

# Characteristics of Current Smokers versus Former Smokers with COPD and Their Associations with Smoking Cessation Within 4.5 Years: Results from COSYCONET

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**Background:** Many patients with chronic obstructive pulmonary disease (COPD) continue smoking. We used data from the “real-life” COSYCONET COPD cohort to evaluate whether these patients differed from patients with COPD who either had ceased smoking prior to inclusion or ceased during the follow-up time of the study.

**Methods:** The analysis was based on data from visits 1–5 (covering 4.5 years), including all patients with the diagnosis of COPD who were either ex-smokers or smokers and categorized as GOLD 1–4 or the former GOLD 0 category. We compared the characteristics of smokers and ex-smokers at baseline (visit 1), as well as the course of lung function in the follow-up of permanent ex-smokers, permanent smokers and incident ex-smokers (smokers at visit 1 who ceased smoking before visit 5). We also identified baseline factors associated with subsequent smoking cessation.

**Results:** Among 2500 patients who were ever-smokers, 660 were current smokers and 1840 ex-smokers at baseline. Smokers were younger than ex-smokers (mean 61.5 vs 66.0 y), had a longer duration of smoking but fewer pack-years, a lower frequency of asthma, higher forced expiratory volume in 1 sec (FEV<sub>1</sub>, 59.4 vs 55.2% predicted) and higher functional residual capacity (FRC, 147.7 vs 144.3% predicted). Similar results were obtained for the longitudinal subpopulation, comprising 713 permanent ex-smokers, 175 permanent smokers, and 55 incident ex-smokers. When analyzing the time course of lung function, higher FRC, lower FEV<sub>1</sub> and the presence of asthma ( $p < 0.05$  each) were associated with incident cessation prior to visit 5, while less airway obstruction was associated with smoking continuation.

**Conclusion:** These findings, which were consistent in the cross-sectional and longitudinal analyses, suggest that lung hyperinflation was associated with being or becoming ex-smoker. Possibly, it is perceived by patients as one of the factors motivating their attempts to quit smoking, independent from airway obstruction.

**Keywords:** COPD, smoking, smoking cessation, airway obstruction, lung hyperinflation

## Introduction

Despite tobacco smoking being recognized as a major cause of chronic obstructive pulmonary disease (COPD),<sup>1,2</sup> a surprisingly high number of patients with COPD continue to smoke.<sup>3</sup> Even in longitudinal study cohorts, in which one could expect above-average insight into the causes and driving factors of COPD, a significant proportion continues smoking.<sup>4</sup> Many studies have compared non-smoking healthy subjects, smokers without the diagnosis of COPD,<sup>5</sup> and COPD patients who were ex-smokers or current smokers,<sup>6–9</sup> while the number of studies specifically comparing smokers and ex-smokers with COPD is limited.<sup>10,11</sup>

Given the high percentage of current smokers among COPD patients, the question naturally arises as to how patients who have stopped smoking differ from those who continue smoking. The second question is whether clinical and functional characteristics are associated with an increased or decreased likelihood to stop smoking in the future. To address these questions, the COPD cohort COSYCONET (COPD and Systemic Consequences – Comorbidities Network)<sup>4</sup> seems well suited, as it comprises a large number of patients, a follow-up over several years, and a broad panel of clinical and functional indices. The present analysis used data from this cohort with a follow-up time of 4.5 years, to address the topic in four ways. We performed (1) a cross-sectional comparison of ex-smokers and current smokers at baseline, (2) a cross-sectional comparison of patients who remained ex-smokers, or ceased smoking within the follow-up period, or remained smokers, (3) a longitudinal description of the time course of lung function during follow-up for these groups, and (4) we sought to identify baseline characteristics associated with the transition from smoker to ex-smoker during the follow-up.

## Methods

### Study Population

COSYCONET is an ongoing, long-term, observational multi-center cohort of patients with COPD. Patients of Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1 to 4 were included, as well as patients of the former GOLD grade 0 referring to patients with chronic bronchitis without fulfilling the spirometric criterion forced expiratory volume in 1 s to forced vital capacity ratio ( $FEV_1/FVC$ )  $<0.7$ .<sup>12</sup> Details of the COSYCONET study design, baseline characteristics, and in- and exclusion criteria have been described previously.<sup>4</sup> Follow-up visits were conducted at 6, 18, 36 and 54 months after enrolment (visits 2 to 5). The analysis comprised two study populations, first that of visit 1 for cross-sectional analysis, and second that of patients remaining in the study until visit 5 for longitudinal analysis. COSYCONET was approved by the ethics committees of all study centers and conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent. ClinicalTrials.gov: NCT01245933.

