

Baseline characteristics from a 3-year longitudinal study to phenotype subjects with COPD

Crapo, James D.; Gupta, Abhya; Lynch, David A.; Turner, Alice M.; Mroz, Robert M.; Janssens, Wim; Ludwig-Sengpiel, Andrea; Koegler, Harald; Eleftheraki, Anastasia; Risse, Frank; Diefenbach, Claudia

DOI:

[10.1186/s12931-023-02584-2](https://doi.org/10.1186/s12931-023-02584-2)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Crapo, JD, Gupta, A, Lynch, DA, Turner, AM, Mroz, RM, Janssens, W, Ludwig-Sengpiel, A, Koegler, H, Eleftheraki, A, Risse, F & Diefenbach, C 2023, 'Baseline characteristics from a 3-year longitudinal study to phenotype subjects with COPD: the FOOTPRINTS study', *Respiratory research*, vol. 24, no. 1, 290. <https://doi.org/10.1186/s12931-023-02584-2>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

RESEARCH

Open Access



Baseline characteristics from a 3-year longitudinal study to phenotype subjects with COPD: the FOOTPRINTS study

James D. Crapo^{1*}, Abhya Gupta², David A. Lynch³, Alice M. Turner⁴, Robert M. Mroz⁵, Wim Janssens⁶, Andrea Ludwig-Sengpiel⁷, Harald Koegler⁸, Anastasia Eleftheraki⁹, Frank Risse⁹ and Claudia Diefenbach⁹

Abstract

Background FOOTPRINTS[®] is a prospective, longitudinal, 3-year study assessing the association between biomarkers of inflammation/lung tissue destruction and chronic obstructive pulmonary disease (COPD) severity and progression in ex-smokers with mild-to-severe COPD. Here, we present baseline characteristics and select biomarkers of study subjects.

Methods The methodology of FOOTPRINTS[®] has been published previously. The study population included ex-smokers with a range of COPD severities (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages 1–3), ex-smokers with COPD and alpha-1-antitrypsin deficiency (A1ATD) and a control group of ex-smokers without airflow limitation (EwAL). At study entry, data were collected for: demographics, disease characteristics, history of comorbidities and COPD exacerbations, symptoms, lung function and volume, exercise capacity, soluble biomarkers, and quantitative and qualitative computed tomography. Baseline data are presented with descriptive statistical comparisons for soluble biomarkers in the individual GOLD and A1ATD groups versus EwAL.

Results In total, 463 subjects were enrolled. The per-protocol set comprised 456 subjects, mostly male (64.5%). The mean (standard deviation) age was 60.7 (6.9) years. At baseline, increasing pulmonary symptoms, worse lung function, increased residual volume, reduced diffusing capacity of the lung for carbon monoxide (DLco) and greater prevalence of centrilobular emphysema were observed with increasing disease severity amongst GOLD 1–3 subjects. Subjects with A1ATD (n = 19) had similar lung function parameters to GOLD 2–3 subjects, a high residual volume comparable to GOLD 3 subjects, and similar air trapping to GOLD 2 subjects. Compared with EwAL (n = 61), subjects with A1ATD had worse lung function, increased residual volume, reduced DLco, and a greater prevalence of confluent or advanced destructive emphysema. The soluble inflammatory biomarkers white blood cell count, fibrinogen, high-sensitivity C-reactive protein and plasma surfactant protein were higher in GOLD 1–3 groups than in the EwAL group. Interleukin-6 was expressed less often in EwAL subjects compared with subjects in the GOLD and A1ATD groups. Soluble receptor for advanced glycation end product was lowest in GOLD 3 subjects, indicative of more severe emphysema.

Conclusions These findings provide context for upcoming results from FOOTPRINTS[®], which aims to establish correlations between biomarkers and disease progression in a representative COPD population.

Trial registration number: NCT02719184, study start date 13/04/2016.

*Correspondence:

James D. Crapo

crapoj@njhealth.org

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Keywords Chronic obstructive pulmonary disease, Emphysema, FOOTPRINTS[®], Baseline characteristics, Alpha 1 antitrypsin deficiency, Biomarkers, Disease progression

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease primarily of the lungs, and is characterised by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities. COPD is generally attributed to exposure to tobacco and/or harmful air particles [1]. Changes to the small airways in COPD, such as obstructive bronchiolitis and parenchymal destruction (emphysema), can occur alone or in combination, and the relative contributions and severity of each vary between individuals [1].

In the era of precision medicine, phenotyping patients with COPD based on one or more disease characteristics could improve our understanding of pathogenesis and disease progression, as patients do not generally all follow the same trajectory in their disease. As a result, this may allow for more targeted, individualised, and hence efficacious pharmacological and non-pharmacological management. Prospective longitudinal studies can help to assess whether soluble biomarkers (e.g., from whole blood, serum, plasma or sputum), imaging biomarkers and clinical parameters, or combinations therein, may serve as predictors of disease progression in COPD. Several studies in COPD have either completed or are underway to help address this question, including COPDGene [2], ECLIPSE [3], SPIROMICS [4, 5], COSYCONET [6], CanCOLD [7] and the British Lung Foundation early COPD study [8].

FOOTPRINTS[®] (ClinicalTrials.gov: NCT02719184) is a 3-year study aiming to assess the association between soluble biomarkers of inflammation/lung tissue destruction, and imaging and physiological biomarkers, with COPD progression in ex-smokers with mild-to-severe COPD (as per the Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification) [9]. In addition, this study includes a subgroup of 19 subjects with COPD and alpha-1-antitrypsin deficiency (A1ATD), a genetic condition associated with a higher risk of developing emphysema [10]. In A1ATD, emphysema occurs at a younger age and progresses faster as compared with COPD patients without A1ATD [11, 12].

The data from FOOTPRINTS[®] may allow identification of different COPD phenotypes, the biomarkers that help differentiate those phenotypes, and their associated risks for emphysema progression. More detailed information on the methodology of the FOOTPRINTS[®] study has been published previously [13]. Here, baseline demographic and clinical characteristics (lung function,

soluble biomarkers, functional imaging findings and respiratory symptoms) for the study subjects are reported, as well as a descriptive statistical comparison of soluble biomarker levels in the individual GOLD groups and A1ATD group versus ex-smokers without airflow limitation (EwAL).

Methods

Study design

Details of the methodology for the FOOTPRINTS[®] study (NCT02719184) have been published previously [13]. In brief, the FOOTPRINTS[®] study is a multinational, prospective, longitudinal, observational biomarker study.

The study population included subjects with a range of COPD severities (GOLD stage 1: forced expiratory volume in 1 s [FEV_1] \geq 80% predicted; GOLD stage 2: $FEV_1 \geq 50$ – < 80 % predicted; and GOLD stage 3: $FEV_1 \geq 30$ – < 50 % predicted), subjects with COPD and A1ATD, and an EwAL control group. All subjects in this study should have stopped smoking at least 9 months prior to inclusion [9]. The EwAL control group was included to provide a comparison for biomarkers between subjects with and without airflow limitation while controlling for the potential effects of previous smoking.

Inclusion and exclusion criteria

Full details on the inclusion and exclusion criteria for participation in the FOOTPRINTS[®] study have been published previously [13]. Post-bronchodilator FEV_1 /forced vital capacity [FVC] < 70 % was required for inclusion in the COPD and A1ATD groups, and post-bronchodilator FEV_1 /FVC \geq lower limit of normal (as defined by the GOLD 2015 strategy report) was required for inclusion in the EwAL group. Subjects that were heterozygous or homozygous for the A1AT Z or S alleles were not included in the COPD GOLD groups 1–3 and EwAL group. Subjects with A1ATD were required to have a documented (prior to Visit 2) A1ATD of ZZ genotype. Patients in the COPD and A1ATD groups who were currently receiving or planned to receive A1AT augmentation therapy were excluded.

Baseline parameters of interest

At study entry, data were collected for demographic and disease characteristics, history of comorbidities and COPD exacerbations, and soluble biomarkers in various biofluids (whole blood, serum, plasma and induced

sputum). History of comorbidities or COPD exacerbations included an event/disease that had occurred at least once during the lifetime of a subject.

Data on the 6-min walk test (6MWT) were collected for all subjects and symptom questionnaires were conducted for subjects in the COPD and A1ATD groups. Pulmonary symptoms were assessed using the following questionnaires: the COPD Assessment Test (CAT), the modified Medical Research Council (mMRC) dyspnoea score, and St. George's Respiratory Questionnaire (SGRQ). Exercise capacity was assessed via the 6MWT. Baseline quantitative and qualitative X-ray computed tomography (CT) data were collected for all subjects.

Biomarker characterisation

Biomarkers were analysed in several biofluids at study entry and are being assessed up to Week 156. The serum/plasma biomarkers collected include, but are not limited to, neutrophil elastase-specific elastin fragment, other protease-generated neoepitopes such as cathepsin S-cleaved decorin, soluble receptor for advanced glycation end product (sRAGE), surfactant protein D (SP-D), lysyl oxidase-like 2, interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) count and fibrinogen.

