominant groups. Kco % predicted was significantly worse in the emphysema subjects compared to both the air trapping ( $p = 0.02$ ) and AWT ( $p < 0.001$ ) dominant groups. The distribution of GOLD stages between the three groups did not reach statistical significance.

The air trapping dominant group had a significantly higher MEF<sub>50</sub> %predicted compared to the emphysema ( $p = 0.002$ ) and AWT ( $p = 0.02$ ) dominant groups. The RV/TLC% was not different between the groups ( $p = 0.29$ ).

The reported presence of cough ( $p = 0.07$ ) and dyspnea ( $p = 0.55$ ) did not reach significance between the three groups. Mucus production was reported more often in the AWT dominant group compared to the air trapping dominant group ( $p = 0.02$ ). Wheezing was significantly more common in the AWT dominant group compared to the air trapping ( $p = 0.02$ ) and emphysema ( $p = 0.04$ ) dominant groups.

## Differences between mixed morphological groups

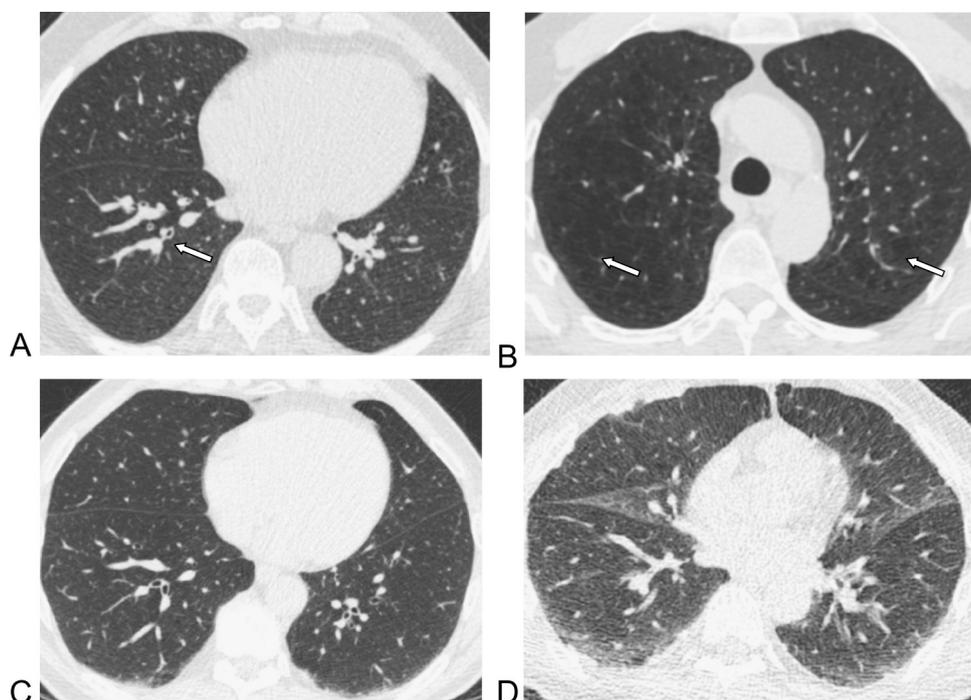
Table 3 lists the differences between the mixed morphological groups based on imaging parameters regarding clinical, and lung function characteristics. Overall, spirometric measurements were significantly lower in the mixed groups compared to the dominant groups, all  $p < 0.05$ .

## Respiratory related hospitalizations

Subjects with respiratory related hospitalizations had a significantly lower FEV<sub>1</sub>, 89.5% (19.6) compared to 95.1% (17.4) for those without ( $p < 0.001$ ). The same was observed for FEV<sub>1</sub>/FVC, 68.5% (11.3) versus 71.05% (9.2) ( $p < 0.001$ ). There were no significant differences in respiratory related hospitalizations between the emphysema, AWT, air trapping and mixed type dominant groups ( $p = 0.09$ ).

## Discussion

In a population of current and former smoking males without and with mild COPD we demonstrated that CT imaging grouped the majority of subjects into either the upper quartile for CT emphysema, CT air trapping or CT AWT, while fewer subjects demonstrated a mixture of CT abnormalities in the upper quartile. Additionally we observed significant differences in clinical characteristics between subjects with dominance for CT measured emphysema, air trapping and AWT, including differences in



**Figure 1** Patients with similar stage of Chronic Obstructive Pulmonary Disease but with different dominant abnormalities of chest Computed Tomography. A: GOLD stage 2 with dominant airways disease. The low-dose inspiratory CT scan illustrates thickened airway walls (white arrow) and absence of emphysema. B: GOLD stage 2 with dominant emphysematous disease. The white arrows point at emphysema. The low-dose inspiratory CT scan visualizes marked emphysematous destruction and note the thinner airway walls compared to figure A. C: GOLD stage 2 with dominant air trapping. The inspiratory low-dose CT scan note the thinner airway walls compared to figure A and the absence of emphysema. D: The ultra low-dose expiratory CT scan shows air trapping in the lower lobes with lower density compared to the middle lobe and lingula and bulging of the fissures. Also note the collapse of airways.

respiratory symptoms and lung function measures. Our data thus provides evidence that also in smokers without or only mild COPD CT may be used as a tool to identify different phenotypes.

