Contrasting the clinical and biological characteristics of young and old COPD patients

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Young COPD patients suffer from significant disease burden, and display an altered biomarker and disease progression profile reflected by an accelerated risk of lung function decline https://bit.ly/4ecdYbF

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Abstract

Background The ECLIPSE study was a large, international, prospective, controlled, observational study that included COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 2–4), as well as smoking and non-smoking participants with normal spirometry, aged 40–75 years, who were followed-up regularly for 3 years. Here we sought to contrast the clinical and biological characteristics of young COPD *versus* controls of similar age and older COPD patients included in ECLIPSE.

Methods We compared 106 young (<50 years) and 488 old (>70 years) COPD patients, as well as 119 young smokers and 92 nonsmoker controls (<50 years) with normal spirometry.

Results Young COPD patients: 1) were more symptomatic than young controls, often reported a family history of chronic bronchitis, emphysema and asthma, as well as a personal history of asthma and bronchitis, and suffered from a similar disease burden to older patients; 2) were at higher risk of substantial forced expiratory volume in 1 s decline over time; and 3) had reduced serum levels of CC16 (a lung-derived anti-inflammatory protein that relates to lung damage) and, at the same time, reduced pro-inflammatory markers compared to older COPD patients.

Conclusions Young COPD patients suffer from significant disease burden, display an altered biomarker and disease progression profile reflected by an accelerated risk of lung function decline highlighting the need for early life diagnosis, prevention approaches and treatment.

Introduction

COPD has been traditionally considered a disease of old people characterised by an accelerated decline of lung function with age due to the inflammatory response elicited by tobacco smoking in so-called susceptible individuals [1]. Recent research, however, has shown that there are many other genetic (other than α_1-antitrypsin deficiency), environmental and host risk factors for COPD [2–5], and that COPD can occur in young individuals [6–9], operationally defined as those younger than 50 years of age [10, 11], with a potential female predominance [12, 13].

Older COPD patients often show increased levels of several pro-inflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6, IL-8, CCL-18 and CCL-19, and reduced levels of anti-inflammatory

pneumo-proteins, like CC16 and surfactant protein D (SP-D) [14] or the soluble receptor for advanced glycation end products (sRAGE) [15]. We recently reported similar findings (CCL-19, sRAGE, CC16 and SP-D) in young individuals (25–35 years of age) with low peak lung function in the Lifelines study, a general population cohort in the Netherlands [16]. Likewise, in the Tasmanian Longitudinal Health Study (TAHS), we observed that high CRP and low CC16 circulating levels measured in mid age (45–53 years) were associated with accelerated lung function decline or no decline, respectively [17]. Based on these previous observations, we hypothesised that some of these circulating biomarkers may also be differentially associated with young and old COPD patients recruited into the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study, a large, international clinical cohort [14, 18–20]. To test this hypothesis, we interrogated the ECLIPSE database to compare the clinical characteristics and circulating levels of the panel of circulating biomarkers determined in the study, both at baseline and during follow-up, in COPD patients younger than 50 years, young controls of similar age (both smokers and nonsmokers) with normal spirometry and COPD patients older than 70 years of age.

Methods

Study design and ethics

The ECLIPSE study (Clinicaltrials.gov NCT00292552) was a prospective, international, controlled, observational cohort study that included 2164 patients with COPD, 337 smokers (>10 pack-years) and 245 nonsmoker participants with normal spirometry, who were followed-up over 3 years [14, 18–20]. The design, methodology and results of ECLIPSE have been extensively published elsewhere [14, 18–20]. Importantly for the analysis of young COPD patients in the current paper, participants with known α_1-antitrypsin deficiency were excluded [19]. All study subjects provided written informed consent. The study was approved by the Ethics Committees of all participating institutions. The ECLIPSE study was supported by GSK.

Participants

ECLIPSE included 317 participants younger than 50 years: 106 with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 2–4), 119 current or former smokers (⩾10 pack-years) with normal spirometry, and 92 never-smokers with normal spirometry. ECLIPSE also included 488 COPD patients (GOLD grades 2–4) older than 70 years. To better delineate potential differences between young and old COPD patients, we also compared the 106 young COPD patients mentioned above with 106 older patients matched individually for sex, smoking status (current/former) and severity of airflow limitation (forced expiratory volume in 1 s (FEV_1)).

Measurements

Demographic and clinical variables and the circulating levels of a panel of biomarkers that include differential blood cell counts, high sensitivity CRP, fibrinogen, IL-6, IL-8, tumour necrosis factor-α (TNF-α), CC16, SP-D and CCL-18 were determined at baseline and after 1 year follow-up as described in detail elsewhere [14]. Emphysema was quantified on inspiratory computed tomography (CT) scans as both the per cent of lung voxels with density <−950 Hounsfield Units (% low attenuation areas: %LAA) and the 15th percentile value (Perc15) [14, 18–20].