Soluble biomarkers from sputum included biomarkers for the neutrophil-derived serine proteases neutrophil elastase, cathepsin G and proteinase 3 activity. These are not reported in this publication.

Quantitative and qualitative CT

Chest CT scans were performed to assess lung disease, including emphysema, air trapping, small airway disease and airway wall thickness. At four time points (Week 0 [i.e., Day 1], Week 52, Week 104 and Week 156), two different scans were performed: (1) a low-dose inspiratory chest CT scan with dose modulation to assess airway walls and emphysema, and (2) an expiratory scan to assess air trapping. The inspiratory CT technique was similar to the reduced dose technique developed for Phase 3 of COPDgene [14]. To optimise assessment of non-reversible air trapping, the chest CT scan was conducted between 1 and 4 h after salbutamol (albuterol) administration.

The Fleischner criteria for CT imaging in COPD were used for visual characterisation of centrilobular and paraseptal emphysema and of airway disease [15]. Quantitative analysis of lung images was performed centrally using LungQ (Thirona B.v., Nijmegen, the Netherlands). Assessments included inspiratory and expiratory volume, emphysema, air trapping and the square root of the wall area of bronchus with an internal perimeter of 10 mm. For emphysema, analyses included lung

density at the 15th percentile point of the CT histogram (PD15), adjusted lung density (ALD) and percentage of lung voxels with attenuation ≤ -950 Hounsfield Units in inspiration (LAA-950) [13]. For air trapping, the analyses included percentage of lung voxels with attenuation ≤ -856 Hounsfield Units (LAA-856) not including parametric response mapping, mean lung density during expiration and the ratio of expiratory and inspiratory volume (function residual capacity [FRC]/total lung capacity [TLC] ratio) [13].

Statistical methods

All baseline data are presented descriptively for each of the subject subgroups, either as mean and standard deviation (SD) for normally distributed variables, median and interquartile range (IQR) for variables deviating from normality, or as number and percentage for categorical variables. To evaluate whether the continuous baseline variables showed a trend across the subject subgroups ordered by disease severity, linear regression (for normally distributed variables) or the Jonckheere-Terpstra test (for non-parametric comparisons) were conducted. For categorical variables with ≥ 2 categories, a Cochran-Armitage test for trend or a Cochran-Mantel-Haenszel test was applied, respectively. If a trend was not established, a Chi-squared test was performed to investigate associations. All soluble biomarkers were log₂-transformed. Due to a high number of values below the limit of quantification, IL-6 was analysed as a categorical variable, with a lower limit of quantification equal to 3.12 ng/L used as a cut-off for categorisation. All analyses were hypothesis-generating and no correction for multiple testing was performed. Analyses were conducted using SAS v9.4.

Results

Subject disposition

In total, 463 subjects were enrolled into the FOOTPRINTS[®] study (Fig. 1). Of these, 123 subjects were categorised as GOLD stage 1, 130 as GOLD stage 2, and 129 as GOLD stage 3. Nineteen subjects had COPD and homozygous ZZ A1ATD and 62 were EwAL. Of the 19 subjects in the A1ATD group, 1 subject (5.3%) met the criteria for GOLD stage 1, 5 (26.3%) for GOLD stage 2, 12 (63.2%) for GOLD stage 3, and 1 (5.3%) for GOLD stage 4.

All demographics and analyses are based on the per-protocol set, which comprised 456 subjects (Table 1). Seven subjects were excluded from the per-protocol set due to newly added anti-inflammatory treatment or change to therapy prior to Visit 1, presenting with an immunocompromising condition, significant pulmonary

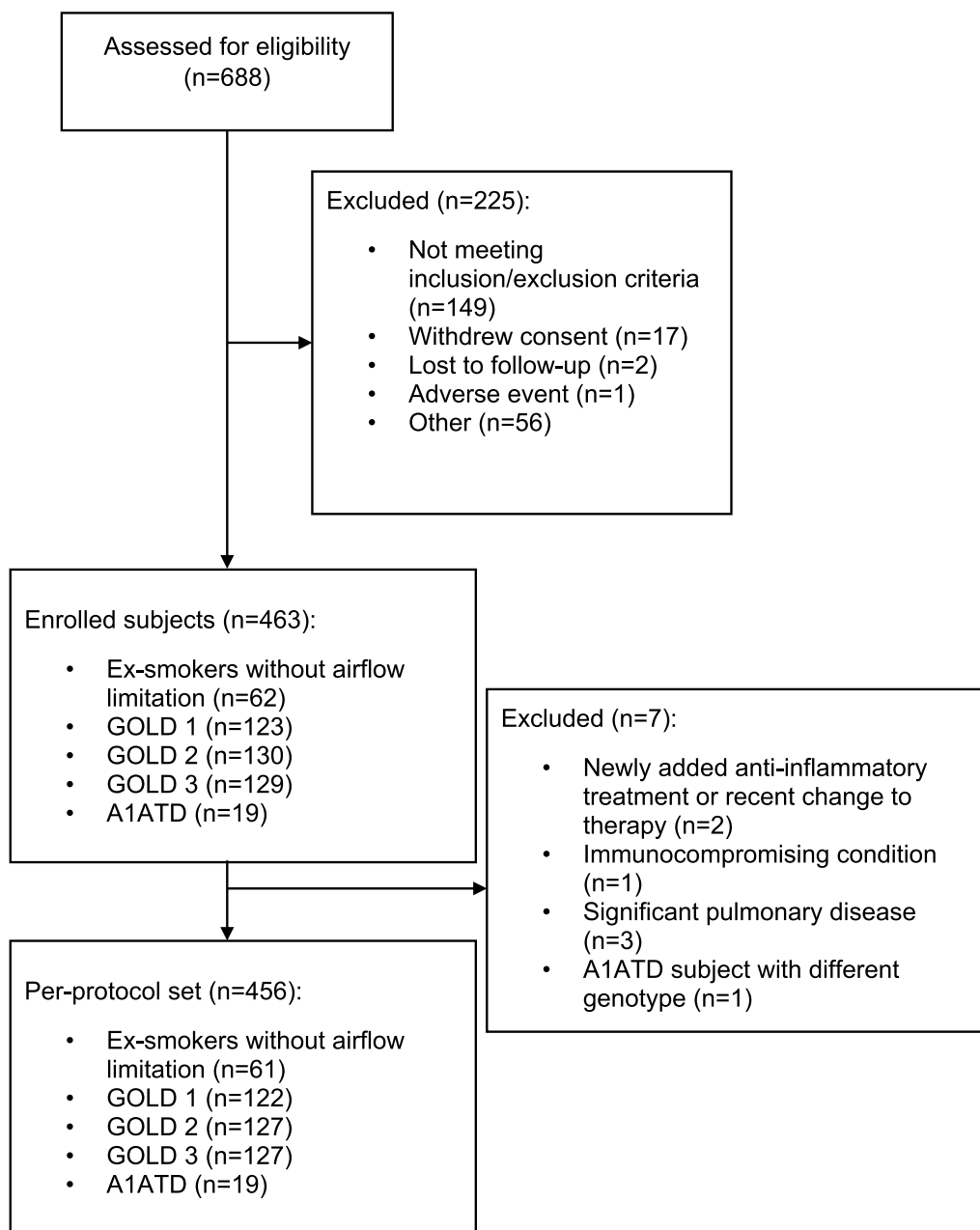


Fig. 1 CONSORT flow diagram. A1ATD alpha-1-antitrypsin deficiency, GOLD Global Initiative for Chronic Obstructive Lung Disease

disease other than COPD, or A1ATD subjects with a genotype other than ZZ.

Baseline characteristics

Selected baseline characteristics are shown in Table 1. The majority of subjects were male (n=294, 64.5%) and the mean (±SD) age was 60.7 (6.9) years. Mean (±SD) body mass index was 26.6 kg/m² (3.8) and mean (±SD) smoking pack history was 43.1 pack-years (19.5). Of note, a higher proportion of subjects in the A1ATD

group were male (84.2%) compared with subjects in the GOLD 1–3 groups (59.8–69.7%) and EwAL group (62.3%). The mean age was lower in the A1ATD group (52.8±9.0) and EwAL group (53.9±6.8) than in the GOLD 1–3 groups (61.8±5.4–62.9±5.6). Smoking pack history was also lower in the A1ATD group (25.2±12.3) and EwAL (32.9±14.6) than in the GOLD 1–3 groups (41.5±17.6–49.2±21.6).