It seems that subjects with relatively lower lung function values, i.e. more progressive disease, more often show a mixed dominant pattern. These results confirm both the notion that dominant morphologic groups indeed exists as was proposed by Nakano et al., and that end-stage centrilobular emphysema is characterized by extensive obliteration of small airways and thickened large airway walls [3,6]. However, to firmly establish phenotypes within COPD, further research is needed, especially combining more subjects' characteristics and the full range of COPD severity.

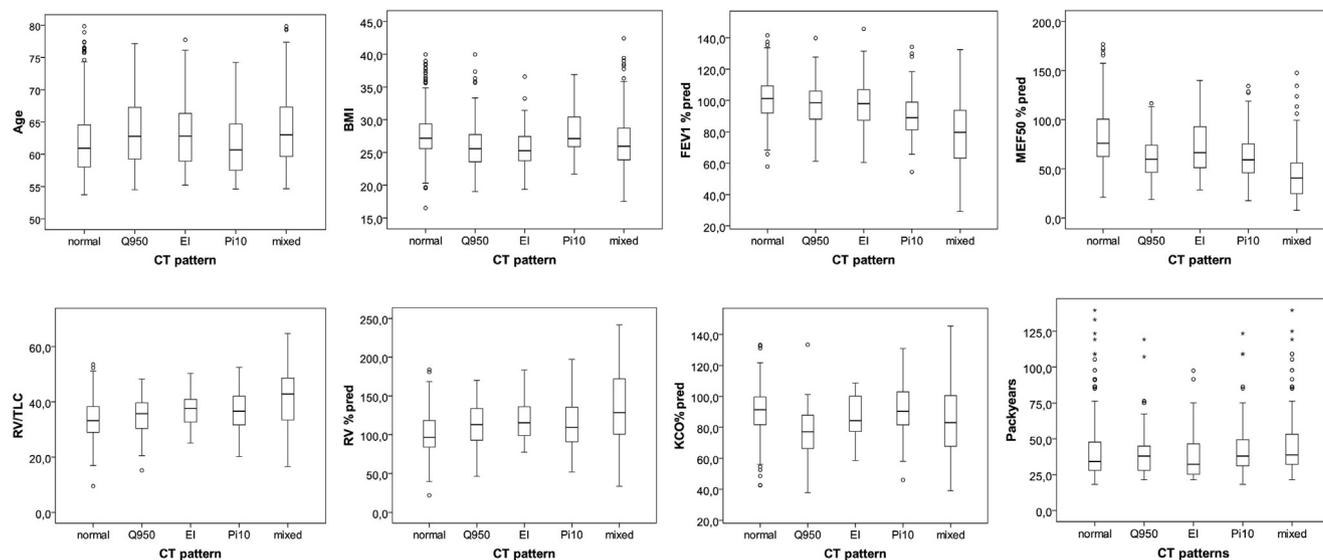
There are suggestions that there could be an association between emphysema and airway wall thickening. Johhassen et al. showed that the effect of airway wall thickening on mortality was only present in subjects with severe emphysema and not in subjects without or with moderate emphysema. Our results show a similar trend as we showed that the mixed morphological groups have lower spirometric values.

The results can be of significance for studies investigating effects of pharmacotherapy of COPD. Especially in the mild stage of the disease, which is most interesting from a therapeutic perspective, these CT measures may be helpful as our data provided dominant groups in

subjects without or with mild COPD. Very recently large randomized controlled trials could not show that pharmacological treatment was beneficial on FEV<sub>1</sub>-decline. [8,9] These studies however did not analyze the effects within different phenotypes of COPD. Using the CT based types one might show effects of therapy within the groups. Our approach can be used to appreciate COPD more as a heterogeneous group of disorders, instead of one disease [26].

A key point of our study is that CT phenotypes are also already recognizable in smokers without or only mild COPD. Although previous studies included COPD subjects with more severe disease (GOLD 2 and higher), our findings on the relation between CT measures and other subject characteristics correspond favorably to previous observations. It has been shown that airway wall thickness is more closely related to worse FEV<sub>1</sub> %predicted, more respiratory symptoms and higher BMI [27–30]. Furthermore, our finding that emphysema dominant subjects show the worst diffusion capacity is expected and confirms a previous study [31].