### Assessments

Baseline characteristics including age, sex, body mass index (BMI) and post-bronchodilator lung function values. We measured  $FEV_1$  and FVC following recommendations and used Global Lung Function Initiative (GLI) equations to express the results as % predicted in order to facilitate interpretation.<sup>13</sup> Body plethysmography was used to determine functional residual capacity (FRC) and residual volume (RV), using European Coal and Steel Community (ECSC) reference values.<sup>14</sup> Single-breath diffusing capacity for carbon monoxide (CO) included the transfer factor (TLCO) and its coefficient (KCO, ratio of TLCO to alveolar volume), expressed as % predicted relative to GLI reference values.<sup>15</sup> In addition, 6-minute walking distance (6MWD) was assessed following a standard protocol,<sup>4</sup> expressed as percent of published predicted values.<sup>16</sup>

Patients were categorized into spirometric GOLD grades 0 ( $FEV_1/FVC \geq 0.7$ ) or 1 to 4 ( $FEV_1/FVC < 0.7$ ), and as GOLD groups A, B or E based on symptoms assessed via the modified Medical Research Council (mMRC) dyspnea scale.<sup>2</sup> Besides the COPD Assessment Test (CAT),<sup>17–19</sup> we used the Saint George's Respiratory Questionnaire (SGRQ) including its Activity, Impact and Symptoms domains<sup>20</sup> for the assessment of disease-related quality of life.<sup>21</sup> The assessment of self-reported comorbidities was based on patient-reported physician-based diagnoses<sup>22,23</sup> and included asthma, cardiac failure and coronary artery disease; the latter two were combined into cardiac disease.<sup>24</sup> These two comorbidities were chosen, as their presence might be hypothesized to be associated with the likelihood of smoking cessation. The ankle-brachial index (ABI) was used as a marker of peripheral vascular state.<sup>25</sup>

## Smoking History and Status

A detailed smoking history was assessed upon enrolment. History included total years of smoking, pack-years, the age at initiation and since quitting, as well as whether parents had smoked or there were other smokers in the household. Patients were categorized at baseline into current and ex-smokers; never-smokers were excluded from the present analysis and have been characterized in this cohort previously.<sup>26</sup> Smoking status was assessed at each visit until visit 5. Based on this, the group of incident ex-smokers could be defined as patients who were smokers at visit 1 and reported smoking cessation at visit 5.

## Study Questions

First, baseline characteristics of active and previous smokers at enrolment were compared. Second, we used the follow-up data and compared baseline characteristics in the three groups of permanent ex-smokers, permanent smokers, and incident ex-smokers. This was done in order to test the consistency of our findings between data upon inclusion and data after follow-up. Third, the course of lung function over follow-up was analyzed for these three groups. Fourth, factors at baseline were identified that were associated with smoking cessation during follow-up.

## Statistical Analysis

For descriptive purposes, mean values and standard deviations (SD) or numbers and percentages are given, depending on the type of data. Differences between two groups were analyzed using non-parametric Mann–Whitney-U statistics, in case of categorical variables using Fisher's exact for  $2 \times 2$  tables. In case of more than three groups or categories, chi-square statistics were computed, or the Kruskal–Wallis test was applied, with Bonferroni-adjusted post hoc comparisons via the Mann–Whitney-U-test. Mixed linear models (GLM) with repeated-measures design and logit link (equivalent to longitudinal logistic regression analysis) were used to examine the time course of lung function in relation to smoking status. To identify predictors of smoking cessation during follow-up, binary logistic regression analysis was used, taking patient characteristics at visit 1 as predictors and the transition from smoker to incident ex-smoker until visit 5 as binary outcome. For all computations, the software package IBM SPSS Statistics (Version 26.0.0.0, Armonk, NY, USA) was employed.

## Results

### Study Population

COSYCONET enrolled 2741 patients with a diagnosis of COPD at visit 1, with GOLD grades available for 2721 patients (Figure 1). A total of 217 patients were never-smokers, with smoking history not available for 4 patients; these were excluded. The remaining 2500 patients comprised 660 active smokers and 1840 ex-smokers, with 363 categorized as former GOLD 0. At visit 5, 943 patients remained in the study.