Data analysis

Results are presented as n, range, proportion or mean±SD. After testing for the normality of their distribution, continuous and discrete variables were compared between groups and over time using ANOVA, Kruskal–Wallis, t-test, Mann–Whitney or the χ^2 test as appropriate. Statistical significance was defined by a two-tailed p-value <0.05. All statistics were computed with R using custom scripts.

Results

Clinical characteristics

Young COPD patients versus young controls

As detailed in table 1, at recruitment into ECLIPSE young COPD patients were slightly older than young controls, but sex and body composition measures were similar. Cumulative smoking exposure (pack-years) was higher in young COPD patients than in smoker controls, but the proportion of current smokers was lower. Young COPD patients reported a family history of chronic bronchitis, emphysema and asthma, as well as a personal history of asthma and bronchitis more often. They also reported chronic bronchitis and received treatment with respiratory medications frequently. Airflow limitation was moderate in 50% of young COPD patients (grade 2) but severe (35% grade 3) or very severe (16% grade 4) in another 50% of participants; 52% of young patients did not report any exacerbation the previous year, but the remaining 48% reported one or more. Arterial oxygen saturation was lower in young COPD. The prevalence of cardiovascular diseases, depression, nutritional depletion, cachexia and osteoporosis was higher in young

TABLE 1 Characteristics of young COPD patients, smoker controls and nonsmoker controls at baseline

