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Risk for COPD with Obstruction of Active Smokers with Normal Spirometry and Reduced Diffusion Capacity

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Abstract

Background—Smokers are assessed for COPD using spirometry, with COPD defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as airflow limitation not fully reversible with bronchodilators. There is a subset of smokers with normal spirometry (by GOLD criteria), who have a low diffusion capacity (DLCO), a parameter linked to emphysema and small airway disease. The natural history of these “normal spirometry/low DLCO” smokers is unknown.

Methods—From a cohort of 1570 smokers in the New York City metropolitan area, all of whom had normal spirometry, two groups were randomly selected for lung function follow-up: smokers with normal spirometry/normal DLCO (n=59) and smokers with normal spirometry/low DLCO (n=46). All had normal history, physical examination, CBC, urinalysis, HIV status, α1-antitrypsin level, chest X-ray, FEV1, FVC, FEV1/FVC ratio and total lung capacity (TLC). Throughout the study, all continued to be active smokers.

Findings—In the normal spirometry/normal DLCO group assessed over 45 ± 20 months, 3% developed GOLD-defined COPD. In contrast, in the normal spirometry/low DLCO group, followed over 41 ± 31 months, 22% developed GOLD-defined COPD.

Interpretation—Despite appearing “normal” by GOLD, smokers with normal spirometry but low DLCO are at significant risk for developing COPD with obstruction to airflow.

Introduction

Chronic obstructive pulmonary disease (COPD), the 3rd leading cause of mortality in the US and Europe, is caused primarily by cigarette smoking [1-3]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a chronic disease state

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characterized by airflow limitation not fully reversible with bronchodilators [1,2]. The GOLD criteria classify COPD into 4 stages based on post-bronchodilator forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) [2]. With these criteria, if smokers have normal post-bronchodilator spirometry, they are considered to have normal lung function. While the evaluating physician will counsel the patient to stop smoking, the normal post-bronchodilator spirometry reassures both the patient and the physician that the patient does not have COPD and is at no higher risk for COPD than other smokers with normal post-bronchodilator spirometry.

Although the GOLD criteria are widely used [1,4-6], it has been recognized that some smokers with normal spirometry have low diffusion capacity (DLCO), a parameter associated with alveolar destruction and possibly small airways disease both components of COPD [7-10]. The DLCO measurement is not part of the GOLD criteria and is not used as a routine screening tool because of the lack of portability, cost of the equipment, the expertise to carry out of the measurement, and the time involved [1,11].

In the context that COPD is associated with both airway and alveolar disease [8], we asked: are smokers with normal post-bronchodilator spirometry but low DLCO at greater risk for developing COPD compared to smokers with normal post-bronchodilator spirometry and normal DLCO? To answer this question, we evaluated a group of cigarette smokers who answered advertisements in the New York Metropolitan region for assessment of lung health. After clinical assessment, we characterized 2 groups: “normal spirometry/low DLCO” – smokers with normal post-bronchodilator spirometry and total lung capacity (TLC) but low DLCO; and control “normal spirometry/normal DLCO” – smokers with normal post-bronchodilator spirometry, normal TLC and normal DLCO. A randomly chosen subset of these groups were asked to return for repeated lung function over time. Strikingly, with an average follow-up of <4 yr, compared to smokers with normal spirometry/normal DLCO, a significant number of smokers in the normal spirometry/low DLCO group developed GOLD criteria-defined COPD, i.e., smokers who have normal post-bronchodilator spirometry but low DLCO are at a higher risk for developing COPD with obstruction to airflow compared to smokers with normal post-bronchodilator and normal DLCO.

Methods

Recruitment, Screening and Pulmonary Function Tests

Smokers were recruited from the New York metropolitan area via advertisements in newspapers and websites under a protocol approved by the Weill Cornell Medical College and New York/Presbyterian Hospital Institutional Review Board. Healthy nonsmokers were also recruited to calculate the 95% normal range for PFTs [12]. All subjects gave their informed written consent prior to any clinical evaluations or procedures. The study population was randomly chosen, using screening assessment and inclusion and exclusion criteria as detailed in Supplemental Data. Pulmonary function tests (PFTs) were performed according to ATS/ERS standards [11,13], and PFT machine calibrations were performed at the recommended intervals as described in the ATS/ERS guidelines [11] (see Supplemental Data).