### Comparison of Ex-Smokers and Current Smokers at Baseline

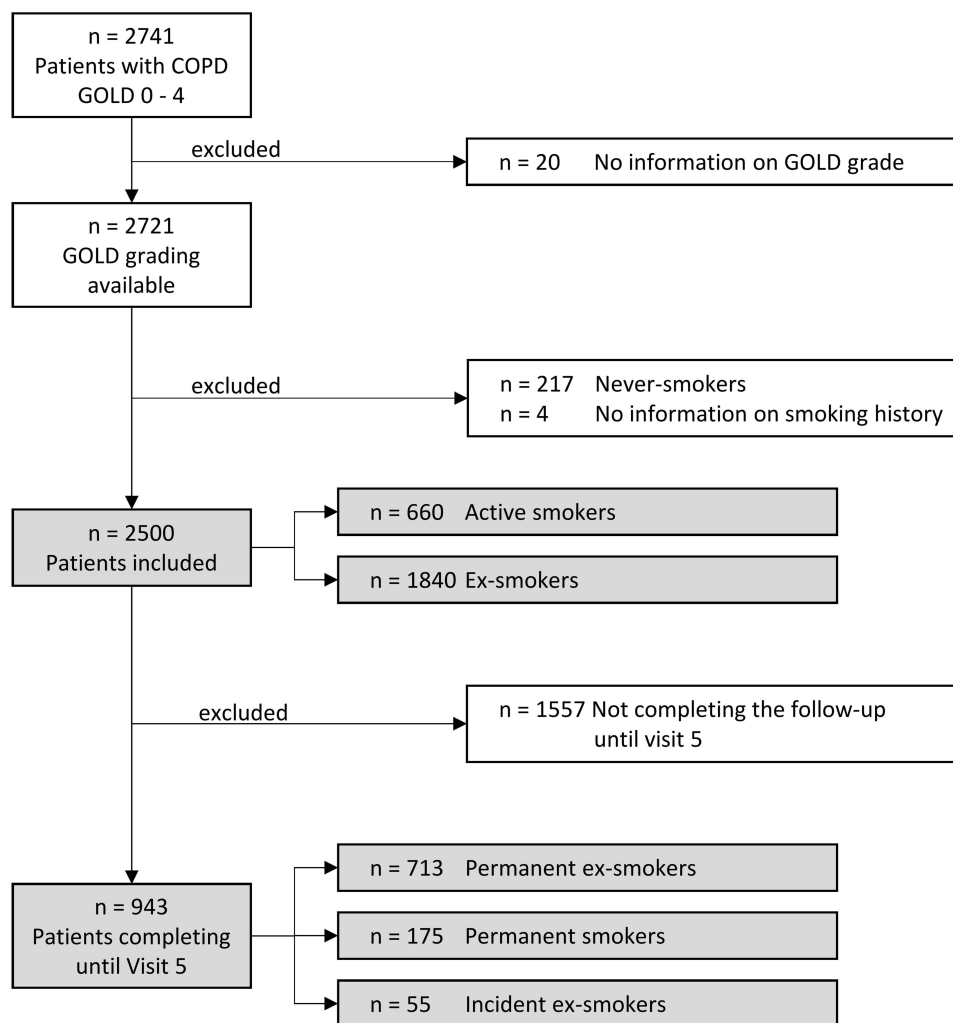
#### Smoking History

On average, current smokers had a lower number of pack-years ( $p < 0.001$ ) but a longer duration of smoking ( $p < 0.001$ ) and started smoking at a younger age ( $p = 0.013$ ) than ex-smokers (Table 1). Ex-smokers had ceased smoking on average (SD) 13.2 (12.7) years prior to enrolment. The status of active versus ex-smoker significantly ( $p < 0.001$ ) was associated with the number of parents who had smoked. When none had smoked, the percentage of active smokers was 21.1%, when one had smoked, 26.2%, and when both had smoked, 34.6%. The proportion of current smokers was also higher if other persons in the household smoked (46.0% vs 21.7%,  $p < 0.001$ ).

#### Clinical and Functional Characteristics

Current smokers were more likely to be female than ex-smokers ( $p < 0.001$ , Table 1), were on average about 4.5 years younger than ex-smokers ( $p < 0.001$ ) and had a lower BMI ( $p < 0.001$ ). There were also differences in the distribution of GOLD grades and groups ( $p < 0.001$ ), with grades 3 and 4 and group E being less common in active smokers.

FEV<sub>1</sub> % predicted, FVC % predicted, FEV<sub>1</sub>/FVC, FRC % predicted and RV % predicted were all significantly higher in smokers, while KCO % predicted was lower ( $p < 0.05$  each, Table 1). There were no significant differences in TLCO % predicted. ABI was significantly lower in smokers compared to ex-smokers ( $p = 0.005$ ). CAT total score did not significantly



**Figure 1** Flow chart of study population. Grey boxes indicate the study populations.

differ between groups (Table 1). SGRQ total score ( $p = 0.004$ ) and the Activity domain ( $p < 0.001$ ) were lower (ie, better) in current smokers than ex-smokers, whereas the Symptoms domain was higher (ie, worse;  $p < 0.001$ ). There were no significant differences in the proportion of asthma or cardiac disease. 6MWD % predicted did not differ between smokers and ex-smokers ( $p = 0.23$ ).

## Comparison of Baseline Characteristics of Permanent Ex-Smokers, Permanent Smokers and Incident Ex-Smokers

### Smoking Status

None of the ex-smokers at visit 1 started smoking during follow-up. Among the 943 patients at visit 5, 713 were permanent ex-smokers, 175 permanent smokers, and 55 incident ex-smokers (Table 2). Among the incident ex-smokers, the numbers of patients who had stopped smoking at visits 2, 3, 4 and 5, were 15, 40, 48, and 55, respectively.

According to post-hoc comparisons, the average smoking pack-years at baseline were higher in the permanent ex-smokers than the two other groups, while their total years of smoking were smallest ( $p < 0.001$ ). With two smoking parents, the proportion of permanent smokers was higher and that of permanent ex-smokers lower than if either none or one of the parents had smoked ( $p = 0.020$ ). In addition, the proportion of permanent smokers was highest if other persons in the household were current smokers ( $p < 0.001$ ), whereas the likelihood of quitting smoking was highest when no other persons in the household smoked ( $p = 0.032$ ).