	Young COPD		Smokers		Nonsmokers		ANOVA, Kruskal–Wallis or proportion test p-value
	n	Mean±SD or n (%)	n	Mean±SD or n (%)	n	Mean±SD or n (%)	
Demographics and exposures							
Age years	106	47.3±2.69***	119	45.7±2.93	92	45.0±3.24$^{\#\#\#}$	**<0.0001**
Female	106	41 (39)	119	58 (49)	92	53 (58)$^{\#\#}$	0.15
Body mass index kg·m^{-2}	106	26.53±7.07	119	26.11±4.59	92	27.04±5.7	0.43
Fat free mass index kg·m^{-2}	106	15.01±7.11	119	14.96±4.76	89	15.07±5.05	0.15
Fat mass index kg·m^{-2}	106	11.51±3.18	119	11.15±2.9	89	11.47±3.33	0.29
Cigarette smoking pack-years	106	34.7±17.0***	119	24.8±11.6¶¶¶	92	0±0$^{\#\#\#}$	**<0.0001**
Current smoker	106	65 (61)**	119	94 (79)¶¶¶	92	0 (0)$^{\#\#\#}$	**0.0027**
Family history							
Chronic bronchitis	106	39 (37)***	119	17 (14)	92	13 (14)$^{\#\#\#}$	**0.0001**
Emphysema	106	32 (30)***	119	9 (8)	92	6 (7)$^{\#\#\#}$	**<0.0001**
Asthma	106	27 (25)	119	21 (18)	92	12 (13)$^{\#}$	0.15
Symptoms and treatments							
mMRC score	105	2.5±1.5***	119	0.6±1.2¶	88	0.2±0.7$^{\#\#\#}$	**<0.0001**
SGRQ-C total score	102	50.4±20.21***	112	8.1±10.0¶	68	3.0±3.7$^{\#\#\#}$	**<0.0001**
Fatigue score (FACIT)	104	33.8±10.7***	118	44.7±6.9	91	46.8±5.9$^{\#\#\#}$	**<0.0001**
Chronic bronchitis	106	49 (46)***	119	11 (9)¶	92	2 (2)$^{\#\#\#}$	**<0.0001**
Ever had asthma	97	38 (39)***	118	7 (6)	90	2 (2)$^{\#\#\#}$	**<0.0001**
Any respiratory medicines	106	95 (90)***	119	15 (13)¶	92	3 (3)$^{\#\#\#}$	**<0.0001**
Lung physiology							
FEV_1/FVC (post-BD) %	106	60.3±14.9***	119	100.3±6.4	92	102.8±6.8$^{\#\#\#}$	**0.0007**
FEV_1 (post-BD) % ref.	106	50.0±17.5***	119	107.8±10.3¶¶¶	92	114.9±12.4$^{\#\#\#}$	**<0.0001**
FVC (post-BD) % ref.	106	85.3±18.6***	119	112.0±11.6	92	116.5±12.5$^{\#\#\#}$	**<0.0001**
Arterial oxygen saturation %	106	95.5±2.1***	119	97.7±1.3	90	97.3±3.4$^{\#\#\#}$	**<0.0001**
Comorbid diseases							
Ever been told had heart attack	101	7 (7)**	118	0 (0)	92	0 (0)$^{\#}$	**0.0008**
Nutritionally depleted [51]	106	26 (25)	119	17 (14)	91	11 (12)$^{\#}$	**0.047**
Cachexia [52]	106	14 (13)*	119	5 (4)	91	2 (2)$^{\#\#}$	**0.0082**
Bone density (HU) thoracic spine 10	81	193.6±50.3	96	198.5±43.2¶¶¶	76	234.0±51.5$^{\#\#\#}$	**<0.0001**
Ever been told had reflux/heartburn	101	27 (27)	115	25 (22)	90	15 (17)	0.40
Depression (CESD score)	106	13.3±11.9***	118	7.4±8.6	90	5.2±4.9$^{\#\#\#}$	**<0.0001**
Imaging							
%LAA	86	11.99±11.93***	110	1.39±1.74	79	3.66±4.04$^{\#\#\#}$	**<0.0001**
Lowest 15th percentile	86	−933.91±29.2***	110	−888.4±26.89¶¶¶	79	−909.76±29.44$^{\#\#\#}$	**<0.0001**
Blood counts and biomarkers							
White blood cell count (×10^6·mL^{-1})	100	8.13±2.42*	115	7.55±2.39¶¶¶	89	6.2±1.45$^{\#\#\#}$	**0.0004**
Total neutrophils (×10^6·mL^{-1})	100	5.26±2.16*	115	4.71±1.97¶¶¶	89	3.92±1.2$^{\#\#\#}$	**0.0002**
Lymphocytes (×10^6·mL^{-1})	100	2.18±0.7	115	2.21±0.63¶¶¶	89	1.8±0.5$^{\#\#\#}$	**<0.0001**
Monocytes (×10^6·mL^{-1})	100	0.46±0.2	115	0.42±0.18¶¶¶	89	0.31±0.14$^{\#\#\#}$	**<0.0001**
Eosinophils (×10^6·mL^{-1})	100	0.19±0.14	115	0.18±0.11	89	0.15±0.11	0.074
Basophils (×10^6·mL^{-1})	100	0.03±0.02	115	0.02±0.02	89	0.02±0.01	0.21
High-sensitivity C-reactive protein mg·L^{-1}	105	4.18±4.94*	118	2.52±4.12¶¶¶	92	2.48±5	**0.0006**
Fibrinogen mg·dL^{-1}	105	421.7±93.11***	119	376.53±64.71¶¶¶	92	348.73±77.71$^{\#\#\#}$	**<0.0001**
Interleukin-6 pg·mL^{-1}	92	4.34±19.03***	109	0.82±0.83¶¶¶	87	0.62±0.85$^{\#\#}$	**<0.0001**
Interleukin-8 pg·mL^{-1}	99	12.95±21.37	117	23.99±77.78	89	5.17±4.95	0.30
TNF-α pg·mL^{-1}	99	16.28±33.19**	116	22.37±28.15	91	8.61±14.7$^{\#\#\#}$	**0.0025**
CC16 ng·mL^{-1}	100	3.74±1.92***	117	5.73±2.84¶¶¶	91	6.53±2.42$^{\#\#}$	**<0.0001**
Surfactant protein D ng·mL^{-1}	100	133.9±82.08	117	124.36±71¶¶¶	91	76.39±37.08$^{\#\#\#}$	**0.0006**
CCL-18 ng·mL^{-1}	92	93.09±32.57	112	82.32±45.01	85	77.33±28.6	0.35

Bold type for p-values denotes statistical significance. mMRC: modified Medical Research Council; SGRQ-C: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BD: bronchodilator; HU: Hounsfield Units; CESD: Center for Epidemiological Studies Depression; LAA: low attenuation area; TNF-α: tumour necrosis factor-α. Symbols indicate the statistical significance of differences between groups (*post-hoc* comparisons t-test or Mann–Whitney) as follows: 1) young COPD *versus* smokers, p-value <0.05 (*), p<0.01 (**), p<0.001(***); 2) young COPD *versus* nonsmokers, p-value <0.05 ($^{\#}$), p<0.01 ($^{\#\#}$), p<0.001($^{\#\#\#}$); and 3) smokers *versus* nonsmokers, p-value <0.05 (¶), p<0.01 (¶¶), p<0.001(¶¶¶).

COPD patients. CT emphysema was more severe in young COPD patients, albeit some controls with normal spirometry also showed a small degree of emphysema on CT, which may nowadays qualify them as pre-COPD [21] (table 1).