Study Groups and Assessment

A total of 2302 active smokers were assessed. Based on the inclusion/exclusion criteria, a subset of 1570 active smokers were determined to be eligible. Of these, 1173 were phenotyped as “normal spirometry/normal DLCO” and 397 as “normal spirometry/low DLCO” based on their DLCO predication values (see Supplemental Data). A subset of these subjects were randomly contacted and asked to return for additional PFT assessments. The groups assessed over time included 59 smokers with normal spirometry/normal DLCO and 46 smokers with normal spirometry/low DLCO (Supplemental Data, Table I).

Statistical Analysis

Statistical analysis was performed as detailed in Supplemental Data.

Role of the Funding Source

The funding sources of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report or the decision to submit this report for publication.

Results

Study Population

Both the normal spirometry/normal DLCO and the normal spirometry/low DLCO groups had a preponderance of males and individuals of African-American descent, but had a similar distribution of gender, age and ethnicity (Table I). The 2 groups were assessed over a similar time period (Supplemental Figure 1) and the age at the last assessment was similar (49±8 *vs* 50±9, respectively, $p>0.9$); there were no differences in the smoking history, cough or sputum scores, MMRC scale, or urine nicotine and cotinine levels between the two groups ($p>0.05$, all comparisons). Percent emphysema as assessesd by quantitative HRCT was not significantly different between the groups ($p>0.8$, Supplemental Figure 2). Except for slightly higher C-reactive protein (CrP) levels in the normal spirometry/low DLCO group, other serology (erythrocyte sedimentation rate, immunoglobulin E level and hepatitis C positive/negative) were not significantly different between the groups ($p>0.1$, all comparisons). The BMI was lower in the normal spirometry/low DLCO group ($p<0.002$). Comparison of the lung function assessment between the 2 groups revealed, by definition, a difference in DLCO and DLCO/VA ($p<10^{-4}$, both comparisons). Of the other PFT parameters evaluated, all were within normal range, with the normal spirometry/low DLCO group having a normal but lower VC, FEV1, FEV1/FVC and TLC ($p<0.03$, all comparisons). When the groups were divided into African-American, European and Hispanic descendants, there there was no significant difference attributed to etnicicty in any of the above parameters within the groups or between the groups ($p>0.05$, all comparisons).

Lung Function Over Time

In the normal spirometry/normal DLCO group, the FEV1 % predicted remained normal in 58 of 59 subjects and the FVC % predicted remained normal in all 59 subjects throughout the follow-up period (Figure 1A, B). The DLCO in this group remained normal in 44 of 59

(75%), but interestingly, decreased to the normal spirometry/low DLCO category (DLCO<80% predicted) in 15 of 59 subjects (25%), suggesting that a significant number of active smokers with normal spirometry/normal DLCO will progress to have low DLCO over an average of <4 yr (Figure 1C). Only 2 of the 59 (3%) active smokers in the normal spirometry/normal DCLO group developed COPD GOLD I as defined by the GOLD criteria [3] (FEV1/FVC<0.7, FEV1>80% predicted, post-bronchodilators), one subject at month 34 and the second at month 72 from baseline (Figure 1D).

In the normal spirometry/low DLCO group, the FEV1 % predicted remained normal in 44 of 46 subjects and the FVC % predicted remained normal in all 46 subjects (Figure 2A, B). The DLCO in this group remained low (<80% predicted) in 45 of 46 subjects (Figure 2C). In contrast to the normal spirometry/normal DLCO, 10 out of 46 (22%) active smokers in the normal spirometry/low DLCO group developed airflow limitation consistent with the GOLD criteria for COPD [3] [FEV1/FVC<0.7, 9 with GOLD I (FEV1 ≥80% prediced, post-bronchodilators) and 1 with GOLD II (80% predicted<FEV1>50% predicted); Figure 2D, Table II, $p<0.009$].

Comparison of the last lung function assessment to the baseline lung function within the normal spirometry/normal DLCO group showed no significant difference in the FEV1 or FVC % predicted ($p>0.3$, both comparisons), but a significant decrease in the DLCO % predicted and FEV1/FVC % observed ($p<10^{-4}$, both comparisons, Figure 3 A-D). We did not assess whether this was or was not associated with symptoms, such as cough, sputum or dyspnea at the last time point. Assessment of the last lung function to the baseline lung function within the normal spirometry/low DLCO group showed no change in FEV1, FVC or DLCO % predicted ($p>0.06$, all comparisons), but a significant reduction in FEV1/FVC % observed ($p<10^{-11}$, Figure 3 E-H). Comparison of the rate of change of the FEV1/FVC over time from baseline to last assessment of the normal spirometry/normal DLCO group to the normal spirometry/low DLCO group showed a significantly greater decrease over time for the normal spirometry/low DLCO group (normal spirometry/low DLCO −0.14±0.18 % change in FEV1/FVC/month compared to the normal spirometry/normal DLCO −0.07±0.11 % change, $p<0.02$).