**Table 1** Patient Characteristics at Visit 1

Variable	All Patients n = 2500	Ex-Smokers n = 1840	Current Smokers n = 660	p value
Age (y)	64.8 ± 8.5	66.0 ± 8.4	61.5 ± 8.0	<0.001
Height (cm)	170.9 ± 9.0	171.0 ± 8.9	170.5 ± 9.4	0.194
Sex (m/f) (%)	1520/980 (60.8/39.2%)	1159/681 (63.0/37.0%)	361/299 (54.7/45.3%)	<0.001
BMI (kg/m <sup>2</sup> )	27.1 ± 5.4	27.4 ± 5.3	26.3 ± 5.7	<0.001
Years of smoking (y)	37.4 ± 12.1	34.9 ± 12.5	44.2 ± 7.8	<0.001
Pack-years	56.3 ± 36.5	59.3 ± 38.2	42.8 ± 23.7	<0.001
Age at smoking initiation (y)	17.7 ± 4.4	17.9 ± 4.3	17.4 ± 4.7	0.013
FEV <sub>1</sub> % predicted	56.3 ± 21.0	55.2 ± 21.2	59.4 ± 19.9	<0.001
FVC % predicted	78.6 ± 19.0	77.7 ± 19.2	81.1 ± 18.4	<0.001
FEV <sub>1</sub> /FVC	0.548 ± 0.137	0.542 ± 0.139	0.567 ± 0.129	<0.001
FRC % predicted	145.2 ± 37.6	144.3 ± 39.0	147.7 ± 33.2	0.002
RV % predicted	167.7 ± 53.2	167.0 ± 54.9	169.4 ± 48.4	0.024
TLCO % predicted	58.3 ± 22.2	58.5 ± 22.8	58.0 ± 20.5	0.747
KCO % predicted	65.2 ± 23.0	66.5 ± 23.6	61.6 ± 20.8	<0.001
ABI	1.18 ± 0.15	1.19 ± 0.14	1.17 ± 0.15	0.005
6MWD (% predicted)	65.6 ± 16.4	65.2 ± 16.8	66.4 ± 15.4	0.230
Cardiac disease	522 (20.9%)	394 (21.4%)	128 (19.4%)	0.289
Asthma	421 (16.8%)	322 (17.5%)	99 (15.0%)	0.146
CAT score	18.0 ± 7.4	18.0 ± 7.3	18.2 ± 7.4	0.504
SGRQ Total	42.9 ± 20.1	43.6 ± 20.2	40.9 ± 19.7	0.004
Activity	57.2 ± 26.2	59.4 ± 26.1	51.0 ± 25.5	<0.001
Impact	30.0 ± 20.8	30.5 ± 21.1	28.7 ± 19.9	0.098
Symptoms	55.4 ± 21.3	54.0 ± 21.1	59.1 ± 21.4	<0.001
GOLD grades 0–4	363/191/887/824/235 14.5/7.6/35.5/33.0/9.4%	266/129/612/634/199 14.5/7.0/33.3/34.5/10.8%	97/62/275/190/36 14.7/9.4/41.7/28.8/5.5%	<0.001
GOLD group A/B/E	1005/602/884 40.3/24.2/35.5%	692/458/685 37.7/25.0/37.3%	313/144/199 47.7/22.0/30.3%	<0.001

**Notes:** P values refer to the comparison of the smoker and ex-smoker groups using the Mann–Whitney-U-test. Mean values and standard deviations or numbers and percentages are given.

**Abbreviations:** BMI, body-mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; RV, residual volume; TLCO, carbon monoxide transfer factor; KCO, transfer factor coefficient (ratio of TLCO to alveolar volume); ABI, ankle-brachial index; 6MWD, 6-minute walking distance; CAT, COPD Assessment Test; SGRQ, Saint George's Respiratory Questionnaire; GOLD, Global Initiative for Chronic Obstructive Lung Disease; cardiac disease comprises cardiac failure and coronary artery disease.

## Clinical and Functional Characteristics

Groups did not significantly differ in the distributions of sex or GOLD groups, but there was a difference ( $p < 0.001$ ) in spirometric GOLD grades, with grades 3 and 4 being less frequent in permanent smokers. Age was highest in the group of permanent ex-smokers ( $p < 0.001$ ). FEV<sub>1</sub>% predicted, FVC % predicted, FEV<sub>1</sub>/FVC, FRC %