During 3-year follow-up, 5% of young COPD patients died *versus* 1% of smoker and 1% of never-smoker controls (p=0.26). Supplementary table S1 shows that the proportion of young COPD patients with modified Medical Research Council score >2 or depression [22] increased during follow-up, but not in controls. On average, lung function remained relatively constant over time in young COPD patients and declined slightly in controls (particularly in smokers) (supplementary table S1).

Young versus older COPD patients

Table 2 shows that, at baseline, age was significantly different (by design) and that the proportion of females was higher in the young COPD patients group. Fat mass index was lower in younger COPD patients. Cumulative smoking exposure (pack-years) was higher in older patients (likely reflecting their longer exposure to tobacco across their life), but the proportion of current smokers was higher in young patients. Family history of emphysema was more prevalent in young patients too. Fatigue was slightly more frequent in older patients, but chronic bronchitis and a previous diagnosis of asthma were more prevalent in younger patients. Treatments were similar in both groups. Of note the severity of airflow limitation was similar in both groups but arterial oxygen saturation was lower in older patients. Comorbidities were also more prevalent in older patients albeit they were not absent in young COPD patients, except for depression (which was more often reported in young COPD individuals), with increasing prevalence over 3 years of observation. Emphysema was more severe in older COPD patients. These cross-sectional results were largely unchanged when young COPD patients were compared with older COPD patients individually matched for sex, smoking status and FEV_1, except for a higher prevalence of a previous diagnosis of asthma in young COPD patients (supplementary table S2).

On average, changes during follow-up were similar in young and old COPD patients, independent of individual matching (supplementary tables S3 and S4). Yet, figure 1 shows that when young and old COPD patients were matched for sex, baseline FEV_1 and smoking status (current/former), and we stratified FEV_1 changes over time using the same categories described in the entire ECLIPSE cohort [23], FEV_1 remained stable or improved (modestly or substantially) in 27% of both young and older patients, but the proportion of young COPD patients experiencing substantial FEV_1 decline during follow-up tended to be higher than in older patients (48% *versus* 34%, p=0.05).

Circulating biomarkers

Most circulating biomarkers determined at baseline were higher in young COPD patients than young controls, except for the proportion of circulating lymphocytes and levels of TNF-α and CC16, which were lower than in smoker controls (table 1, figure 2). On the other hand, compared with old COPD patients at baseline, younger patients showed increased circulating lymphocyte values but reduced levels of eosinophils, CRP, fibrinogen, IL-6, CC16 and CCL-18 (table 2, figure 3). Finally, in the ECLIPSE study these biomarkers were also quantified in younger and older COPD patients at 1-year follow-up. Supplementary tables S3 (all population) and S4 (matched older patients) show that, by and large, there were no significant changes from baseline, except for CC16 levels that remained stable (and low) in young COPD patients but fell in older patients.

Discussion

This analysis of the ECLIPSE cohort: 1) confirms that the burden of disease in young people with COPD is substantial and similar to that of older ones (table 2); 2) shows that young patients are at risk of substantial lung function decline over time (figure 1); and 3) identifies significant differences in the pattern of circulating biomarkers between young and old patients. Whereas the former are characterised by reduced CC16 levels (suggesting more lung damage despite their younger age), the latter demonstrate a more pro-inflammatory profile. Collectively, these observations contribute to better delineate the clinical and biological characteristics of young COPD patients.

Previous studies

The prevalence of COPD in individuals aged 20–50 years in the general population ranges between 2% and 6% [24, 25]. Previous studies reported that young COPD patients are often females [12, 13], experience respiratory symptoms and poor health status [26, 27], use healthcare resources frequently [28], often report a history of family respiratory diseases [12, 28], can suffer moderate–severe airflow limitation, gas trapping, and reduced diffusing capacity [12, 26–29], and have CT emphysema [28, 30] and comorbidities despite their young age [31]. During follow-up, young COPD patients have an increased risk

TABLE 2 Comparison of young (<50 years of age) and old (>70 years of age) COPD patients at baseline