Assessment of the 46 smokers with normal spirometry/low DLCO who were followed over time showed that the distribution of male to female and African-Americans to Eauropeans or Hispanics was similar in the 10 individuals who developed COPD *vs* the 36 who did not (Supplemental Table I). The smoking history, cough and sputum scores, and MMRC scale and serology were also similar in both groups and the age at the last assessment was similar (54±7 *vs* 48±9, respectively, $p>0.09$). Percent emphysema assessed by HRCT was not significantly different between the groups ($p>0.05$). The 10 individuals who developed COPD had lower, but within the normal range, FEV1/FVC % observed at baseline compared to the 36 individuals who did not developed COPD ($p<0.003$). All other lung function parameters were similar between the 2 groups ($p>0.05$, all comparisons). On the average, there were no differences in the time of follow-up, number of lung function tests or intervals between lung function tests ($p>0.1$, all comparisons). There were no significant differences in any of the parameters or in the prevelnce of COPD development between African-Americans, Europeans or Hispanics within and between the low DLCO smokers

who developed COPD and those who did not (p>0.09, all comparisosns). The assessment of using DLCO levels at baseline as a predictor for development of COPD yielded an area under the curve (AUC) score of 0.75; i.e., DLCO levels can be used to predict COPD development within 41 months with accuracy of 75%.

In addition to using a cutoff of FEV1/FVC<0.7 to define developing COPD and DLCO % predicted<80% to define low DLCO, a 95% range of normal DLCO % predicted and FEV1/FVC [12] was calculated based on the lung function of a 405 healthy nonsmoker dataset (Supplemental Methods) and used to compare the study population prevalence of developing COPD. Using the normal range for FEV1/FVC and DLCO % predicted calculated for each gender and ethnicity based on this dataset yielded the same results, with significantly higher prevalence of developing COPD (defined as FEV1/FVC <95% normal) in the normal spirometry/low DLCO group *vs* the normal spirometry/normal DLCO group (low DLCO = below 95% range).

Discussion

Cigarette smoking represents the major risk factor for the development of COPD, although only a fraction of smokers develop the disease [1,2,5,6,14]. Identification of those smokers at higher risk represents an important step in that the early detection of COPD leads to early therapeutic intervention [1,2,15]. Spirometry with bronchodilators is the gold standard tool to screen smokers for COPD [1]. In this study we focused on evaluating the addition of the DLCO parameter to identify smokers at risk for the development of COPD. We observed that in a population of 2302 active smokers randomly recruited in the New York metropolitan area responding to advertisements to assess lung health in active cigarette smokers, 17% had the phenotype of normal spirometry/low DLCO, i.e., the phenotype of low DLCO is quite common among active smokers with normal spirometry. Strikingly, of 105 active smokers randomly chosen for follow-up lung function studies over an average of <4 yr, 22% with the normal spirometry/low DLCO phenotype developed COPD by the GOLD criteria, compared to only 3% of the normal spirometry/normal DLCO phenotype. These observations suggest that the normal spirometry/low DLCO phenotype is at higher risk for developing COPD than normal spirometry/normal DLCO.

Low DLCO in Otherwise Healthy Smokers

The DLCO assesses the potential of the lung for gas exchange [16]. A pathologic correlate of decreased DLCO in smokers is the destruction of the pulmonary capillary bed, and a low DLCO in the context of a normal TLC suggests alveolar destruction, i.e., emphysema [8,16]. A good correlation between low DLCO and emphysema on chest computed tomography has been reported [17,18]. Consistent with these observations, active smokers with normal spirometry but low DLCO have high circulating levels of endothelial microparticles derived from apoptotic pulmonary capillary endothelium [19]. Decreased DLCO has also been correlated with small airway disease in the presence of severe expiratory airflow limitation and hyperinflation [20].

Our observation that 17% of active smokers responding to advertisements to assess lung health had a normal spirometry/low DLCO phenotype suggests that, despite a normal

spirometry, a significant number of active smokers have a low DLCO, an observation consistent with a number of other studies. Interestingly, while the phenotype of smokers with normal spirometry but low DLCO is recognized, there are no data regarding what happens to lung function over time in these individuals.

