

From GOLD 0 to Pre-COPD

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The diagnosis of chronic obstructive pulmonary disease (COPD) currently requires the demonstration of poorly reversible airflow limitation, defined as a post-bronchodilator FEV₁/FVC <0.7 (1–3). Although some have argued that the lower limit of normal rather than a fixed value to define obstruction may be more accurate and theoretically more appropriate, recent pooled data from multiple NIH cohorts demonstrate that the fixed FEV₁/FVC ratio <0.70 provides discrimination of COPD-related hospitalization and mortality that is equal to or better than other thresholds and the lower limit of normal (4).

At present, FEV₁/FVC remains the most robust and widely available marker of airflow limitation (5), although it may be less sensitive than some other measures (e.g., forced oscillometry). Likewise, FEV₁ is one of the most powerful predictors of clinically relevant outcomes, including symptoms, exacerbations, and mortality (6, 7). Spirometry is inexpensive and widely

available, even in many developing countries. Yet, at the same time, at an individual level, FEV₁ may not fully indicate the extent of disease severity and progression, which may instead be manifest by symptoms, exacerbations, and increased risk of death. Furthermore, significant lung damage may have already occurred before abnormalities in FEV₁ are evident. Identifying individuals who will eventually develop airflow obstruction consistent with a diagnosis of COPD may enable therapeutic interventions with the potential to modify the course of disease.

In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease, proposed an “at-risk” stage (GOLD stage 0). It was defined by the presence of risk factors (smoking) and symptoms (chronic cough and sputum production) in the absence of spirometric abnormalities that cross the diagnostic

threshold for COPD (3). This category was later abandoned because not all these individuals progressed to COPD (8). In retrospect, this may not have been the best decision, as many other medical disciplines have adopted the concept of “predisease” status (e.g., prediabetes, prehypertension, precancer, or preeclampsia). In those disciplines, predisease does not imply that all will develop the disease, but rather, the classification identifies an especially at-risk population for closer follow-up and risk management. Here, we propose to adopt a similar concept in the field of COPD. As has been highlighted in the recent perspective by Martinez and colleagues (9, 10), more is becoming understood about the pathogenesis of early COPD and the importance of identifying such individuals, in particular, for the development of disease-modifying therapies. In this perspective, our goal is to review the evidence available today that supports the need for the recognition of individuals at risk for COPD and discuss whether it is

(Received in original form August 27, 2020; accepted in final form November 19, 2020)

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*J.W. is Editor-in-Chief and M.K.H. and G.J.C. are Associate Editors of *AJRCCM*. Their participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

Supported by NIH grant HL138188.

Author Contributions: M.K.H., A.A., B.R.C., G.J.C., D.M.G.H., N.R., A.P., R.A.S., J.W., and C.F.V. all contributed to the conception and writing of this manuscript.

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Am J Respir Crit Care Med Vol 203, Iss 4, pp 414–423, Feb 15, 2021

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Originally Published in Press as DOI: 10.1164/rccm.202008-3328PP on November 19, 2020

Internet address: www.atsjournals.org

time to consider the evolution of the GOLD stage 0 concept to that of “pre-COPD” from a clinically relevant perspective (11). Although not an official GOLD document, this manuscript was generated on the basis of discussions within the GOLD Science Committee for the purposes of engaging the scientific community around the concept of pre-COPD.

Disease Burden among At-Risk Individuals

Symptomatic individuals with “normal” spirometric results are a heterogeneous group with a variety of abnormalities, including cough, sputum production, dyspnea, exacerbation-like events, and radiographic features that in some cases are similar to the clinical and radiographic presentation of patients with spirometrically confirmed COPD (12, 13). In the COPDGene (Genetic Epidemiology of COPD) cohort, roughly 43% of smokers with a normal FEV₁/FVC ratio had emphysema, gas trapping, or airway wall thickening on computed tomography (CT). Twenty-three percent of these individuals had a modified Medical Research Council (MRC) dyspnea score ≥ 2 compared with 4% of never-smokers and 22% of individuals with GOLD stage 1 COPD (12). Furthermore, chronic bronchitis symptoms among unobstructed participants are also associated with impaired quality of life, reduced walk distance, and increased exacerbation-like events (14).

In SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study), another NIH-funded cohort of smokers, roughly half of the smokers without airflow obstruction had a COPD Assessment Test score ≥ 10 and exacerbation rates similar to those of symptomatic subjects at GOLD stages 1–2 (15). These symptomatic individuals without spirometrically defined obstruction also displayed airway wall thickening on CT and elevated airway mucin concentrations, pointing to a pathologic basis for their symptoms (16). Similar findings were also observed in the Canadian population-based CanCOLD (Canadian Cohort Obstructive Lung Disease) cohort in whom exacerbation-like events were again seen among individuals without airflow obstruction. These subjects also had worse health-related quality of life

and were more likely to miss social activities and work (13).

Individuals with symptoms but without spirometrically defined obstruction compose a heterogeneous group, with some having dyspnea and others having chronic bronchitis. CT may show no abnormality or may demonstrate airway wall thickness, gas trapping, and even emphysema (12, 15). Of note, some of these individuals may never develop spirometrically defined airflow obstruction, whereas others will experience rapid lung function decline and develop full-blown disease (17–21).

In SPIROMICS, 42% of symptomatic smokers without spirometrically defined obstruction were prescribed bronchodilators, and 23% were prescribed inhaled corticosteroids, suggesting physicians believed the symptoms warranted treatment (15). However, very few therapeutic clinical trials have been conducted in these individuals, and clear evidence on the effects of treatment with either bronchodilators or inhaled corticosteroids does not exist. To address this knowledge gap, the NHLBI has funded the currently enrolling RETHINK (Redefining Therapy in Early COPD) trial (NCT 02867761) to examine whether symptomatic smokers without spirometrically defined obstruction derive benefit from inhaled bronchodilator therapy.

Symptoms as a Biomarkers of Disease Progression

Several studies have examined the relationship between respiratory symptoms in unobstructed individuals and the subsequent development of COPD (Table 1). In a Swedish cohort of over 6,000 middle-aged and older subjects, the 10-year cumulative incidence of COPD was 13.5% (17). Cough, sputum production, and chronic productive cough were significantly associated with incident COPD in women, whereas dyspnea and wheeze were significantly associated with incident COPD in men. SAPALDIA (Swiss Study on Air Pollution and Lung Disease in Adults), with a cohort of over 5,000 individuals, also found that chronic bronchitis was associated with incident COPD, as defined by prebronchodilator spirometric results (rate ratio, 1.23; 95% confidence interval, 1.00–1.51) (22).

In the ARIC (Atherosclerosis Risk in Communities) cohort, both smokers and nonsmokers with any chronic respiratory symptom but prebronchodilator FEV₁ in the normal range had an increased risk of mortality (hazard ratio [HR], 1.5) (23), although whether this related to the subsequent development of COPD in some of these subjects is unknown. Among another Norwegian cohort of men aged 40–59, subjects at GOLD stage 0 had an increased risk of death (HR, 1.35) (24). The CARDIA (Coronary Artery Risk Development in Young Adults) study reported that any respiratory symptom, including cough or phlegm, episodes of bronchitis, wheeze, shortness of breath, and chest illness, was associated with a 2.71-ml/yr excess decline in FEV₁ ($P < 0.001$), a 2.18-ml/yr excess decline in FVC ($P < 0.001$), and a 1.63 odds ratio (OR) for development of incident obstruction (18). Cough-related symptoms specifically were associated with a 1.56 OR for development of visually assessed emphysema on Year 25 CT scans.

Other studies have examined chronic bronchitis symptoms more specifically. In the Copenhagen City Heart study, chronic bronchitis symptoms were associated with an excess loss of 19 ml/yr, with a stronger association noted in men (25). However, although 20.5% of smokers with chronic bronchitis at baseline had developed COPD at 15 years, 18.5% of smokers without symptoms at baseline had also developed COPD. Furthermore, smokers without symptoms represented the majority of individuals who developed COPD (8). The ECRHS (European Community Respiratory Health Survey) cross-sectional study of over 18,000 adults aged 20–44 years in 16 countries (26) demonstrated the prevalence of chronic cough and phlegm to be 11.8% (27). Compared with those without respiratory symptoms, symptomatic subjects were more likely to be current smokers, report respiratory infections before the age of 5 years, and report the presence of occupational exposures to vapors, dust, or fumes. Longitudinal follow-up of this cohort identified chronic cough and phlegm as an independent predictor of incident COPD (incident rate ratio, 1.85). Probably because of its multidimensionality and the variety of its causes, dyspnea alone was not associated with incident disease (incident rate ratio,

Table 1. Association between Symptoms and Lung Function Decline among Individuals at GOLD Stage 0