Variables	Young COPD		Old COPD		t-test/Mann–Whitney/Fisher p-value
	n	Mean±SD or n (%)	n	Mean±SD or n (%)	
Demographics and exposures					
Age years	106	47.3±2.69	488	72.2±1.6	**<0.0001**
Female	106	41 (39)	488	136 (28)	**0.035**
Body mass index kg·m^{-2}	106	26.53±7.07	488	26.15±4.74	0.56
Fat free mass index	106	15.01±7.11	478	13.39±4.8	0.15
Fat mass index	106	11.51±3.18	478	12.78±2.84	**<0.0001**
Pack-years	106	34.7±17.0	488	50.08±28.9	**<0.0001**
Current smoker	106	65 (61)	488	124 (25)	**<0.0001**
Family history					
Chronic bronchitis	106	39 (37)	488	142 (29)	0.13
Emphysema	106	32 (30)	488	102 (21)	**0.041**
Asthma	106	27 (25)	488	83 (17)	0.053
Symptoms and treatments					
mMRC score	105	2.46±1.51	471	2.54±1.43	0.60
SGRQ-C total score	102	50.4±20.2	459	48.4±20.4	0.33
FACIT fatigue score	104	33.8±10.7	477	35.9±10.9	**0.047**
Chronic bronchitis	106	49 (46)	488	165 (34)	**0.019**
Ever had asthma	97	38 (39)	448	100 (22)	**0.0012**
Any respiratory medicines	106	95 (90)	488	455 (93)	0.22
Inhaled corticosteroids	106	10 (9)	488	79 (16)	0.098
Inhaled steroids+bronchodilators	106	53 (50)	488	273 (56)	0.28
Lung physiology					
FEV_1 (post-BD) % ref.	106	50.0±17.5	488	49.2±15.0	0.66
FVC (post-BD) % ref.	106	85.3±18.6	488	86.6±19.1	0.83
FEV_1/FVC (post-BD) %	106	60.3±14.9	488	60.3±14.7	0.71
Arterial oxygen saturation %	106	95.5±2.1	488	94.2±2.9	**<0.0001**
Comorbid diseases					
Ever been told had heart failure	99	3 (3)	461	57 (12)	**0.0039**
Ever been told had arrhythmia	98	9 (9)	449	80 (18)	**0.035**
Diabetes-related condition	106	6 (6)	488	65 (13)	**0.031**
Ever been told had diabetes	105	4 (4)	479	64 (13)	**0.0039**
Ever been told had osteoporosis	98	4 (4)	445	71 (16)	**0.0011**
Ever been told had osteoarthritis	100	8 (8)	444	73 (16)	**0.030**
Ever been told had peptic ulcer	105	4 (4)	479	64 (13)	**0.0039**
Ever been told had depression requiring treatment	104	23 (22)	479	49 (10)	**0.0016**
Depression (CESD total score)	106	13.3±11.9	478	9.8±7.5	**0.048**
Imaging					
%LAA	86	11.99±11.93	396	18.15±11.99	**<0.0001**
Lowest 15th percentile	86	−933.91±29.2	396	−949.91±26.68	**<0.0001**
Blood counts and biomarkers					
White blood cell count (×10^6·mL^{-1})	100	8.13±2.42	472	7.95±2.37	0.43
Total neutrophils (×10^6·mL^{-1})	100	5.26±2.16	471	5.38±2.12	0.36
Lymphocytes (×10^6·mL^{-1})	100	2.18±0.7	471	1.82±0.66	**<0.0001**
Monocytes (×10^6·mL^{-1})	100	0.46±0.2	471	0.5±0.24	0.22
Eosinophils (×10^6·mL^{-1})	100	0.19±0.14	471	0.23±0.17	**0.022**
Basophils (×10^6·mL^{-1})	100	0.03±0.02	471	0.03±0.02	0.96
High-sensitivity C-reactive protein mg·l^{-1}	105	4.18±4.94	473	7.19±10.99	**0.0013**
Fibrinogen mg·dL^{-1}	105	421.7±93.11	486	475.93±105.02	**<0.0001**
Interleukin-6 pg·mL^{-1}	92	4.34±19.03	432	6.9±49.17	**<0.0001**
Interleukin-8 pg·mL^{-1}	99	12.95±21.37	473	15.02±43.27	0.84
TNF-α pg·mL^{-1}	99	16.28±33.19	476	38.3±158.89	0.55
CC16 ng·mL^{-1}	100	3.74±1.92	477	7.17±4.17	**<0.0001**
Surfactant protein D ng·mL^{-1}	100	133.9±82.08	477	145±73.86	0.055
CCL-18 ng·mL^{-1}	92	93.09±32.57	396	122.19±44.77	**<0.0001**

Bold type for p-values denotes statistical significance. mMRC: modified Medical Research Council; SGRQ-C: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BD: bronchodilator; HU: Hounsfield Units; CESD: Center for Epidemiological Studies Depression; LAA: low attenuation area; TNF-α: tumour necrosis factor-α.