Risk Markers for COPD in Smokers

Identification of markers that trigger early intervention in smokers is important in that even mild COPD is associated with increased mortality [21]. Parameters that help identify the "most vulnerable" smokers, include age, gender, cough, sputum production, dyspnea, continuation of smoking and pack-yr [1,2,5,6,14,22-28].

In smokers, the prevalence of COPD increases with age [6]. A 25 yr follow-up study found that the incidence of COPD for active smokers was 35.5%, with age being a significant predictor for the development of COPD [5]. Advanced age was found significantly related to the incidence of COPD in 7 and 10 yr follow-up studies [26,27]. In the present study, there was no difference in age between the normal spirometry/normal DLCO and normal spirometry/low DLCO groups or within the normal spirometry/low DLCO group, when comparing the individuals who developed COPD and those who did not.

In addition to age, cough and sputum production have been found by prospective studies to identify individuals with higher risk of developing COPD [24,26]. A study of Japanese male smokers and nonsmokers demonstrated that productive cough was an independent risk factor for the development of COPD [28]. These data contrast with the studies by Fletcher et al [25] and Vestbo et al [14] that mucus hypersecretion in smokers is a benign condition. In our study there were no differences in cough and sputum scores between the active smokers with normal spirometry/low DLCO and normal spirometry/normal DLCO. Further, the individuals followed over time with normal spirometry/low DLCO who developed COPD did not differ in terms of symptoms compared to those who did not develop COPD.

The data pertaining to gender in the development of COPD are conflicting. Studies of smokers, ex-smokers and nonsmokers over 7 and 10 yr did not identify gender as a risk factor [26,27]. However, a study using the GOLD criteria found that despite similar smoking history, men are more susceptible to development of COPD [23], and male smokers have more emphysema than female smokers [22]. In the present study, the development of COPD was gender independent.

All individuals in our study continued to be active smokers. Continuation of smoking has been found to be an important risk factor to the development of COPD. In the Lung Health Study, smoking cessation significantly slowed the progression to COPD [1,2,5,15].

Implications

The central observation in this study is that, among active smokers with normal spirometry and normal lung volumes, a decreased DLCO is a risk factor for progression to COPD. These observations need to be verified by larger, randomized trials. Further, the identification of the "low DLCO" phenotype is complicated by ethnic variations in "normal" DLCO, and significant attention must be focused on quality control. However, with these

caveats, the concept that active smokers with normal spirometry/low DLCO are at significantly higher risk for the development of COPD over an average period of <4 yr than a comparable group of active smokers with normal spirometry/normal DLCO has important implications.

First, the data suggest that DLCO measurement could be an additional tool for early detection of the smoker at risk for COPD, and thus help contribute to early intervention.

Second, while the measurement of DLCO is not presently suitable for routine screening, engineering technology could be developed to make the DLCO an early, inexpensive, reproducible measurement, suitable for routine office visits and field use for epidemiologic studies.

Third, in the past, the DLCO has not been measured in large epidemiologic studies such as SPIROMICS and COPDGene [29,30]. While there are many reasons (mostly cost) for this, the observation that a significant percent of active smokers have a low DLCO and of these, a significant percent will develop COPD in an average of <4 yr, has significant implications for the "risk for COPD" parameters assessed in these studies.