We could, however, not show significant differences in respiratory related hospitalizations between the different CT based groups. This is explained because the included group of subjects is relatively healthy and subsequently the number of hospitalizations in this group is low. A recent study including only COPD subjects showed that airway wall thickening and emphysema were related with exacerbation



**Figure 2** Box plots of different phenotypes based on CT parameters and subject demographics and results from lung function tests (FEV<sub>1</sub> %predicted, MEF<sub>50</sub> %predicted, RV/TLC, RV %predicted and Kco %predicted). CT groups; normal, all measures below the upper quartile; Q950, emphysema in the upper quartile; EI, air trapping in the upper quartile; Pi10, airway wall thickening in the upper quartile; mixed, more than one CT measure in the upper quartile.

frequency. However, exacerbation rate in that study was self-reported and thus also included less severe exacerbations not requiring hospitalization [32]. In another study, lung function did relate with respiratory related hospitalization and it seems that in a relatively healthy group of subjects CT metrics do not associate with respiratory related hospitalizations [33].

A strength of our study is that we were able to include a large number of subjects who all underwent extensive pulmonary function testing, and that we studied mild stages of COPD. However, future longitudinal studies are

needed to confirm and extend our findings. Our study also has some limitations. Firstly, although for CT emphysema and airway wall dimensions pathological correlation studies are available, there is no true pathological correlation for the ratio between expiratory and inspiratory of mean lung density, which we used to assess air trapping in this study [34,35]. There is no real consensus on which cut-off value of quantitative CT measures is the most appropriate and we therefore choose to use the 75th percentile. Although this is not based on a correlation with pathology specimens, in daily practice this may prove to be an

**Table 2** Characteristics of the subjects per computed tomography (CT) based on predominant phenotype. Significance levels of difference between the three groups.

|  | Emphysema dominant >P75 (n = 143) | Air trapping dominant >P75 (n = 91) | Airway wall thickening dominant >P75 (n = 133) | Significance for group differences, p-value |
|--|-----------------------------------|-------------------------------------|--|---|
| Age (yrs)                                  | 63.7 ± 5.5                        | 63.2 ± 5.3                          | 61.5 ± 4.8                                     | <b>0.02</b>                                 |
| Smoking (packyears)                        | 39.0 ± 15.6                       | 37.6 ± 14.9                         | 41.7 ± 17.0                                    | 0.138                                       |
| Current smoker (N, %)                      | 70, 49.0%                         | 55, 60.4%                           | 80, 60.2%                                      | 0.13  |
| BMI (kg/m <sup>2</sup> )                   | 25.9 ± 3.5                        | 25.6 ± 3.1                          | 28.1 ± 3.5                                     | <b>&lt;0.001</b>                            |
| FEV <sub>1</sub> (%pred)                   | 97.7 ± 14.8                       | 97.7 ± 16.0                         | 90.6 ± 13.7                                    | <b>&lt;0.001</b>                            |
| FEV <sub>1</sub> /FVC (%)                  | 68.6 ± 7.2                        | 72.2 ± 7.3                          | 71.0 ± 7.2                                     | <b>&lt;0.001</b>                            |
| MEF <sub>50</sub> (%pred)                  | 61.3 ± 20.6                       | 71.8 ± 26.4                         | 63.2 ± 23.0                                    | <b>0.02</b>                                 |
| RV/TLC (%)                                 | 35.0 ± 7.0                        | 37.2 ± 6.4                          | 36.6 ± 7.2                                     | 0.293                                       |
| Kco (%pred)                                | 76.6 ± 15.7                       | 86.7 ± 12.8                         | 91.7 ± 17.9                                    | <b>&lt;0.001</b>                            |
| Cough present (N, %)                       | 33, 25.8%                         | 26, 31.7%                           | 47, 39.5%                                      | 0.07  |
| Mucus present (N, %)                       | 38, 29.5%                         | 18, 22.8%                           | 47, 39.2%                                      | <b>0.04</b>                                 |
| Dyspnea present (N, %)                     | 35, 26.1%                         | 18, 21.7%                           | 34, 28.6%                                      | 0.055                                       |
| Wheeze present (N, %)                      | 19, 14.8%                         | 12, 14.8%                           | 32, 26.9%                                      | <b>0.03</b>                                 |
| Respiratory related hospitalization (N, %) | 15, 10.5%                         | 3, 3.3%                             | 8, 6.0%  | 0.09  |

Values in bold represents p value lower than 0.05.