As disease severity increased, the proportion of subjects with multiple comorbidities increased (Table 1);

Table 1 Subject demographics

	EwAL	GOLD 1	GOLD 2	GOLD 3	A1ATD
Enrolled subjects, n	62	123	130	129	19
Per-protocol subjects, n	61	122	127	127	19
Male, n (%)	38 (62.3)	85 (69.7)	76 (59.8)	79 (62.2)	16 (84.2)
Age, years	53.9 (6.8)	62.0 (6.2)	61.8 (5.4)	62.9 (5.6)	52.8 (9.0)
BMI, kg/m ²	26.48 (2.74)	27.16 (3.43)	26.66 (4.07)	26.33 (4.32)	25.06 (3.87)
Smoking history, pack-years	32.9 (14.6)	41.5 (17.6)	46.1 (18.2)	49.2 (21.6)	25.2 (12.3)
Subjects with ≥ 1 comorbidities ^a , n (%) ^b	NA	84 (68.9)	108 (85.0)	97 (76.4)	14 (73.7)
Subjects with ≥ 3 comorbidities ^a , n (%) ^b	NA	33 (27.0)	50 (39.4)	51 (40.2)	4 (21.1)
History of COPD exacerbations, n (%)					
Yes	NA	30 (24.6)	48 (37.8)	71 (55.9)	12 (63.2)
No	NA	88 (72.1)	79 (62.2)	55 (43.3)	7 (36.8)
Missing	NA	4 (3.3)	0 (0.0)	1 (0.8)	0 (0.0)

Age, BMI and smoking history are mean (SD). A1ATD subjects are not included in the GOLD 1–3 columns

A1ATD alpha-1-antitrypsin deficiency, BMI body mass index, COPD chronic obstructive pulmonary disease, EwAL ex-smokers without airflow limitation, GOLD Global Initiative for Chronic Obstructive Lung Disease, NA not assessed, SD standard deviation

^a Pneumonia, pulmonary fibrosis, chronic respiratory failure, asthma–chronic pulmonary disease overlap syndrome, obstructive sleep apnoea, bronchiectasis, pleural effusion, lung cancer, angina pectoris, ischaemic heart disease (incl. myocardial infarction), systemic arterial hypertension, hypotension, aneurysm, syncope, cardiac arrhythmia, heart failure, cerebrovascular disease, diabetes mellitus, obesity, hyper-/dyslipidaemia, cholecystitis, cholecystolithiasis, colitis, gastroesophageal reflux disease, dementia, cognitive impairment, depression, anxiety, osteoarticular disorders

^b Data were missing for four subjects in the GOLD 1 group, one in GOLD 3, and one in the A1ATD group

27.0% of GOLD 1 subjects had ≥ 3 comorbidities compared with 39.4% of GOLD 2 and 40.2% of GOLD 3 subjects. The most common comorbidities ($>10\%$ prevalence) in GOLD 1, 2 and 3 subjects were, respectively, systemic arterial hypertension (36.1%, 40.9%, 49.6%), hyper-/dyslipidaemia (20.5%, 31.5%, 29.1%), pneumonia (4.9%, 19.7%, 22.8%), gastroesophageal reflux disease (14.8%, 15.7%, 15.7%), depression (9.0%, 17.3%, 15.7%), osteoarticular disorders (10.7%, 18.1%, 14.2%), diabetes (13.1%, 13.4%, 11.0%), anxiety (6.6%, 14.2%, 14.2%) and obesity (4.9%, 12.6%, 12.6%). Further details are given in the supplementary material (Additional file 1). Of the subjects in the A1ATD group, 21.1% had ≥ 3 comorbidities, but, as noted above, this was a younger population, with subjects being on average 10 years younger.

The percentage of prior COPD exacerbations (defined as an exacerbation that had occurred at least once during the lifetime of a subject) increased with increasing disease severity (as per GOLD classification): 24.6%, 37.8% and 55.9% of GOLD 1, GOLD 2 and GOLD 3 subjects, respectively, had experienced a previous COPD exacerbation. Overall, 40.8% of COPD subjects had a documented COPD exacerbation in their medical history.

Further information on baseline characteristics are available in Additional file 1.

Symptom questionnaires and 6MWT

Symptom questionnaires were conducted for subjects in the GOLD 1–3 and A1ATD groups, but not for the EwAL group. As shown in Table 2, increasing disease

severity was associated with an increase in symptoms. Symptom scores in the A1ATD group were intermediate between those of the GOLD 1 and 3 groups. Increasing disease severity was associated with increases in the mean CAT score (GOLD 1: 11.2 [SD 5.7]; GOLD 2: 14.7 [SD 6.2]; GOLD 3: 16.6 [SD 7.2]; A1ATD: 13.4 [SD 7.4], $P < 0.0001$), the proportion of subjects with a CAT score ≥ 10 (GOLD 1: 62.3%; GOLD 2: 78.0%; GOLD 3: 79.5%; A1ATD: 63.2%, $P = 0.0335$), the proportion of subjects with an mMRC dyspnoea score ≥ 2 (GOLD 1: 11.5%; GOLD 2: 32.3%; GOLD 3: 60.6%; A1ATD: 47.4%, $P < 0.0001$) and the proportion of subjects with an SGRQ score ≥ 25 (GOLD 1: 50.8%; GOLD 2: 69.3%; GOLD 3: 83.5%; A1ATD: 73.7%, $P < 0.0001$).

Increasing disease severity was associated with a reduction in distance covered in the 6MWT (GOLD 1: 489.3 m [SD 91.7 m]; GOLD 2: 458.0 m [SD 101.3 m]; GOLD 3: 403.8 m [SD 121.7 m], $P < 0.0001$). The 6MWT distance for subjects with A1ATD (508.6 m [SD 114.4 m]) was numerically higher than in any of the GOLD groups, but lower than in the EwAL group (573.1 m [SD 100.3 m]).

Lung function and lung volume

Airflow limitation

At baseline, patients with the greatest disease severity (as defined by the GOLD 1–4 classification system) had the poorest lung function (Table 3; Fig. 2). Patients with COPD and A1ATD also had worse lung function than EwAL. Lung function parameters for the A1ATD group

Table 2 Symptom questionnaires and 6-min walk test

	EwAL	GOLD 1	GOLD 2	GOLD 3	A1ATD	P-value
Per-protocol subjects, n	61	122	127	127	19	
CAT total score	NA	11.2 (5.7)	14.7 (6.2)	16.6 (7.2)	13.4 (7.4)	< 0.0001
CAT total score, n (%)						
< 10	NA	45 (36.9)	28 (22.0)	26 (20.5)	7 (36.8)	0.0335*
≥ 10	NA	76 (62.3)	99 (78.0)	101 (79.5)	12 (63.2)	
mMRC dyspnoea score, n (%)						
< 2	NA	107 (87.7)	86 (67.7)	50 (39.4)	10 (52.6)	< 0.0001*
≥ 2	NA	14 (11.5)	41 (32.3)	77 (60.6)	9 (47.4)	
SGRQ total score, n (%)	NA	25.2 (14.4)	34.7 (15.4)	43.0 (16.5)	37.7 (22.3)	< 0.0001
< 25	NA	58 (47.5)	38 (29.9)	20 (15.7)	5 (26.3)	< 0.0001*
≥ 25	NA	62 (50.8)	88 (69.3)	106 (83.5)	14 (73.7)	
Missing		2 (1.6)	1 (0.8)	1 (0.8)	0 (0.0)	
SGRQ activity score	NA	35.6 (20.2)	48.9 (20.0)	60.1 (18.3)	54.8 (28.1)	< 0.0001
SGRQ impacts score	NA	17.0 (13.3)	24.0 (16.4)	32.8 (17.9)	27.2 (21.8)	< 0.0001
SGRQ symptoms score	NA	33.3 (19.4)	42.8 (19.1)	44.9 (22.5)	40.2 (22.5)	0.0020
Total distance covered in 6 MWT, m	573.1 (100.3)	489.3 (91.7)	458.0 (101.3)	403.8 (121.7)	508.6 (114.4)	< 0.0001

All data are presented as mean (SD) unless noted otherwise

6MWT 6-min walk test, A1ATD alpha-1-antitrypsin deficiency, CAT COPD Assessment Test, EwAL ex-smokers without airflow limitation, GOLD GOLD, Global Initiative for Chronic Obstructive Lung Disease, mMRC modified Medical Research Council, NA not assessed, SD standard deviation, SGRQ St. George's Respiratory Questionnaire

*Cochran–Armitage test for trend. A linear regression test was used for other variables