**Table 2** Patient Characteristics at Visit 1 of the Longitudinal Cohort with Follow-Up Until Visit 5

	Permanent Ex-Smokers n = 713	Permanent Smokers n = 175	Incident Ex-Smokers n = 55	p value
Age (y)	64.8 ± 8.0 **, **	59.8 ± 7.7	60.8 ± 7.3	<0.001
Height (cm)	171.3 ± 8.7	170.9 ± 9.9	171.8 ± 7.6	0.884
Sex (m/f)	437/276 (61.3/38.7%)	95/80 (54.3/45.7%)	29/26 (52.7/47.3%)	0.137
BMI (kg/m <sup>2</sup> )	27.4 ± 5.1	26.9 ± 5.2	26.1 ± 5.0	0.114
Years of smoking (y)	34.0 ± 11.9 **, **	42.8 ± 7.8	43.1 ± 6.4	<0.001
Pack-years	59.5 ± 38.2 **, **	43.1 ± 20.2	35.7 ± 20.0	<0.001
Age at smoking initiation (y)	17.8 ± 4.1 *	17.0 ± 4.1	17.7 ± 4.4	0.014
FEV <sub>1</sub> % predicted	60.1 ± 20.0	67.6 ± 17.9 *, ***, **	57.0 ± 20.0	<0.001
FVC % predicted	82.4 ± 17.6	87.1 ± 16.7 *	82.1 ± 19.2	0.011
FEV <sub>1</sub> /FVC	0.560 ± 0.129	0.608 ± 0.122 *, ***, **	0.535 ± 0.114	<0.001
FRC % predicted	138.5 ± 34.4	140.2 ± 28.6	160.7 ± 33.2 **, ***, **	<0.001
RV % predicted	159.3 ± 48.3	159.2 ± 42.6	184.9 ± 47.3 **, ***, **	<0.001
TLCO % predicted	62.8 ± 22.0	65.2 ± 20.6	61.3 ± 17.3	0.113
KCO % predicted	69.8 ± 22.9	68.0 ± 22.1	64.5 ± 15.9	0.168
ABI	1.20 ± 0.14	1.18 ± 0.14	1.20 ± 0.12	0.594
6MWD (% predicted)	69.6 ± 14.4	71.0 ± 15.3	70.0 ± 11.9	0.543
Cardiac disease	134 (18.8%)	27 (15.4%)	10 (18.2%)	0.585
Asthma	135 (18.9%)	14 (8.0%)	14 (25.5%)	0.001
CAT total score	16.9 ± 7.0	17.4 ± 6.9	17.7 ± 7.4	0.602
SGRQ Total	38.6 ± 18.7	37.2 ± 18.4	38.5 ± 21.1	0.680
Activity	53.0 ± 25.5 *	44.1 ± 24.9	48.5 ± 25.7	<0.001
Impact	25.6 ± 18.8	26.1 ± 19.1	26.2 ± 20.8	0.959
Symptoms	51.7 ± 20.8 *	57.8 ± 19.7	57.2 ± 23.8	0.001
GOLD grade 0–4	107/73/284/211/38 15.0/10.2/39.8/29.6/5.3%	33/25/87/28/2 18.9/14.3/49.7/16.0/1.1%	3/6/26/17/3 5.5/10.9/47.3/30.9/5.5%	0.001
GOLD group A/B/E	330/151/232 46.3/21.2/32.5%	98/33/43 56.3/19.0/24.7%	31/11/13 56.4/20.0/23.6%	0.105

**Notes:** P values refer to the comparison of the three groups using the Kruskal–Wallis-test, with Bonferroni-adjusted post hoc comparisons at an overall significance level of 0.05 (\* permanent ex-smokers vs permanent smokers, \*\* permanent ex-smokers vs incident ex-smokers, \*\*\* permanent smokers vs incident ex-smokers). Mean values and standard deviations or numbers and percentages are given.

**Abbreviations:** BMI, body-mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; RV, residual volume; TLCO, carbon monoxide transfer factor; KCO, transfer factor coefficient (ratio of TLCO to alveolar volume); ABI, ankle-brachial index; 6MWD, 6-minute walking distance; CAT, COPD Assessment Test; SGRQ, Saint George's Respiratory Questionnaire; GOLD, Global Initiative for Chronic Obstructive Lung Disease; cardiac disease comprises cardiac failure and coronary artery disease.

predicted and RV % predicted differed significantly between the three groups ( $p < 0.05$  each), while BMI, TLCO % predicted, KCO % predicted, 6MWD % predicted and ABI did not. The results of adjusted pairwise comparisons are indicated in Table 2.

The three groups also did not differ significantly in terms of CAT score or SGRQ total score or Impact domain. In contrast, the SGRQ Symptom domain was highest (ie, worst) and the Activity domain lowest (ie, best) in the permanent smokers ( $p < 0.001$ ). Asthma was much more frequent in incident ex-smokers compared to permanent smokers ( $p = 0.001$ ; Table 2).

## Time Course of FEV<sub>1</sub> and FRC During Follow-Up for Permanent Ex-Smokers, Permanent Smokers, or Incident Ex-Smokers