Finally, the findings suggest that in smokers, a normal spirometry post-bronchodilator test may give a false sense of "normal", in that a significant subgroup may have a low DLCO, and that subgroup is at a significant risk for developing COPD with obstruction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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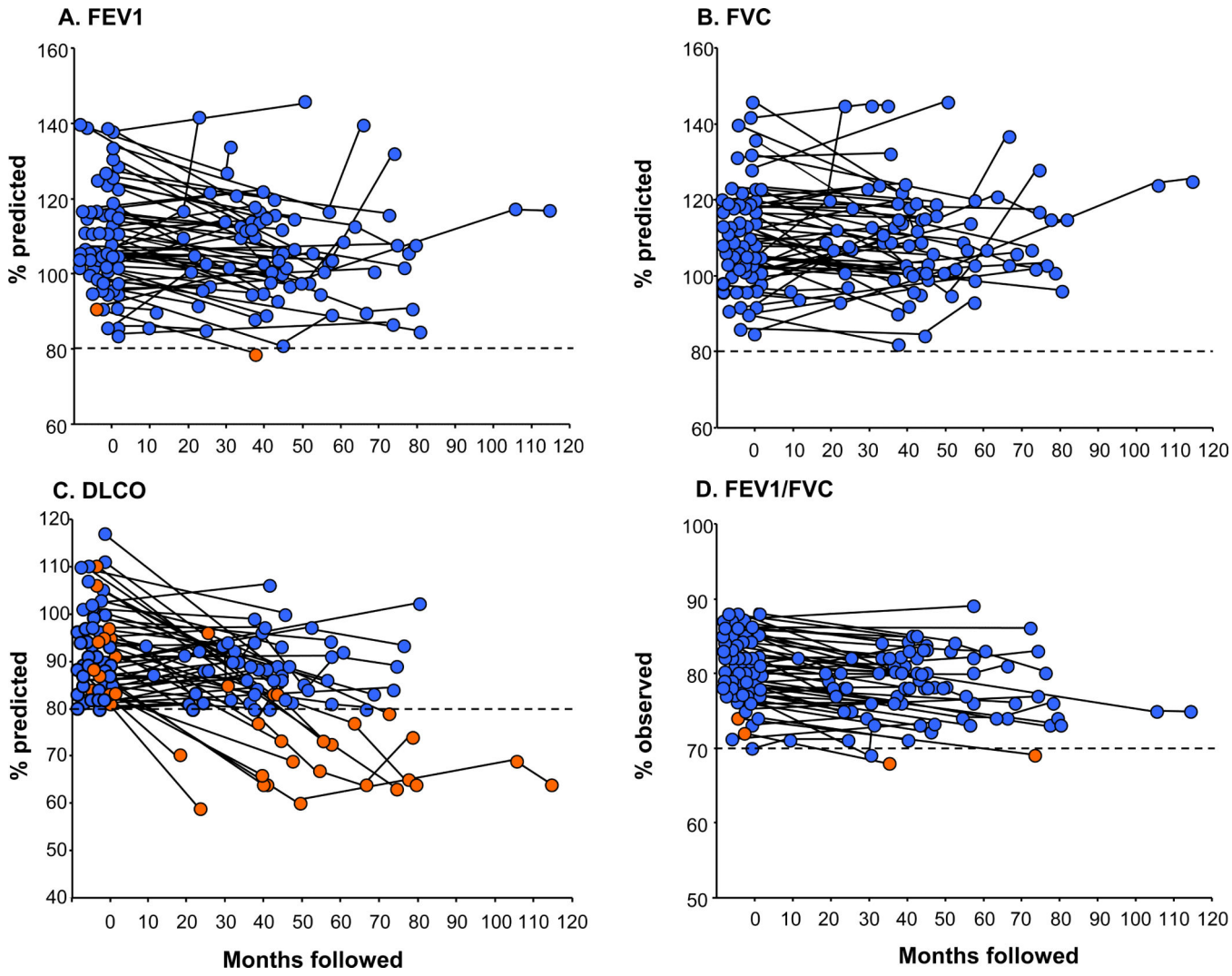

Figure 1.

Lung function assessment over time of 59 active smokers with baseline normal history, physical exam and laboratory tests, and with normal spirometry, lung volumes, and normal diffusion capacity (normal spirometry/normal DLCO). The abscissa shows time in months. Each symbol represents an individual, with lines connecting the follow-up data over time for the same individual. The dashed lines represent the limit of normal. Orange data points indicate individuals that initially had normal values at baseline but became abnormal over time. Blue data points indicate individuals that had normal values at baseline and remained normal over time.**A.** FEV1 (% predicted); **B.** FVC (% predicted); **C.** DLCO (% predicted); and **D.** FEV1/FVC (% observed).