Table 3 Post-bronchodilator lung function and lung volume measurements

	EwAL	GOLD 1	GOLD 2	GOLD 3	A1ATD	P-value
Per-protocol subjects, n	61	122	127	127	19	
Airflow limitation						
FEV ₁ , L	3.48 (0.77)	2.66 (0.54)	1.97 (0.46)	1.17 (0.29)	1.85 (0.85)	< 0.0001
% predicted FEV ₁	102.1 (12.2)	87.4 (9.4)	65.0 (9.7)	39.6 (7.6)	50.4 (20.3)	< 0.0001
FEV ₁ /FVC, %	78.8 (5.7)	63.4 (5.4)	54.6 (8.6)	38.2 (9.0)	40.6 (13.4)	< 0.0001
FVC, L	4.42 (0.97)	4.22 (0.85)	3.66 (0.90)	3.16 (0.89)	4.54 (1.38)	< 0.0001
% predicted FVC, %	102.2 (10.9)	107.7 (13.2)	93.8 (13.5)	82.6 (15.1)	96.9 (17.6)	< 0.0001
Body plethysmography						
TLC, L	6.81 (1.27)	6.70 (1.29)	6.60 (1.44)	7.02 (1.58)	8.16 (1.53)	0.0217
RV, L	2.27 (0.54)	2.51 (0.66)	2.91 (0.96)	3.64 (1.02)	3.63 (0.81)	< 0.0001
% predicted RV, %	106.5 (21.3)	111.5 (26.0)	129.0 (38.0)	161.8 (44.4)	163.0 (27.2)	< 0.0001
DL _{CO}						
DL _{CO} , mmol/min/kPa						
Mean (SD)	11.36 (7.66)	13.34 (8.64)	9.36 (6.52)	7.16 (5.14)	5.19 (2.02)	< 0.0001*
Median	8.77	9.28	6.75	5.18	4.78	
Range (Q1–Q3)	4.41	12.83	7.69	5.59	2.34	
% predicted DL _{CO}	89.2 (16.1)	79.8 (21.3)	63.4 (18.1)	51.5 (17.5)	51.1 (12.7)	< 0.0001
DL _{CO} /VA, mmol/min/kPa						
Mean (SD)	1.88 (1.20)	2.25 (1.36)	1.79 (1.19)	1.61 (1.20)	0.83 (0.19)	< 0.0001*
Median	1.38	1.48	1.23	1.04	0.85	
Range (Q1–Q3)	0.43	2.39	1.62	1.83	0.09	

All values are mean (SD)

A1ATD alpha-1-antitrypsin deficiency, DL_{CO} diffusing capacity of the lung for carbon monoxide, EwAL ex-smokers without airflow limitation, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease, kPa kilopascal, mmol millimole, RV residual volume, SD standard deviation, TLC total lung capacity, VA alveolar volume

*Jonckheere–Terpstra test for trend. A linear regression test was used for other variables

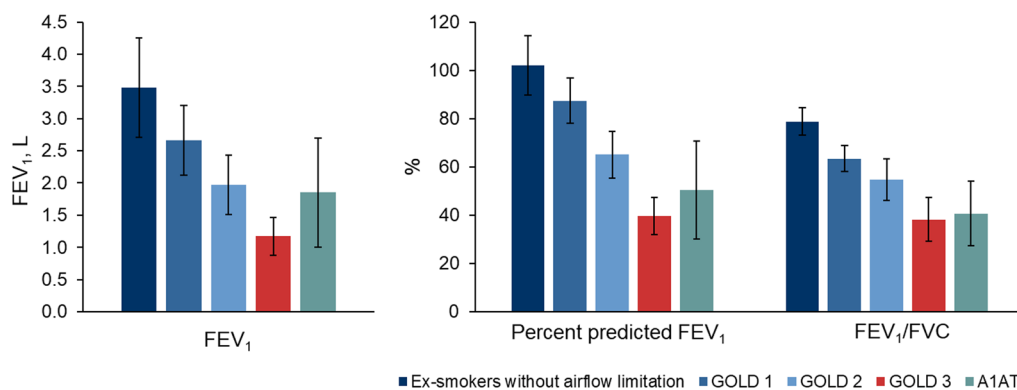


Fig. 2 Lung function parameters. A1ATD alpha-1-antitrypsin deficiency, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease

were similar to the GOLD stage 2/3 groups, with the exception of FVC.

Across GOLD groups 1–3, mean FEV₁ was highest in GOLD 1 (2.66 L [SD 0.54 L]) and lowest in GOLD 3 subjects (1.17 L [SD 0.29 L]). Mean FEV₁ was lower in GOLD groups 1–3 and subjects with A1ATD (1.85 L [SD 0.85 L]) than in EwAL (3.48 L [SD 0.77 L]). Mean percent predicted FEV₁ was 87.4% [SD 9.4%] in GOLD 1 subjects and decreased with increasing disease severity to 39.6% [SD 7.6%] in GOLD 3 subjects ($P < 0.0001$). The mean percent predicted FEV₁ was 50.4% (SD 20.3%) in subjects with A1ATD and 102.1% (SD 12.2%) in the EwAL group. Mean FVC also decreased with increasing disease severity (GOLD 1: 4.22 L [SD 0.85 L]; GOLD 2: 3.66 L [SD 0.90 L]; GOLD 3: 3.16 L [SD 0.89 L], $P < 0.0001$), and, overall, was highest in subjects with A1ATD (4.54 L [SD 1.38 L]). The EwAL control group had a mean FVC of 4.42 L (SD 0.97 L). The mean FEV₁/FVC ratio was 63.4% (SD 5.4%) in GOLD 1 subjects and reduced with increasing disease severity to 38.2% (SD 9.0%) in GOLD 3 subjects ($P < 0.0001$). Subjects with A1ATD had a mean FEV₁/FVC ratio of 40.6% (SD 13.4%) and the EwAL control group FEV₁/FVC ratio was 78.8% (SD 5.7%).

Plethysmography

Table 3 shows post-bronchodilator lung function and lung volume measurements at baseline. Increasing disease severity was associated with increasing mean residual volume (GOLD 1: 2.51 L [SD 0.66 L]; GOLD 2: 2.91 L [SD 0.96 L]; GOLD 3: 3.64 L [SD 1.02 L], $P < 0.0001$). Residual volume was high in subjects with A1ATD (3.63 L [SD 0.81 L]) and comparable with GOLD 3 COPD subjects, whereas it was lowest in EwAL (2.27 L [SD 0.54 L]).

TLC values generally increased with increasing disease severity (GOLD 1: 6.70 [SD 1.29]; GOLD 2: 6.60 [SD 1.44]; GOLD 3: 7.02 [1.58], $P = 0.0217$). The highest

mean TLC was observed in the A1ATD group (8.16 L [SD 1.53 L]), whereas TLC for EwAL was 6.81 L (SD 1.27 L).

Additional lung function tests

Increasing disease severity and A1ATD were associated with reduced diffusing capacity of the lung for carbon monoxide (DL_{CO}), ($P < 0.0001$) (Table 3). The mean percent predicted DL_{CO} was 79.8% (SD 21.3%) in GOLD 1 subjects, 63.4% (SD 18.1%) in GOLD 2 subjects, 51.5% (SD 17.5%) in GOLD 3, subjects and 51.1% (SD 12.7%) in subjects with A1ATD.

The mean DL_{CO}/alveolar volume ratio was highest in GOLD 1 subjects (2.25 mmol/min/kPa [SD 1.36 mmol/min/kPa]) and decreased with disease severity (GOLD 3: 1.61 mmol/min/kPa [SD 1.20 mmol/min/kPa]). Overall, mean DL_{CO}/alveolar volume was lowest in the A1ATD group (0.83 mmol/min/kPa [SD 0.19 mmol/min/kPa] vs 1.88 mmol/min/kPa [SD 1.20 mmol/min/kPa] in EwAL). Further DL_{CO} parameters are available in Additional file 1.

Soluble biomarkers

For the majority of biomarkers presented in Fig. 3, the mean expression levels or concentration increased with disease severity. A linear increase in the level of WBC ($P < 0.0001$), fibrinogen ($P = 0.0249$), hsCRP ($P = 0.0002$) and plasma SP-D ($P = 0.0194$) was observed whereas sRAGE levels linearly decreased with disease severity ($P < 0.0001$), indicative of more severe emphysema. In all GOLD groups (GOLD 1–3), levels of WBC, fibrinogen, hs-CRP and plasma SP-D were numerically higher compared with the EwAL group. Further soluble biomarker parameters are available in Additional file 1.

No association was detected between IL-6 positive expression and disease severity ($P = 0.0701$). IL-6 was expressed less often in the EwAL subjects compared with