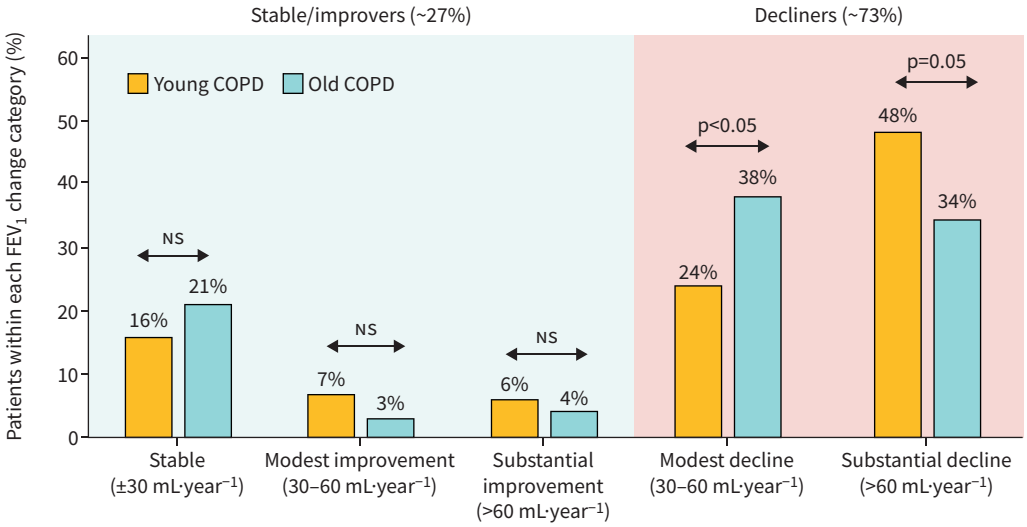

FIGURE 1 Proportion of young (⩽50 years of age) and old (>70 years of age) COPD patients individually matched for sex, baseline FEV_1 and smoking status (current/former) following different lung function trajectories during follow-up. FEV_1: forced expiratory volume in 1 s; NS: nonsignificant. For further explanation, see text.

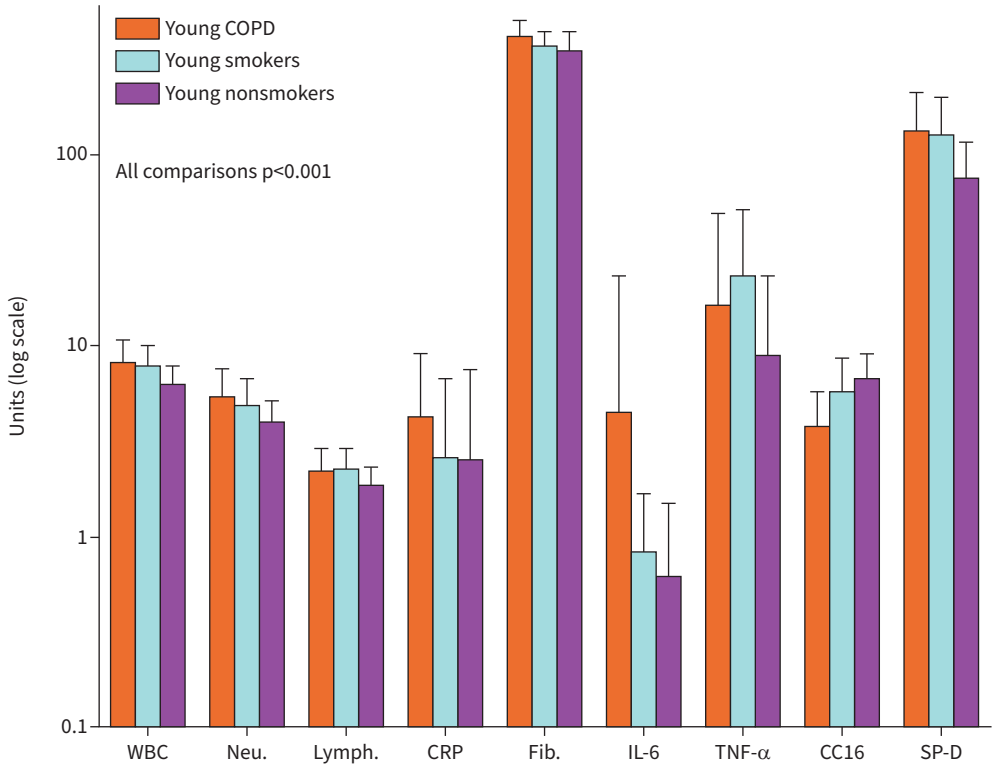

FIGURE 2 Levels of circulating biomarkers in young COPD patients and young controls with normal spirometry (both smokers and nonsmokers). Please note the logarithmic scale (absolute values are shown in table 1). For further explanation, see text. WBC: white blood cells; Neu.: neutrophils; Lymph.: lymphocytes; CRP: C-reactive protein; Fib.: fibrinogen; IL-6: interleukin-6; TNF-α: tumour necrosis factor-α; SP-D: surfactant protein D.