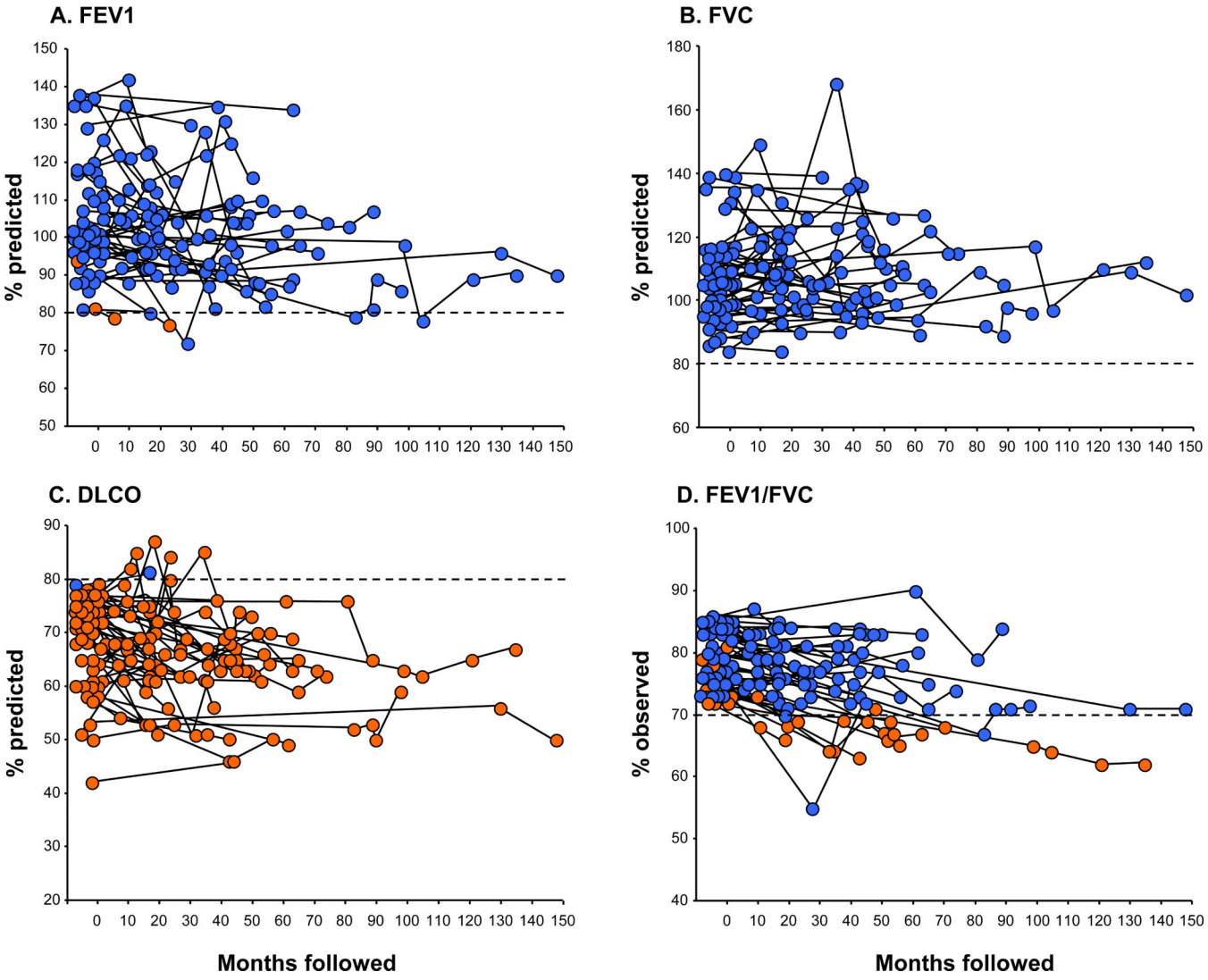

Figure 2.

Lung function assessment over time in 46 active smokers with normal history, physical exam and laboratory tests, and with normal spirometry, lung volumes, but low diffusion capacity (normal spirometry/low DLCO). The abscissa shows time in months. Each symbol represents an individual, with lines connecting the follow-up data over time for the same individual. The dashed lines represent the limit of normal. Orange data points indicate individuals that initially had normal values but became abnormal over time. Blue data points indicate individuals that had normal values at baseline and remained normal over time. **A.** FEV1 (% predicted); **B.** FVC (% predicted); **C.** DLCO (% predicted); and **D.** FEV1/FVC (% observed).