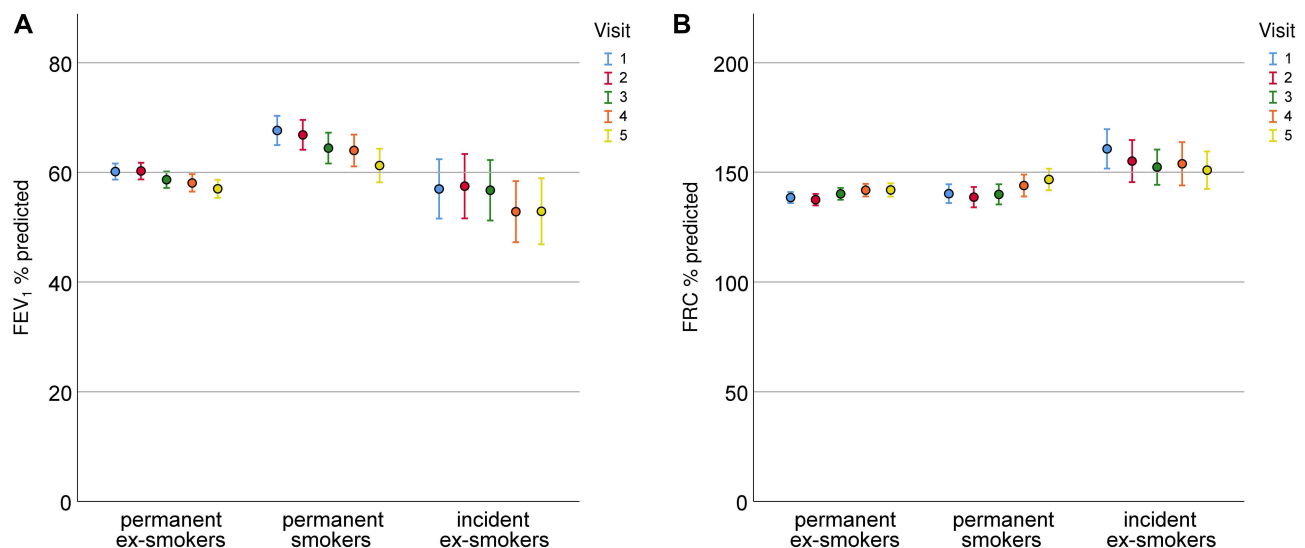
FEV<sub>1</sub>% predicted and FRC % predicted were selected to monitor the time course of lung function (Figure 2A and B, respectively). The initially higher value of FEV<sub>1</sub>% predicted in permanent smokers was maintained over 4.5 years; incident ex-smokers had the highest average FRC % predicted, especially upon inclusion.

Analysis by a generalized linear model including visit, age and group as well as an interaction between visit and group confirmed that in the group of permanent smokers, the FEV<sub>1</sub> rate of decline over time was greater than in permanent ex-smokers ( $p < 0.001$ ), while it was similar to that of incident ex-smokers. Regarding FRC % predicted, the elevated baseline values in incident ex-smokers was confirmed ( $p < 0.001$ ), with its rate of decline over time differing from those of the other two groups ( $p < 0.001$  each).

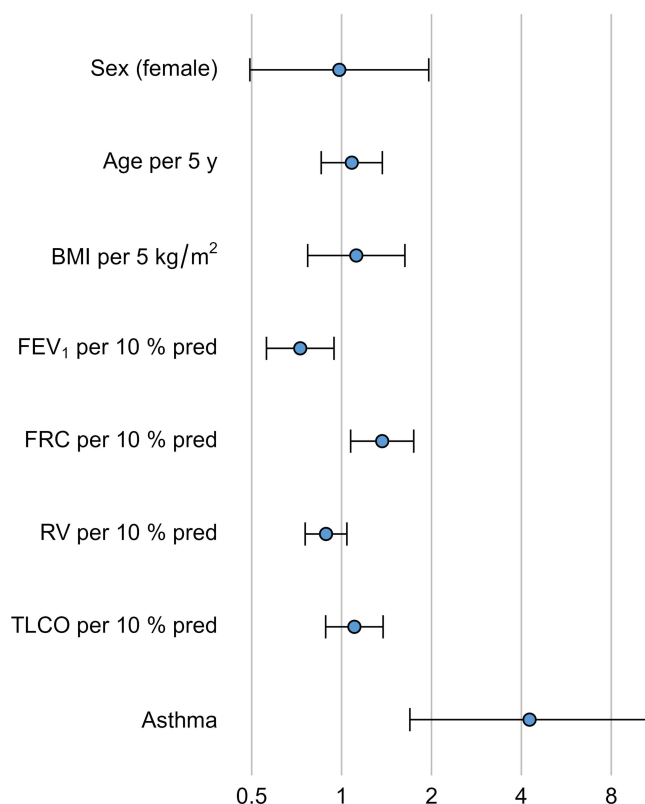
## Identification of Predictors of Smoking Cessation During Follow-Up

Using logistic regression analysis, we aimed to identify characteristics at visit 1 that were related to smoking cessation or maintenance at visit 5. In order to avoid complications from the inclusion of correlated predictors, a stepwise approach was used, comprising the separate analysis of different sets of potentially relevant predictors. We first included the SGRQ domains and GOLD groups as simultaneous predictors. These variables had no predictive value for smoking cessation. In the next step, lung function variables were analyzed, using FEV<sub>1</sub>% predicted, FRC % predicted, RV % predicted and TLCO % predicted as simultaneous predictors, together with age, sex and BMI, to cover different aspects of respiratory function. Only FEV<sub>1</sub>% predicted and FRC % predicted were significantly ( $p < 0.05$ ) associated with smoking cessation. When using comorbidities as predictors, only asthma was significant ( $p = 0.001$ ).