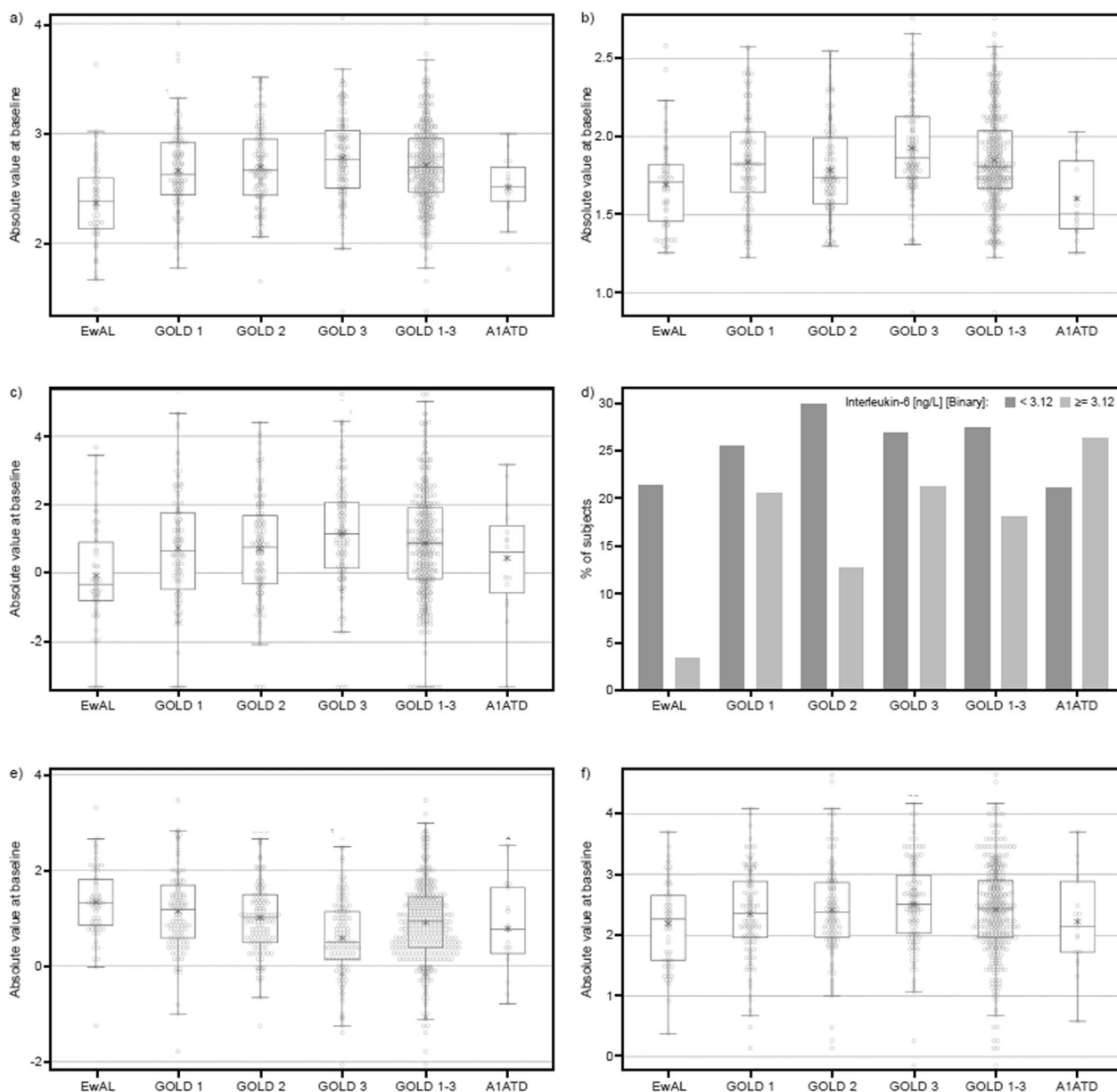


Fig. 3 Distribution of inflammatory biomarkers at baseline by diagnosis group: **a** WBC, **b** fibrinogen, **c** hs-CRP, **d** IL-6, **e** sRAGE, **f** plasma SP-D. All biomarker values (except for IL-6) are log₂ transformed. WBC, sRAGE: $P \leq 0.0001$; hs-CRP: $P = 0.0002$; plasma SP-D: $P = 0.0194$; fibrinogen: $P = 0.0249$, linear regression for subject groups ordered by disease severity (Kruskal–Wallis test used for fibrinogen). No association was observed between positive expression of IL-6 and subject groups (chi-square test, $P = 0.0701$). A1ATD alpha-1-antitrypsin deficiency, Abs absolute, EwAL ex-smokers without airflow limitation, GOLD Global Initiative for Chronic Obstructive Lung Disease, hs-CRP high-sensitivity C-reactive protein, IL-6 interleukin 6, SP-D surfactant protein D, sRAGE soluble receptor for advanced glycation end product, WBC white blood count

GOLD 1–3 and A1ATD subjects, of whom 13%–26% expressed IL-6 (Fig. 3d).

Qualitative CT data

Increasing disease severity was associated with a greater prevalence of centrilobular emphysema (Cochran–Mantel–Haenszel test, $P < 0.0001$) (Fig. 4). Emphysema was

present in all subjects in the A1ATD group, and in 41.0% of the EwAL group. Among GOLD subjects, the prevalence of advanced destructive emphysema was higher in GOLD 3 (GOLD 1: 9.0%; GOLD 2: 13.4%; GOLD 3: 31.5%), as well as the prevalence of confluent emphysema (GOLD 1: 13.1%; GOLD 2: 24.4%; GOLD 3: 26.8%). The Fleischner classification does not provide a separate

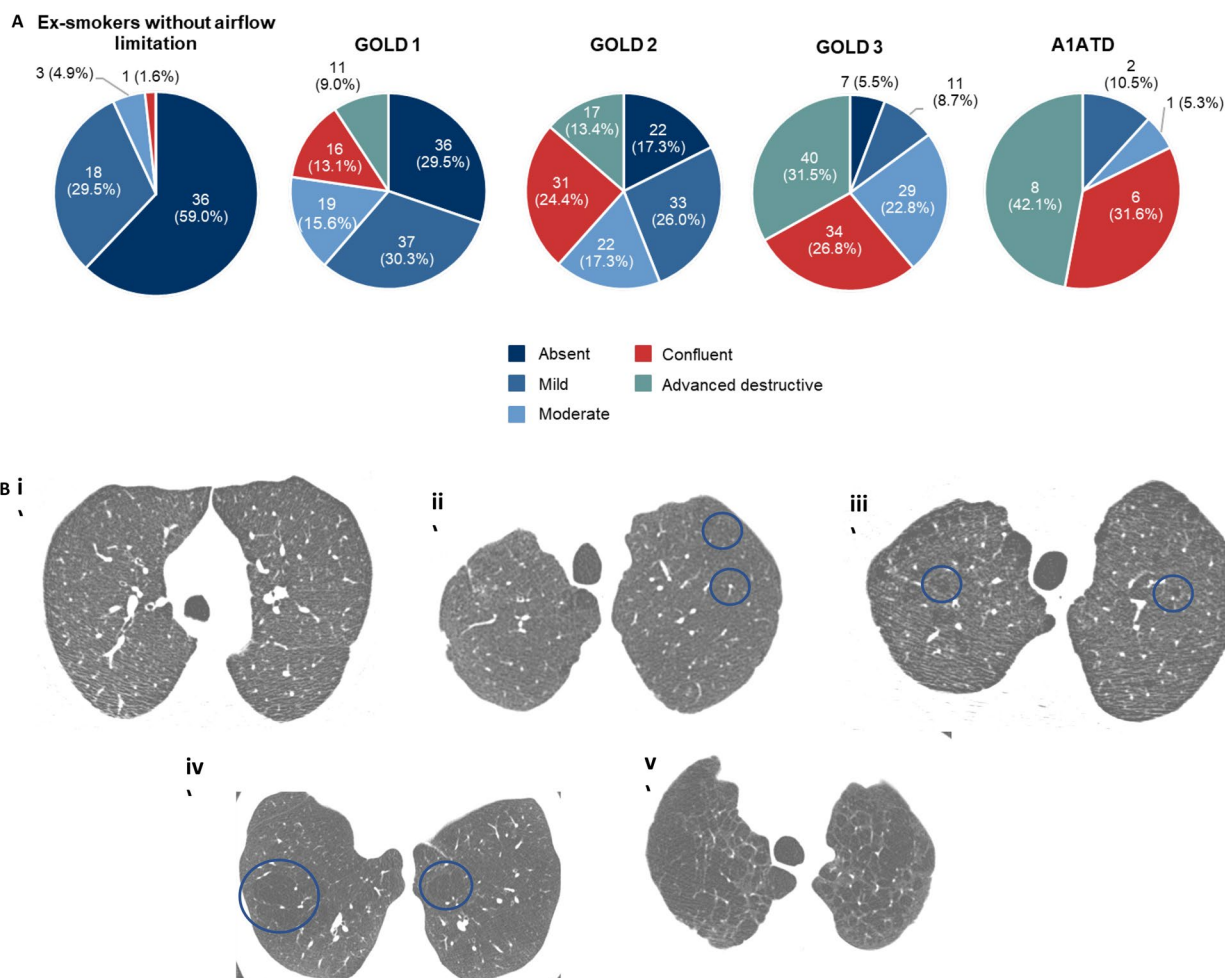


Fig. 4 Centrilobular emphysema on CT (**A**) and CT images showing typical emphysema findings for each category i) absent, ii) mild, iii) moderate, iv) confluent, v) advanced destructive (**B**). Percentages do not total 100% due to missing data (missing: EwAL, 3.3%; GOLD 1, 2.5%; GOLD 2, 1.6%; GOLD 3, 3.9%; A1ATD, 10.5%)

category for panlobular emphysema [15], which would be graded as either confluent or advanced destructive; these findings were present in 14 (82%) of 17 subjects with A1ATD.