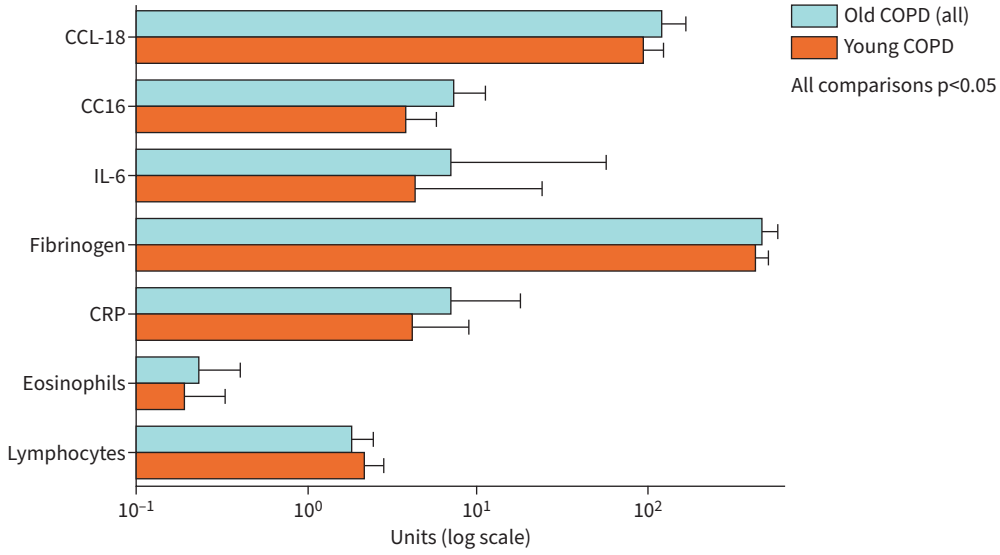

FIGURE 3 Levels of several circulating biomarkers in young and old COPD patients. Please note the logarithmic scale (absolute values are shown in table 2). For further explanation, see text. CRP: C-reactive protein; IL-6: interleukin-6.

of hospitalisations and death [27, 31, 32]. Our observations in the ECLIPSE cohort reported here are in keeping with these previous observations but expand them by contrasting young COPD patients, controls of similar age with normal spirometry (both smokers and nonsmokers) and older COPD patients.

Interpretation of novel findings

Cumulative smoking exposure was significantly higher in young COPD patients than in smokers with normal spirometry, albeit the proportion of current smokers was lower, perhaps because they were more symptomatic (table 1). The higher cumulative smoking exposure in young COPD individuals may have contributed to the severity of airflow limitation at this young age, but we cannot exclude that young individuals with COPD may be genetically more susceptible to the damaging effects of smoking [33, 34]. In keeping with some previous observations [12, 13], the proportion of females was higher in younger than older patients. Likewise, the observation that young COPD patients frequently reported a personal and family history of respiratory diseases provides further support to the relevance of genetics [35, 36] and early life events in the pathogenesis of COPD [5, 37]. Overall, these effects can damage the lungs and/or impede their normal development in young patients, which may then be reflected in reduced levels of circulating CC16 [14, 38–41].

Sanchez-Salcedo *et al.* [29] reported in the BODE cohort that lung function decline was similar in young and older COPD patients and that both groups have a similar proportion of rapid decliners. These observations are in line with our findings here. Figure 1 shows that FEV_1 remained stable (or improved) during follow-up in about a quarter of patients (both young and old), whereas it declined (modestly or substantially) in three-quarters of them, also young and old, hence confirming that COPD is not always characterised by accelerated lung function decline [2, 23]. Our study extends the observations by Sanchez-Salcedo *et al.* [29] by showing that the proportion of young patients with substantial FEV_1 decline tended to be higher (48% *versus* 34%, p=0.05) than in older patients (figure 1). To account for potential differences in baseline spirometric values (likely to be larger in young patients), FEV_1 decline was calculated based on a mixed model with random slope and random intercept, which considers that baseline values may be different. On the other hand, given that both groups were individually matched for smoking status, these observations support that young COPD patients (particularly females) may be more susceptible to the effects of smoking.