Finally, we combined the four lung function parameters, age, sex, BMI and asthma diagnosis in order to reveal whether they were statistically independent predictors. FEV<sub>1</sub>% predicted ( $p = 0.016$ ), FRC % predicted ( $p = 0.012$ ) and a history of asthma ( $p = 0.002$ ) were again significantly associated with smoking cessation (Figure 3). The odds for smoking cessation within 4.5 years were increased by factor 4.26 (95% CI: 1.69, 10.72) in individuals with a diagnosis of



**Figure 2** (A) Time course of FEV<sub>1</sub>% predicted in permanent ex-smokers, permanent smokers and incident ex-smokers over visits 1 to 5. (B) Time course of FRC % predicted in permanent ex-smokers, permanent smokers and incident ex-smokers over visits 1 to 5. Mean values and 95% confidence intervals are shown. Only patients remaining in the study until visit 5 were included in this graph.



**Figure 3** Variables associated with smoking cessation within the follow-up period of 4.5 y. Only patients who were smokers at visit 1 were included, and odds ratios and their 95% % confidence intervals are given for the various predictors at visit 1. BMI = body mass index, FEV<sub>1</sub> = forced expiratory volume in 1 s, FRC = functional residual capacity, RV = residual volume, TLCO = diffusing capacity of the lung for carbon monoxide. The odds ratios refer to characteristics of patients at visit 1 in terms of the number of units as indicated and relative to the mean of the whole study population.

asthma at visit 1, by 1.37 (1.07, 1.74) for a 10% higher value in FRC % predicted, and by 1.38 (1.06, 1.78) for a 10% lower value in FEV<sub>1</sub>% predicted.

## Discussion

This study addressed the question which characteristics are shown by patients with COPD who still smoke. For this purpose, we compared patients who continued smoking with those who either had stopped smoking in the past or during a 4.5-year follow-up. When comparing smokers with ex-smokers upon inclusion, smokers had better spirometric lung function and reported more respiratory symptoms in terms of the SGRQ symptoms domain, but less burden from the disease as reflected in the Activity domain. Compared to ex-smokers, their smoking was less intense as indicated by the lower number of pack-years with longer duration of smoking.

Over the follow-up period, patients who were still smoking 4.5 years after inclusion showed the lowest airway obstruction in terms of FEV<sub>1</sub> upon inclusion and over the follow-up time, whereas obstruction was similar in those who quit and those who had quit before. In contrast, lung hyperinflation in terms of FRC was similar in permanent smokers and permanent ex-smokers. Those who quit during the study (incident ex-smokers) showed the highest degree of hyperinflation at all visits, with a slight improvement over time (see Figure 2). In addition, the comorbidity asthma correlated with a higher probability of becoming ex-smoker. It therefore seemed that patients with COPD who continued smoking were those with less airway obstruction and lower frequency of asthma, whereas patients who stopped smoking had higher lung hyperinflation and obstruction and more often asthma.

The fact that so many patients with COPD continue to smoke seems especially astonishing in patients who participate in a long-term study, such as COSYCONET, as one might assume a greater-than-average awareness of the role of smoking in these patients. None of the ex-smokers upon inclusion became smokers, while during the follow-up 24% of



230 smokers stopped smoking and remained ex-smokers. We did not have detailed information on the participation in smoking cessation programs over the follow-up, but at the time of visit 5, 16% of permanent ex-smokers, 26% of permanent smokers and 33% of incident ex-smokers reported to have ever participated in a smoking cessation program, with no significant difference between permanent smokers and incident ex-smokers (Fisher's exact test). The observation that the majority of these cessations (49/55) occurred until visit 3, ie in the first third of the 4.5-year follow-up period, seems to support the assumption that the participation in the cohort study was a large motivating factor in cessation.

The observation that patients who quit smoking during the observation period showed markedly higher lung hyperinflation than those who continued smoking is of special interest. These patients also showed more hyperinflation than those who had already ceased smoking. On the other hand, they had a similar degree of airway obstruction as those who already had ceased smoking upon inclusion. The association between a high degree of lung hyperinflation and a higher likelihood to quit smoking was confirmed by the multiple regression analysis, while other potential determinants, ie elevated residual volume and impaired diffusing capacity, did not play a role.

In the absence of imaging data, we cannot determine whether hyperinflation also indicated a higher degree of lung emphysema, but the observation of a lower KCO in smokers and a tendency for lower KCO in permanent smokers would be compatible with this assumption. In addition, upon inclusion, ABI showed worse values in current smokers than ex-smokers. While KCO was adjusted for age by the use of predicted values, this was not the case for ABI. To elucidate the difference, we performed an additional regression analysis of the baseline data using the two groups of smokers vs ex-smokers, age, sex and FEV<sub>1</sub>% predicted as predictors. As a result, the small unadjusted difference in ABI of 0.021 units (Table 1) increased to 0.035 units when accounting for the covariates including age and airway obstruction, which are known to have an association with ABI.<sup>25</sup> Thus, the vascular impairment in smokers was more pronounced than indicated by the raw data, in line with the hypothesis that smoking has particularly adverse effects on the vascular system, as reflected by ABI and KCO in our study.