Quantitative CT data

When assessing lung volumes by quantitative CT, a linear increase in expiratory volume and a linear decrease in PD15 and ALD were observed with increasing disease severity ($P < 0.0001$ for all comparisons) (Table 4). Mean expiratory volume increased from 2.83 L (SD 0.67 L) in EwAL subjects to 4.78 L (SD 1.24 L) in GOLD 3 subjects. PD15 decreased from 91.2 g/L (SD 19.4 g/L) in EwAL subjects to 47.8 g/L (SD 24.9 g/L) in GOLD 3 subjects. PD15 was 44.4 g/L (SD 21.1 g/L) in A1ATD subjects. Similarly, ALD decreased from 88.50 g/L (SD 13.90 g/L) in EwAL subjects to 54.8 g/L

(SD 23.1 g/L) in GOLD 3 subjects. ALD was 50.9 g/L (SD 18.2 g/L) in A1ATD subjects. A linear increase was also established for inspiratory volume with increasing disease severity (EwAL: 5.80 L [SD 1.30 L]; GOLD 1: 6.42 L [SD 1.28 L]; GOLD 2: 6.31 L [SD 1.35 L]; GOLD 3: 6.63 L [SD 1.45 L], $P < 0.0001$). Subjects in the A1ATD group had higher mean inspiratory (8.07 L [SD 1.73 L]) and expiratory (5.33 L [SD 1.51 L]) volumes than subjects in the GOLD 1–3 groups and the EwAL group.

The mean FRC/TLC ratio, a measure of air trapping, was 0.570 (SD 0.118) in GOLD 1 subjects versus 0.722 (SD 0.097) in GOLD 3 subjects. Ex-smoker controls had the lowest FRC/TLC ratio (0.499 [SD 0.112]). Values for GOLD 2 subjects (0.629 [SD 0.102]) and A1ATD subjects (0.653 [SD 0.121]) were between the values for GOLD 1 and GOLD 3 subjects.

Table 4 Qualitative and quantitative CT scans

	EwAL	GOLD 1	GOLD 2	GOLD 3	A1ATD	P-value
Per-protocol subjects, n	61	122	127	127	19	
Qualitative CT						
Centrilobular emphysema, N (%)						<0.0001*
Absent	36 (59.0)	36 (29.5)	22 (17.3)	7 (5.5)	0 (0.0)	
Mild	18 (29.5)	37 (30.3)	33 (26.0)	11 (8.7)	2 (10.5)	
Moderate	3 (4.9)	19 (15.6)	22 (17.3)	29 (22.8)	1 (5.3)	
Confluent	1 (1.6)	16 (13.1)	31 (24.4)	34 (26.8)	6 (31.6)	
Advanced destructive	0 (0.0)	11 (9.0)	17 (13.4)	40 (31.5)	8 (42.1)	
Missing	2 (3.3)	3 (2.5)	2 (1.6)	5 (3.9)	2 (10.5)	
Quantitative CT						
Inspiratory volume, L	5.80 (1.30)	6.42 (1.28)	6.31 (1.35)	6.63 (1.45)	8.07 (1.73)	<0.0001
Expiratory volume, L	2.83 (0.67)	3.65 (1.01)	4.01 (1.14)	4.78 (1.24)	5.33 (1.51)	<0.0001
PD15, g/L	91.2 (19.4)	75.1 (19.0)	66.2 (22.2)	47.8 (24.9)	44.4 (21.1)	<0.0001
ALD, g/L	88.5 (13.9)	86.2 (21.4)	72.4 (21.7)	54.8 (23.1)	50.9 (18.2)	<0.0001
LAA-950, %	3.2 (2.8)	7.4 (7.2)	12.7 (9.9)	21.3 (12.3)	26.4 (12.0)	
LAA-856, %	7.5 (8.4)	23.0 (14.0)	36.3 (17.5)	53.5 (17.2)	51.3 (19.4)	
Pi10, mm	1.8 (0.4)	2.2 (0.5)	2.5 (0.5)	2.6 (0.4)	2.0 (0.4)	<0.0001
MLD in expiration	-689.1 (44.6)	-743.0 (43.5)	-776.8 (43.9)	-822.3 (40.5)	-808.4 (62.1)	<0.0001
FRC/TLC ratio	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)	0.7 (0.1)	0.7 (0.1)	<0.0001

All values are mean (\pm SD)

ALD adjusted lung density, A1ATD alpha-1-antitrypsin deficiency, CT computed tomography, EwAL ex-smokers without airflow limitation, FRC functional residual capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease, LAA-856 lung voxels with attenuation \leq -856 Hounsfield Units, LAA-950 lung voxels with attenuation \leq -950 Hounsfield Units, MLD mean lung density, PD15 lung density at the 15th percentile of the CT histogram, Pi10 square root of wall area of bronchus with internal perimeter of 10 mm, SD standard deviation, TLC total lung capacity

* Cochran–Mantel–Haenszel test. A linear regression test was used for all other variables

Discussion

The longitudinal observational FOOTPRINTS[®] study aims to identify biomarkers that are associated with COPD progression, in particular emphysema progression, over a 3-year period. Results from this study are expected to help address an unmet need to better understand different COPD phenotypes and their associated biomarkers. This could allow the use of biomarkers for diagnosis, to identify high-risk patients and to guide treatment options in a more targeted, precision-based manner. COPD diagnosis and treatment requires more than assessment of lung function. Biomarkers may help to better understand the biology, prognosis and treatment options suitable for different COPD phenotypes. In a study by Lowe et al. [2], for example, CT scans identified that 41% of the “healthy” EwAL subjects had centrilobular emphysema, indicating that emphysema progression had already occurred, although it was not possible to detect by traditional spirometry.

The baseline demographics and clinical characteristics of the FOOTPRINTS[®] study subjects, including lung function parameters, soluble biomarkers, qualitative and quantitative CT, and symptoms, are provided here. These data allowed us to compare characteristics

between subjects grouped by COPD severity (GOLD stages 1–3), subjects with A1ATD and EwAL subjects.

As expected, at baseline, increasing COPD severity was associated with worsening lung function, increased expiratory lung volume and a reduction in DL_{CO}. Compared with EwAL, A1ATD was also associated with worsening lung function, increased lung volumes and a reduction in DL_{CO}. Of note, TLC was highest in the A1ATD group compared with the other groups; however, this could be a result of the higher proportion of male and younger subjects in the A1ATD group. Levels of soluble inflammatory biomarkers such as WBC count, fibrinogen, hs-CRP and plasma SP-D increased linearly by disease severity, with higher levels observed in the GOLD 3 group. Previous studies have demonstrated increases in the expression of these inflammatory biomarkers to be associated with the progression of COPD [16, 17]. Of note, levels of fibrinogen were numerically higher in the GOLD 1 group than in the GOLD 2 group. Compared with EwAL, mean biomarker values for the A1ATD group were generally higher, except for fibrinogen, which was slightly lower for the A1ATD group. IL-6 levels were numerically lower in the EwAL group compared with GOLD 1–3 and A1ATD subjects.

Levels of sRAGE were highest in EwAL subjects and decreased linearly with increasing disease severity, with lowest values observed in the GOLD 3 group, indicative of more severe emphysema. This is in keeping with previous studies, which have suggested lower blood sRAGE to be associated with more severe airflow obstruction and emphysema [18]. Similarly, in the A1ATD group, levels of sRAGE were numerically lower than in the EwAL group, again indicative of more severe emphysema.

When assessing lung density by quantitative CT, we noted a clear and expected decrease in PD15 with increasing COPD severity, as has been shown in previous studies [19]. There was also an increase in expiratory and inspiratory volume with increasing disease severity. As disease severity increased, the presence of centrilobular emphysema increased (as assessed by qualitative CT), as did the presence of advanced destructive emphysema. As expected, subjects in the A1ATD group had the highest prevalence of confluent or advanced destructive emphysema, which presumably corresponds to panlobular emphysema (panlobular emphysema is not separately classified in the Fleischner system) [15]. Although the EwAL group did not have airflow limitation (as defined by the 2015 GOLD strategy report [9]), centrilobular emphysema was present in 36% of subjects, indicating that emphysema progression had already occurred in many of these subjects, likely a result of their 33 pack-year smoking history. Several other studies have demonstrated a substantial proportion of smokers without airflow limitation to have CT evidence of structural changes such as emphysema and airway wall thickening [2, 20, 21]. For example, in a cohort of over 4000 current and former smokers from the COPDGene study who did not meet spirometric criteria for COPD, a significant number (24%; 72 of 300) had evidence of emphysema [20]. In a study by Tan and colleagues [7] comparing ever-smokers with and without COPD against never-smokers with and without COPD using the radiological methodology of Barr et al. [22], emphysema was found in 12.8% and 10.2% in never-smokers with and without a diagnosis of COPD, compared with 54.8% and 26.0% in ever-smokers with and without a diagnosis of COPD, respectively. Thus, emphysema is strongly related to smoking history. Further analyses of the COPDGene study data suggest that a substantial proportion of smokers who do not meet the criteria for COPD, but have respiratory symptoms and imaging abnormalities, are at significant risk of death and spirometric disease progression [2]. This result highlights the importance of finding appropriate markers to identify subjects early who are at risk of disease progression. Given the high proportion of EwAL subjects who had centrilobular emphysema in our study (41%), this raises the question of whether this

group could be considered an early disease group rather than a true control group.