To our knowledge, this is the first study to contrast a panel of circulating biomarkers in young COPD, young controls and elder COPD patients. We found that the circulating levels of CC16, a homodimeric protein with anti-inflammatory and pro-repair properties mainly produced by club cells in the distal airways [14, 38–41], were significantly lower in young COPD patients than in controls of similar age (table 1, figure 2) and older COPD patients (table 2, figure 3). Further, these low CC16 levels remained

low and unchanged during follow-up in young COPD, whereas they decreased in older COPD patients (supplementary tables S3 and S4). These observations in a clinical COPD cohort like ECLIPSE are in line with those reported by Guerra *et al.* [39] in the general population, where they found that low serum CC16 levels were associated with reduced lung function in childhood, that there was significant intra-subject tracking of CC16 values from birth up to age 32 years, and that low CC16 levels were associated with smoking, accelerated lung function decline and development of moderate airflow limitation in adulthood [41]. On the other hand, we also observed that several inflammatory markers were higher in young COPD patients than in young controls (table 1, figure 2), but lower than in older COPD subjects (table 2, figure 3). Collectively, these observations pinpoint different mechanisms (*i.e.*, endotypes) in young and old COPD and suggest that in young participants the disease is more likely to relate to lung damage (lower CC16 levels), whereas in older patients it is a more pro-inflammatory condition, which may in turn contribute to the high prevalence of multimorbidity in older patients [42, 43].

Clinical implications

We confirmed that the burden of disease in young COPD patients is substantial and similar to that of older COPD patients, and their risk of future significant FEV_1 decline is substantial (figure 1). Thus, it would be important to raise the level of suspicion to diagnose COPD in younger individuals, particularly in females with a previous history of respiratory disease and depression, as well as to intensify smoking cessation programmes in this highly addicted population. In this context, it is of note that the recent paper by Aaron and co-workers [44] shows that a proactive strategy to identify COPD patients in the community can lead to significant clinical benefit. Although mean age in their study was 63 years [44], a similar approach can be explored in younger individuals. On the other hand, whether pharmacological interventions other than smoking cessation can modify disease progression in young COPD patients remains unknown, because there have been no studies specifically addressing this group of COPD patients. Of note, however, a pre-specified analysis of the 356 COPD patients younger than 50 years in the UPLIFT trial showed that tiotropium reduced the rate of decline of FEV_1, suggesting possible disease modification by bronchodilator therapy in younger patients with COPD [24]. Collectively, these findings support the urgent need for randomised clinical trials in young COPD patients [11]. CC16 and CRP levels may help to better define their endo-phenotype [45] and potentially guide a differential use of anti-inflammatory treatment in young (less inflamed) and old (more inflamed) COPD patients, although this is a hypothesis that requires research [11]. Notably, the level of circulating eosinophils, a biomarker currently recommended for guiding therapy in COPD [45–47], was significantly lower in young *versus* old COPD patients (figure 3).

Strengths and limitations

The comparison of young COPD patients, young controls with normal spirometry of similar age (both smokers and nonsmokers) and older COPD patients, both cross-sectionally and longitudinally, are strengths of our study. Likewise, we believe that this is the first study to contrast a panel of circulating biomarker among these three groups of subjects. On the other hand, we acknowledge several potential limitations including its relatively small sample size, that we studied only smoking-related COPD [18, 19] and no other COPD etiotypes [48], that ECLIPSE did not include GOLD grade 1 patients, that information on early life factors such as low birthweight and prematurity or socioeconomic status, among others, that may influence/promote reduced peak lung function in early adulthood [2, 5, 49] was not collected, and that ECLIPSE did not include patients from low-income countries. Likewise, 3-year follow-up may be too short to fully assess lung function trajectories over time and survival bias in old COPD patients can be a major confounding factor, although recent research has shown that young individuals with reduced peak lung function can die prematurely [32]. Accordingly, these observations would need validation in independent cohorts that address these limitations.

Conclusions

The burden of disease in young COPD patients is substantial; they are at risk of significant lung function decline over time, and they are associated with a distinct pattern of circulating biomarkers, particularly characterised by decreased levels of the circulating pneumoprotein CC16 (suggesting more lung damage) and a less pro-inflammatory pattern (*e.g.* CRP) than older COPD patients. Collectively, these results indicate that young COPD patients deserve early diagnosis, careful monitoring and prompt specific therapeutic intervention following appropriately designed randomised controlled trials [26, 42, 50].

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Data availability: Study protocol and main results have been extensively published before. This is a new analysis of the original ECLIPSE database. Data sharing should be requested from GSK.

This study is registered at www.clinicaltrials.gov with identifier number NCT00292552.

Ethics statement: The ECLIPSE study was approved by the Ethics Committees of all participating institutions.

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