**Table 3** Characteristics of the subjects per computed tomography (CT) in the mixed morphological groups.

|   | All CT<br>measures >P75<br>(n = 53) | Emphysema and<br>air trapping >P75<br>(n = 64) | Emphysema and<br>airway wall<br>thickening >P75<br>(n = 18) | Airway wall<br>thickening<br>and air<br>trapping >P75<br>(n = 71) | Significance<br>for group<br>differences,<br>p-value |
|---|-------------------------------------|--|---|---|--|
| Age (yrs)                                     | 64.5 ± 4.8                          | 64.0 ± 5.5                                     | 63.6 ± 6.5  | 62.8 ± 6.0  | 0.394  |
| Smoking (packyears)                           | 45.5 ± 18.6                         | 45.5 ± 21.9                                    | 43.4 ± 16.1   | 44.4 ± 19.0   | 0.965  |
| Current smoker (N, %)                         | 30, 56.6%                           | 41, 64.0%                                      | 10, 55.6%   | 39, 54.9%   | 0.725  |
| BMI (kg/m <sup>2</sup> )                      | 25.9 ± 4.3                          | 25.0 ± 3.9                                     | 28.4 ± 4.6  | 27.9 ± 3.7  | <0.001   |
| FEV <sub>1</sub> (%pred)                      | 64.2 ± 19.6                         | 84.4 ± 21.3                                    | 84.1 ± 18.9   | 80.3 ± 17.7   | <0.001   |
| FEV <sub>1</sub> /FVC (%)                     | 51.9 ± 10.9                         | 60.3 ± 10.4                                    | 65.0 ± 9.0  | 65.8 ± 9.0  | <0.001   |
| MEF <sub>50</sub> (%pred)                     | 25.7 ± 14.4                         | 44.1 ± 25.3                                    | 48.8 ± 22.5   | 49.1 ± 22.6   | <0.001   |
| RV/TLC (%)                                    | 44.9 ± 13.4                         | 42.6 ± 10.1                                    | 35.8 ± 8.7  | 40.1 ± 10.5   | 0.367  |
| Kco (%pred)                                   | 76.3 ± 16.7                         | 71.1 ± 18.3                                    | 94.5 ± 9.4  | 93.0 ± 20.3   | <0.001   |
| Cough present (N, %)                          | 30, 61.2%                           | 27, 44.3%                                      | 9, 52.9%  | 21, 33.9%   | 0.034  |
| Mucus present (N, %)                          | 21, 45.7%                           | 30, 50.0%                                      | 8, 53.3%  | 17, 27.4%   | 0.045  |
| Dyspnea present (N, %)                        | 25, 52.1%                           | 29, 46.8%                                      | 6, 40.0%  | 29, 43.9%   | 0.798  |
| Wheeze present (N, %)                         | 20, 44.4%                           | 16, 27.1%                                      | 7, 46.7%  | 24, 36.9%   | 0.250  |
| Respiratory related<br>hospitalization (N, %) | 3, 5.7%                             | 4, 6.3%  | 1, 5.6%   | 2, 2.8%   | 0.804  |

Values in bold represents p value lower than 0.05.

attractive cut-off. We choose not to correct for lung volume since no studies yet showed this is more accurate when compared with the gold standard for emphysema, i.e. pathology specimen. In addition lung volume correction is deemed to play a significant role mainly in follow-up studies [36]. Secondly, our study has a cross-sectional design and one cannot exclude that the dominant groups are just at various stages of a single disease. However, we think it would be highly unlikely that subjects could start at various distinct imaging patterns within a single disease. Also the differences in multiple variables between the groups suggest that these are indeed independent groups of subjects. This would confirm the existence of emphysema dominant and AWT dominant groups on CT, and we propose to add the lung density ratio in further phenotype research [6]. Thirdly, we used pre-bronchodilator spirometry, low-dose CT protocols and obtained hospitalization data from a validated national database of physician recorded discharge diagnosis. Differences between groups may have become significant if exacerbations of COPD that did not require hospitalization would also have been available. Fourthly, no female subjects were included. Lastly, we concentrated only on emphysema, air trapping and airway wall thickening and did not investigate signs of interstitial lung disease (i.e. measures of ground glass, bronchiectasis, etc.) which is gaining importance in these heavy smokers [37].

In conclusion, our study provides further evidence that even smokers with no or only mild COPD can show specific and independent groups of disease. CT measures of emphysema, airway wall thickening and air trapping may aid in the detection of 'treatable' COPD groups (in more advanced disease), and may aid in prognostication regarding pulmonary disease progression and co-morbidities in COPD.

## Conflict of interest

Harry de Koning is member of the medical advisory board of Roche Diagnostics. The other authors state that they have no conflicts of interest.

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FMH, PJ and ER were responsible for the concept and design of the study and the statistical analyses and are guarantor of the paper. BG and ER were responsible for the quantification of emphysema and air trapping. MS and ER were responsible for the airway wall thickness quantification. OM, HG, JW, PZ, HK, CA, MO, RV, II, and MP assisted in designing the study and writing of the manuscript. All authors contributed to writing and all approved the final version of the manuscript.

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