As expected, as disease severity increased, symptoms tended to worsen. Values for subjects in the A1ATD group were generally between those in the GOLD 2 and 3 groups. This may not be surprising, given that the majority of the A1ATD subjects met the criteria for COPD GOLD 3 ($n=12$, 63.2%) or GOLD 2 ($n=5$, 26.3%). Our study also found that mMRC dyspnoea score (<2 and ≥ 2) and SGRQ total score (<25 and ≥ 25) were better discriminators for the COPD GOLD 1–3 groups than CAT score (<10 and ≥ 10), demonstrating a more consistent numerical trend across the groups.

In addition to the FOOTPRINTS[®] study, there are a number of longitudinal studies that are ongoing or completed in patients with COPD, including COPDGene [2], ECLIPSE [3], SPIROMICS [4, 5], COSYCONET [6], CanCOLD [7] and the British Lung Foundation early COPD study (Table 5) [8]. Comparatively, FOOTPRINTS[®] has a number of strengths. The inclusion of the A1ATD subpopulation is unique to the study and provides information on an important but rarely studied subpopulation of patients; these patients present with earlier onset and faster progression of emphysema [12]. Further, at the time FOOTPRINTS[®] was designed and began, no other study had presented an association between biomarkers of extracellular matrix degradation (in this case, sRAGE) and emphysema. Since then, this area has garnered the interest of several other studies [18, 23–25]. Another distinguishing factor is the method for visual assessment of emphysema used in our study; this has been conducted according to the statement by the Fleischner Society [15]. The Fleischner method has been shown to be complementary to quantitative CT assessment and to provide incremental information regarding the likelihood of disease progression, lung cancer [26] and mortality [27, 28].

Conclusions

The FOOTPRINTS[®] study is investigating biomarkers associated with emphysema over a 3-year period to increase the understanding of COPD patient phenotypes, pathogenesis and disease progression. The data reported here document the baseline disease characteristics and biomarkers of subjects in our study, highlighting the substantial burden of COPD and A1ATD. In addition to the baseline biomarker data presented, future analyses will be conducted on sputum biomarkers. Importantly, these findings provide important context to precede the upcoming results from the 3-year study, which aim to establish key correlations between disease progression and biomarkers over time in a representative COPD population.

Table 5 Summary of ongoing or completed longitudinal observational COPD studies

Observational study	Population under study	Key characteristics	Key outcomes	Duration of study (number of visits post-screening)
		COPD subjects	Control subjects	
FOOTPRINTS [13]	382 patients with COPD: • GOLD 1: 123 • GOLD 2: 130 • GOLD 3: 129 19 patients with COPD and A1ATD 62 EwAL limitation	Age (years): • 40–70 • COPD and A1ATD: 30–70 • COPD & A1ATD smoking history ≥ 10 pack-years Subjects with asthma excluded	• EwAL • Smoking history ≥ 20 pack-years • FEV ₁ $\geq 80\%$ predicted • FEV ₁ /FVC \geq LLN Post DL _{CO} $\geq 70\%$ predicted at Visit 1	3 years (5)
COPDgene [2, 29]	> 10,000 current smokers (with or without COPD) and non-smoker subjects across full spectrum of COPD disease severities	• Aged 45–80 years • ≥ 10 pack-year smoking history • Included subjects with asthma	• Non-smokers and smokers without COPD aged 45–80 years • ≥ 10 pack-year smoking history except non-smokers • Included subjects with asthma	10 years (2)
ECLIPSE [3]	> 2000 COPD subjects with GOLD 2–4 COPD • 343 smoking and 223 non-smoking control subjects	• Aged 40–75 years • ≥ 10 pack-year smoking history • Baseline post-bronchodilator FEV ₁ of $< 80\%$ predicted and FEV ₁ /FVC ≤ 0.7	• Aged 40–75 years • Baseline post-bronchodilator FEV ₁ of $> 85\%$ predicted and FEV ₁ /FVC of > 0.7 • Current or ex-smokers with a smoking history ≥ 10 pack-years (smoking controls) or non-smokers with a smoking history of < 1 pack-year	3 years (8)
SPROMICS [5]	> 3200 participants in four strata: 1. Non-smokers 2. Smokers without airflow obstruction 3. Smokers with mild/moderate COPD 4. Smokers with severe COPD	Aged 40–80 years • > 20 pack-year smoking history • FEV ₁ /FVC < 0.7 • FEV ₁ $> 50\%$ predicted for mild/moderate COPD and $< 50\%$ predicted for severe	Aged 40–80 years • < 1 pack-year smoking history for non-smokers • > 20 pack-year smoking history for smokers without airflow limitation • FEV ₁ /FVC > 0.7 • FVC $> LLN$	3 years (3)
COSYCONET [6] (NCT01245933)	• 2291 patients across COPD GOLD stages 1–4 • 206 patients with GOLD “0” ^a	• Aged 40–90 years • 8%/35%/32%/9% GOLD 1–4 • 24%/68%/8% currently smoking/ex-smokers/never-smokers • Mean of 40–50 pack-years for currently smoking and ex-smokers	No control population in this study	9 years (7)

Table 5 (continued)

Observational study	Population under study	Key characteristics		Key outcomes	Duration of study (number of visits post-screening)
		COPD subjects	Control subjects		
CanCOLD [7]	<ul style="list-style-type: none"> • 2295 never-smokers • 2598 ever-smokers 	<ul style="list-style-type: none"> • Aged ≥ 40 years • > 20 pack-year smoking history in ever-smokers • Never-smokers accounted for 29% of COPD patients 	No control population in this study	<ul style="list-style-type: none"> • Lung function testing • Chest CT • Respiratory symptoms and exacerbations 	4 years (visits not listed)
UK-based British Lung Foundation early COPD [8]	<ul style="list-style-type: none"> • Pilot sample of 102 smokers at risk of developing clinical COPD (1000 aim to be recruited) 	<ul style="list-style-type: none"> • Aged 30–45 years • > 10 pack-years smoking history • No/mild airflow limitation 	No control population in this study	<ul style="list-style-type: none"> • Lung function testing • Chest CT 	Unknown

6MWT 6-min walk test, *ATATD* alpha-1-antitrypsin deficiency, *COPD* chronic obstructive pulmonary disease, *CT* computed tomography, *DL_{CO}* diffusing capacity of the lung for carbon monoxide, *EWAL* ex-smokers without airflow limitation, *FEV₁* forced expiratory volume in 1 s, *FVC* forced vital capacity, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *LLN* lower limit of normal, *MRI* magnetic resonance imaging, *SGRQ* St. George's Respiratory Questionnaire

^a FEV₁/FVC > 0.7 and either (i) having a doctor diagnosis of chronic bronchitis and/or (ii) indicating a severity of cough of at least 3 in the respective COPD Assessment Test item and/or (iii) indicating a severity of phlegm of at least 3 in the respective COPD Assessment Test item

^b Sub-cohort of 602 patients, observed for 2.5 years (NCT02629432). A follow-up study is ongoing in 370 patients (NCT03591562)

Abbreviations

6MWT	6-Minute walk test
A1ATD	Alpha-1-antitrypsin deficiency
ALD	Adjusted lung density
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DL _{CO}	Diffusing capacity of the lung for carbon monoxide
EwAL	Ex-smokers without airflow limitation
FEV ₁	Forced expiratory volume in 1 s
FRC	Function residual capacity
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hs-CRP	High-sensitivity C-reactive protein
IL-6	Interleukin-6
LAA-856	Lung voxels with attenuation \leq - 856 Hounsfield Units
LAA-950	Lung voxels with attenuation \leq - 950 Hounsfield Units
mMRC	Modified Medical Research Council
PD15	15th percentile point of the CT histogram
SGRQ	St. George's Respiratory Questionnaire
SD	Standard deviation
SP-D	Surfactant protein D
sRAGE	Soluble receptor for advanced glycation end product
TLC	Total lung capacity
WBC	White blood cell

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-023-02584-2>.

Additional file 1: Table S1. Disease history (for categories with $\geq 5\%$ in any group). **Table S2.** Soluble biomarkers in whole blood and qualitative CT scan data. **Table S3.** DL_{CO} parameters.

Acknowledgements

The authors would like to thank all the volunteers for participating in this study and also extend their thanks to the investigators and study staff. The authors did not receive payment for the development of this manuscript. Vicki Cronin, PhD of Meditech Media, Nucleus Global, provided editorial support and formatting assistance, which was contracted and funded by Boehringer Ingelheim. Boehringer Ingelheim were given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Author contributions

JC, AG, DAL, FR and CD contributed towards the overall concept and design of the original study protocol. CD led the writing of the protocol. JC, AG, DAL, FR and CD provided critical input at all stages. All authors have contributed towards the development of the manuscript, and have read and approved the final manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

Prior presentation

This manuscript includes some content that was previously presented as a poster at the 2020 American Thoracic Society International Conference.