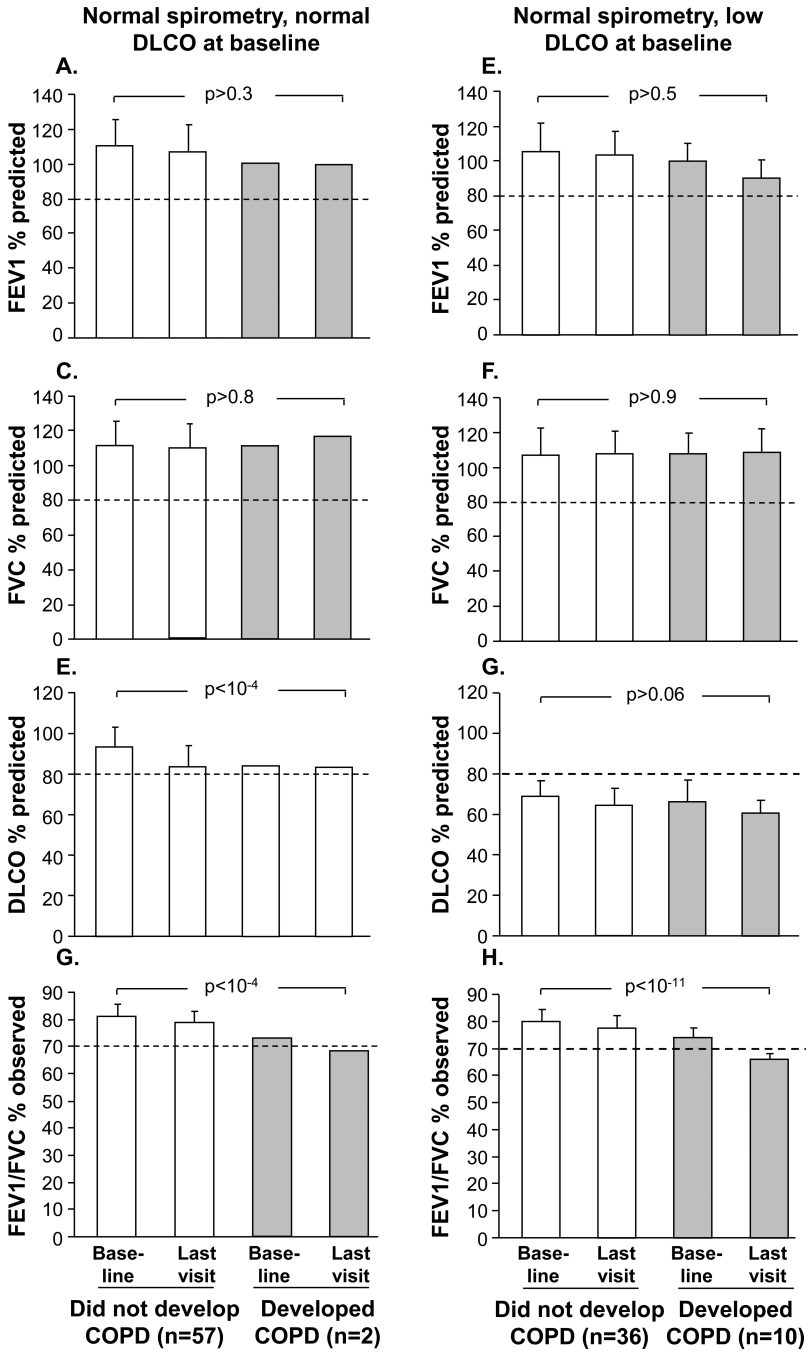

Figure 3.

Lung function changes from baseline to the last pulmonary function test in the normal spirometry/normal DLCO group (**A-D**) and normal spirometry/low DLCO group (**E-H**) comparing individuals who did not develop COPD (white bars) to those who did develop COPD (grey bars). **A, E.** FEV1 (% predicted); **B, F.** FVC (% predicted); **C, G.** DLCO (% predicted); and **D, H.** FEV1/FVC (% observed). Data is presented as mean ± standard deviation.

Table I

Demographics of Study Groups at Baseline[1]