Importantly, the association of elevated FRC and lower FEV<sub>1</sub> with smoking cessation during follow-up was consistent with the findings regarding the baseline data (Figure 2, Table 1). It is important to note that in COPD not only obstruction but especially hyperinflation is a key determinant of dyspnea, particularly upon exertion, and that in many studies a reduction in lung hyperinflation by medical intervention has been found to be linked to improvements of dyspnea and exercise capacity.<sup>27–29</sup>

We do not believe that the lack of data on the patients' psychological characteristics or their participation in smoking cessation programs invalidates our findings, since it is unlikely that the willingness to participate in such programs, or their success, or unknown social or psychological factors were, just by chance, correlated precisely with hyperinflation and obstruction. It seems more likely that the functional parameters were major determinants of the patients' perceptions of their disease state and that these perceptions were linked to the attempts and success of cessation. Our finding is novel in demonstrating the independent role of lung hyperinflation as potential objective marker of the likelihood of smoking cessation, beyond the degree of airway obstruction.

When tentatively introducing three categories of education as covariates into the comparisons of groups,<sup>26</sup> no significant associations were found (data not shown). However, the presence of smokers in the household was associated with smoking cessation, even within the follow-up time of 4.5 years. Given the fact that smoking cessation occurred more often when none of the other persons in the household smoked, the role of social factors in the continuation of habits such as smoking is underlined. The differences in the age at which smoking had been started were small and could not explain or predict smoking habits in the cohort. Among comorbidities, only asthma was associated with smoking cessation during follow-up. We do not know whether this was due to the medical information gained by the patients through participation in the study, but this might be a possibility.

The differences in the distribution of GOLD grades and groups were consistent with the general results that smokers at baseline and permanent smokers over the follow-up experienced fewer limitations from their COPD. In both the cross-sectional and the longitudinal analyses, the CAT sum score did not significantly differ between groups. The SGRQ Activity domain was higher (ie, worse) in the incident ex-smokers compared to the permanent smokers, and also higher in ex-smokers than current smokers, suggesting some association between smoking cessation and disease-related quality

of life. This, however, was not strong enough to be significant in the multiple logistic regression analysis. Interestingly, exacerbation risk in terms of GOLD group E did not play a role.

Criteria for the diagnosis and categorization of COPD are well established.<sup>1,2</sup> Especially, for the analysis of smoking habits, however, it seems reasonable to extend this population by including subjects with symptoms and clinical characteristics of COPD, even though they do not satisfy the functional criterion required by the classical definition.<sup>30</sup> This comprises the group of patients “at risk” or “GOLD 0”<sup>31,32</sup> in general and its subgroup with “preserved ratio impaired spirometry” (PRISm),<sup>12</sup> among which patients with early COPD may be found.<sup>33</sup> We therefore included these patients in the current analysis. The numbers of patients categorized as PRISm or GOLD 0 were, however, too low to allow for a meaningful separate analysis over the follow-up period.

## Limitations

This study comprised cross-sectional and longitudinal elements, the major results of which were consistent. Despite this, a larger study population and a longer follow-up time would have allowed an analysis of the associations between patient characteristics and smoking habits in more detail, potentially including the interference with medication. In addition, more detailed information on attempts to quit smoking from previous times as well as during the follow-up might have been helpful, as well as information on the Fagerstrom test to quantify the degree of nicotine dependence. The asthma diagnosis was based on patient-reported physicians’ diagnoses and medication,<sup>24</sup> and this approach has been successfully used in previous analyses of COSYCONET data.<sup>34</sup> Despite this, it might have been helpful to have had additional markers such as blood eosinophils, but such data were not available in sufficient completeness in the present study population.

## Conclusion

Based on data from a large “real-life” COPD cohort, we found that patients who continued smoking were younger and had a longer duration of smoking but fewer pack-years than ex-smokers. They also had less airway obstruction, but more lung hyperinflation. Consistent with this, in the follow-up a higher degree of hyperinflation was associated with a higher likelihood of smoking cessation, independent from airway obstruction. In addition, the presence of asthma was relevant, while a low degree of airway obstruction was associated with continuation of the smoking habit. These findings suggest that lung hyperinflation may be perceived by patients as major functional deterioration that favors smoking cessation in addition to airway obstruction.

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The study was based on patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933). For further information see 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.

## Data Sharing Statement

COSYCONET is an ongoing, long-term, multi-center observational study the data of which are not intended to be available without demand. If there is interest in the analysis of specific questions, however, there is a formalized procedure for submitting an application to the study office, which will be evaluated by the steering committee on scientific grounds. There is no limitation for this application except proven expertise in COPD studies.

## Ethics Approval and Consent to Participate

The study protocol was approved by the central ethical committee in Marburg (Ethikkommission FB Medizin Marburg) and the respective local ethical committees: Bad Reichenhall (Ethikkommission Bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät Duisburg-Essen); Gießen (Ethikkommission Fachbereich Medizin); Greifswald (Ethikkommission Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik (Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Saarbrücken); Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig); Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz (Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting (Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-Alexander-Universität Erlangen Nürnberg); Rostock (Ethikkommission Universität Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmalleberg (Ethikkommission Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg). The study was performed in accordance with the declaration of Helsinki, and all participants gave their written informed consent.

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## Author Contributions

All authors of this manuscript meet all of the following criteria required for authorship, as they 1) made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas, 2) have drafted or written, or substantially revised or critically reviewed the article, 3) have agreed on the “International Journal of COPD” as the Journal to which the article was submitted, 4) reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage, and 5) agree to take responsibility and be accountable for the contents of the article.

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