Funding

This study was funded and sponsored by Boehringer Ingelheim. The trial clinical monitor for this study was Markus Beck (Boehringer Ingelheim Pharma GmbH & Co. KG, Dept. Clinical Research Germany/Respiratory Diseases, Birkendorfer Str. 65, 88397 Biberach an der Riss, Germany; Phone: +49 (0) 7351 / 54 96 803).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

FOOTPRINTS[®] is being performed in accordance with the International Conference on Harmonisation Tripartite Guideline for GCP, the Japanese GCP regulations and local regulations. The protocol was approved by the authorities and IEC/IRB of the respective institutions where applicable, which included study sites in Belgium, Canada, Denmark, Finland, Germany, Japan, the Republic of Korea, Poland, Spain, Sweden, the United Kingdom and the United States. In the respective countries, the ethics approval preceded the study participant's enrolment. Written informed consent is obtained from all study participants. Notably, any protocol amendments were initiated only after all required legal documentation was reviewed and/or approved by the respective IRB/IEC, as applicable.

Competing interests

JC is a co-principal investigator for the COPDGene study and has received grants from National Institutes of Health/National Heart, Lung, and Blood Institute (NHLBI). AG, HK, AE, FR and CD are employees of Boehringer Ingelheim. DAL has received grants from NHLBI, and personal fees from Boehringer Ingelheim, and Calyx Inc. In addition, DAL has a patent for 'systems and methods for classifying severity of COPD' pending. AMT has received personal fees, payment for educational talks and expenses payments for work on the FOOTPRINTS steering committee from Boehringer Ingelheim, grants and personal fees from AstraZeneca, CSL Behring and Grifols Biotherapeutics, and grants, personal fees and non-financial support from Chiesi. RMM has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Merck Sharp & Dohme, Mundipharma, Novartis and Roche. WJ has received grants from AstraZeneca and Chiesi. AL-S reports receipt of a study fee for involvement in conducting the FOOTPRINTS study.

Author details

¹Department of Medicine, National Jewish Health, Denver, CO, USA. ²TA Inflammation Medicine, Boehringer Ingelheim International GmbH, Biberach an der Riss, Germany. ³Department of Radiology, National Jewish Health, Denver, CO, USA. ⁴Institute of Applied Health Research, University of Birmingham, Birmingham, UK. ⁵2nd Department of Lung Diseases and Tuberculosis, Białystok Medical University, Białystok, Poland. ⁶Department of Chronic Diseases and Metabolism (CHROMETA), Laboratory of Respiratory Diseases and Thoracic Surgery (BREATH), University Hospital Leuven, Louvain, KU, Belgium. ⁷KLB Gesundheitsforschung Lübeck GmbH, Lübeck, Germany. ⁸TA Inflammation Medicine, Boehringer Ingelheim International GmbH, Ingelheim, Germany. ⁹Department of Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany.

Received: 31 July 2023 Accepted: 27 October 2023

Published online: 17 November 2023

References

- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). 2020. https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. Accessed 26 Aug 2022.
- Lowe KE, Regan EA, Anzueto A, Austin E, Austin JHM, Beaty TH, Benos PV, Benway CJ, Bhatt SP, Bleecker ER, et al. COPDGene[®] 2019: redefining the diagnosis of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis.* 2019;6:384–99.
- Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, Hagan G, Knobil K, Lomas DA, MacNee W, et al. Evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE). *Eur Respir J.* 2008;31:869–73.
- Hastie AT, Martinez FJ, Curtis JL, Doerschuk CM, Hansel NN, Christenson S, Putcha N, Ortega VE, Li X, Barr RG, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med.* 2017;5:956–67.

5. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG, et al. Design of the subpopulations and intermediate outcomes in COPD study (SPIROMICS). *Thorax*. 2014;69:491–4.
6. Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, Heinrich J, Schulz H, Glaser S, Holle R, et al. The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline. *Respir Med*. 2016;114:27–37.
7. Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, FitzGerald JM, Marciniuk DD, Maltais F, Buist AS, et al. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. *Thorax*. 2015;70:822–9.
8. Ritchie AJ, Donaldson GC, El-Emir E, Calverley PM, Vestbo J, Wedzicha JA. The British Lung Foundation Early COPD Consortium—recruitment and results from an initial pilot. *Am J Respir Crit Care Med*. 2019;199:A3280.
9. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD: Global Initiative for Chronic Obstructive Lung Disease (2015 report). 2015. <http://goldcopd.org/>. Accessed 3 Aug 2015.
10. Foreman MG, Campos M, Celedon JC. Genes and chronic obstructive pulmonary disease. *Med Clin North Am*. 2012;96:699–711.
11. Brode SK, Ling SC, Chapman KR. Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. *CMAJ*. 2012;184:1365–71.
12. Stockley RA, Edgar RG, Pillai A, Turner AM. Individualized lung function trends in alpha-1-antitrypsin deficiency: a need for patience in order to provide patient centered management? *Int J Chron Obstruct Pulmon Dis*. 2016;11:1745–56.
13. Crapo J, Gupta A, Lynch DA, Vogel-Claussen J, Watz H, Turner AM, Mroz RM, Janssens W, Ludwig-Sengpiel A, Beck M, et al. FOOTPRINTS study protocol: rationale and methodology of a 3-year longitudinal observational study to phenotype patients with COPD. *BMJ Open*. 2021;11: e042526.
14. Hatt CR, Oh AS, Obuchowski NA, Charbonnier JP, Lynch DA, Humphries SM. Comparison of CT lung density measurements between standard full-dose and reduced-dose protocols. *Radiol Cardiothorac Imaging*. 2021;3: e200503.
15. Lynch DA, Austin JH, Hogg JC, Grenier PA, Kauczor HU, Bankier AA, Barr RG, Colby TV, Galvin JR, Gevenois PA, et al. CT-definable subtypes of chronic obstructive pulmonary disease: a statement of the Fleischner Society. *Radiology*. 2015;277:192–205.
16. Szalontai K, Gemes N, Furak J, Varga T, Neuperger P, Balog JA, Puskas LG, Szebeni GJ. Chronic obstructive pulmonary disease: epidemiology, biomarkers, and paving the way to lung cancer. *J Clin Med*. 2021;10:2889.
17. Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic obstructive pulmonary disease biomarkers and their interpretation. *Am J Respir Crit Care Med*. 2019;199:1195–204.
18. Pratte KA, Curtis JL, Kechris K, Couper D, Cho MH, Silverman EK, DeMeo DL, Sciruba FC, Zhang Y, Ortega VE, et al. Soluble receptor for advanced glycation end products (sRAGE) as a biomarker of COPD. *Respir Res*. 2021;22:127.
19. Sorensen L, Nielsen M, Petersen J, Pedersen JH, Dirksen A, de Bruijne M. Chronic obstructive pulmonary disease quantification using CT texture analysis and densitometry: results from the Danish lung cancer screening trial. *AJR Am J Roentgenol*. 2020;214:1269–79.
20. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med*. 2015;175:1539–49.
21. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med*. 2016;374:1811–21.
22. Group COCW, Barr RG, Berkowitz EA, Bigazzi F, Bode F, Bon J, Bowler RP, Chiles C, Crapo JD, Criner GJ, et al. A combined pulmonary-radiology workshop for visual evaluation of COPD: study design, chest CT findings and concordance with quantitative evaluation. *COPD*. 2012;9:151–9.
23. Stolz D, Leeming DJ, Kristensen JHE, Karsdal MA, Boersma W, Louis R, Milenkovic B, Kostikas K, Blasi F, Aerts J, et al. Systemic biomarkers of collagen and elastin turnover are associated with clinically relevant outcomes in COPD. *Chest*. 2017;151:47–59.
24. Bihlet AR, Karsdal MA, Sand JM, Leeming DJ, Roberts M, White W, Bowler R. Biomarkers of extracellular matrix turnover are associated with emphysema and eosinophilic-bronchitis in COPD. *Respir Res*. 2017;18:22.
25. Klont F, Horvatovich P, Bowler RP, van Rikxoort E, Charbonnier JP, Kwiatkowski M, Lynch DA, Humphries S, Bischoff R, Ten Hacken NHT, Pouwels SD. Plasma sRAGE levels strongly associate with centrilobular emphysema assessed by HRCT scans. *Respir Res*. 2022;23:15.
26. Carr LL, Jacobson S, Lynch DA, Foreman MG, Flenaugh EL, Hersh CP, Sciruba FC, Wilson DO, Sieren JC, Mulhall P, et al. Features of COPD as predictors of lung cancer. *Chest*. 2018;153:1326–35.
27. El Kaddouri B, Strand MJ, Baraghoshi D, Humphries SM, Charbonnier JP, van Rikxoort EM, Lynch DA. Fleischner Society visual emphysema CT patterns help predict progression of emphysema in current and former smokers: results from the COPDGene study. *Radiology*. 2021;298:441–9.
28. Lynch DA, Moore CM, Wilson C, Nevrekar D, Jennermann T, Humphries SM, Austin JHM, Grenier PA, Kauczor HU, Han MK, et al. CT-based visual classification of emphysema: association with mortality in the COPDGene study. *Radiology*. 2018;288:859–66.
29. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. *COPD*. 2010;7:32–43.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