	Smokers with normal spirometry		
Parameter	**Normal DLCO**	**Low DLCO**	**p value**
n	59	46	
Gender (male/female)	43/16	31/15	>0.6
Age	45 ± 8	46 ± 8	>0.5
Ethnicity (AA/E/H)[2]	41/10/8	37/5/4	>0.6
BMI (kg/m^2)	28 ± 5	25 ± 5	<0.002
Smoking history[3]			
Pack-yr	24 ± 13	30 ± 15	>0.05
Pack per day	1.0 ± 0.5	1.1 ± 0.6	>0.5
Age of smoking initiation	17 ± 5	17 ± 4	>0.9
Urine nicotine (ng/ml)	1102 ± 1290	951 ± 1285	>0.6
Urine cotinine (ng/ml)	1276 ± 927	1298 ± 894	>0.9
Cough score[4]	1.2 ± 1.3	1.7 ± 1.5	>0.06
Sputum score[4]	1.1 ± 1.3	1.3 ± 1.3	>0.3
MMRC score[4]	0.4 ± 0.6	0.5 ± 0.6	>0.2
% emphysema[5]	2.0 ± 0.02	2.2 ± 0.04	>0.8
Serology[6]			
αl-antitrypsin (mg/dl)	152 ± 24	145 ± 21	>0.1
ESR (mm/hr)	13 ± 11	12 ± 10	>0.7
IgE (IU/mL)	129 ± 208	169 ± 259	>0.4
CrP (mg/Dl)	0.2 ± 0.2	0.3 ± 0.2	<0.005
Hepatitis C (negative/positive)[7]	46/9	39/6	>0.8
Lung function[8]			
VC	114 ± 14	108 ± 14	<0.05
FVC (% predicted)	111 ± 14	104 ± 14	>0.1
FEV1 (% predicted)	111 ± 15	104 ± 14	<0.03
FEV1/FVC (% observed)	81 ± 4	79 ± 5	<0.03
TLC (% predicted)	99 ± 13	94 ± 14	<0.03
RV (% predicted)	90 ± 25	89 ± 37	>0.8
RV/TLC	28 ± 7	31 ± 11	>0.1
DLCO (% predicted)	93 ± 10	68 ± 9	$<10^{-4}$
DLCO/VA (mL/mHg/min/L)	4.4 ± 0.6	3.6 ± 0.7	$<10^{-6}$
Assessment over time			
Time of follow-up (month, mean ± SD, range)	46 ± 21 (5-113)	41 ± 31 (5-146)	>0.4
Number of PFTs (mean ± SD, range)	2 ± 1 (2-6)	3 ± 2 (2-8)	$<10^{-3}$
Interval between PFTs (month, mean ± SD, range)	33 ± 18 (5-73)	18 ± 20 (1-127)	$<10^{-6}$

[1]A total of 105 active smokers were enrolled in the study, including 46 individuals with normal history, physical, general laboratory tests, normal posterior-anterior and lateral chest film, normal spirometry and lung volumes, but low diffusion capacity (DLCO) and 59 with normal spirometry, lung volumes and diffusion capacity. All were followed over time with full lung function studies.

[2]AA – African-American; E - European; H - Hispanic.

[3]Current smoking was verified at baseline by urine nicotine and its derivative cotinine; at subsequent visits for lung function testing, active smoking status was verified by questionnaire.

[4]Cough and sputum scores were each evaluated on a scale of 0-4: 0 = not at all; 1 = only with chest infections; 2 = a few days a month; 3 = several days a wk; 4 - most days a wk.[31] MMRC = Modified Medical Research Council dyspnea scale.[32]

[5]Chest high resolution computed tomography (HRCT); % emphysema at −950 Hounsfield Units (HU).

[6]All individuals tested negative for HIV and had normal levels of α1-antitrypsin; ESR - erythrocyte sedimentation rate; IgE – immunoglobin E; CrP – C-reactive protein; hepatitis C – hepatitis C serology.

[7]Data available for 55 of 59 smokers with normal spirometry and DLCO and 45 of 46 smokers with normal spirometry but low DLCO.

[8]Lung function parameters are presented as percent predicted except the FEV1/FVC ratio, which is presented as percent observed; VC – vital capacity; FVC - forced vital capacity; FEV1 - forced expiratory volume in 1 second; TLC - total lung capacity; RV - residual volume; DLCO - diffusion capacity; and VA – alveolar volume. The DLCO was corrected for hemoglobin and carboxyhemoglobin.[11]

Table II

Progression to COPD in Active Smokers with Normal Spirometry/Low DLCO *vs* Active Smokers with Normal Spirometry/Normal DLCO[1]

	At end of evaluation period	
Group[2]	**% normal**	**% with COPD**
Normal spirometry, normal DLCO	97% (57/59)	3% (2/59)
Normal spirometry, low DLCO	78% (36/46)	22% (10/46)
p value[3]	0.009	

[1] Fifty-nine active smokers with normal spirometry/normal diffusion capacity, and 46 active smokers with normal spirometry/low diffusion capacity (DLCO) were followed over time with full lung function studies to determine the rate of progression to COPD.

[2] Individuals with normal spirometry, lung volumes and normal DLCO were followed for 45±20 months. Individuals with normal spirometry, lung volumes but low DLCO were followed for 41±31months ($p>0.4$).

[3] Chi-square.