Study	Prevalence of Symptoms	Outcome
Copenhagen City Heart (8, 25)	Baseline prevalence of CB: 7.1% of men and 4.8% of women	<ul style="list-style-type: none"> • After 5 and 15 yr, COPD developed in 13.2% and 20.5% of smokers at GOLD stage 0 at enrollment, respectively • At 5 and 15 yr, respectively, 11.6% and 18.5% of smokers without respiratory symptoms also were at GOLD stage 1 or worse • Symptoms at GOLD stage 0 were associated with excess loss of 19 ml/yr in addition to the FEV₁ decline seen in unobstructed smokers without these symptoms
ECRHS (26, 27)	At baseline, 9.2% subjects reported chronic cough and phlegm	<ul style="list-style-type: none"> • The incidence of COPD in subjects who confirmed the presence of chronic cough and phlegm at the end of the follow-up (9.4 cases of 1,000/yr; 95% CI, 5.6–15.9) was fourfold higher than the incidence in subjects who had never reported these symptoms (2.3 cases of 1,000/yr; 95% CI, 1.9–2.9) (incidence rate ratio, 1.85; 95% CI, 1.17–2.93) • The incidence of COPD in subjects with persistent dyspnea (3.2 cases of 1,000/yr; 95% CI, 1.6–6.5) was not significantly different from the incidence of COPD in subjects who had never reported this symptom (2.4 cases of 1,000/yr; 95% CI, 1.9–3.0)
Northern Swedish cohort (17)	At baseline, 41.9% of subjects reported chronic productive cough	<ul style="list-style-type: none"> • The 10-yr cumulative incidence of COPD was 13.5%. The cumulative incidence of COPD among persistent smokers was close to three times the incidence among persistent nonsmokers (24.5% vs. 9.4%, respectively) • When analyzed as an entire cohort, every type of symptom was associated with increased risk for COPD • However, when men and women were analyzed separately, cough, sputum production, and chronic productive cough were significantly associated with incident COPD in women, whereas dyspnea and wheeze were significantly associated with incident COPD in men
SAPALDIA cohort (22)	At baseline, among those without airflow obstruction, 8.1% of subjects reported CB symptoms	<ul style="list-style-type: none"> • CB was associated with incident COPD as defined by prebronchodilator spirometric results (rate ratio, 1.23; 95% CI, 1.00–1.51)
UK MRC cohort (19)	Among smokers, CB prevalence escalated between the ages of 36 and 43 yr from 7.6% to 13.0%	<ul style="list-style-type: none"> • Symptoms were associated with a higher risk of subsequent airflow limitation (ORs, 3.70 and 4.11, respectively) • The longer CB was present across three occasions (ages 43, 53, and 60–64 yr), the greater the concurrent FEV₁ decline, corresponding to an additional decrement of 3.6 ml/yr per occasion that CB was present ($P=0.005$)
TESAOD (20)	CB present in 6.9% (majority current or former smokers)	<ul style="list-style-type: none"> • Incident airflow obstruction among those with CB, 1.37 ($P=0.07$) • Mortality risk was higher among smokers (adjHR, 1.50) than nonsmokers (0.80) and among subjects <50 yr of age (2.22) vs. >50 yr of age (0.96)
ARIC (23)	The prevalence of GOLD stage 0 was 14.5% in a population-based cohort based on prebronchodilator spirometric results and any respiratory symptom, including cough, phlegm, wheeze, and breathlessness. Overall, 20% of those with normal spirometric results reported symptoms	<ul style="list-style-type: none"> • HR, 1.6 for death among participants at GOLD stage 0 as compared with unobstructed individuals without symptoms

(Continued)

Table 1. (Continued)

Study	Prevalence of Symptoms	Outcome
Oslo Norway cohort (24)	The prevalence of GOLD stage 0 was 8.1% in a population-based cohort of men in Oslo, Norway. Overall, 9.7% of those without airflow obstruction demonstrated respiratory symptoms	<ul style="list-style-type: none"> Subjects at GOLD stage 0 using a modified definition (prebronchodilator spirometric results and any respiratory symptom, including dyspnea and phlegm) had increased risk for mortality (HR, 1.35)
CARDIA cohort (18)	The prevalence of any respiratory symptom in a population-based cohort at baseline and Year 2 was 43.9%	<ul style="list-style-type: none"> Respiratory symptoms, including cough or phlegm, episodes of bronchitis, wheeze, shortness of breath, and chest illness were assessed at baseline and Year 2 and examined in conjunction with lung function from Year 5 to Year 30 Report of any symptom was associated with a 2.71-ml/yr excess decline in FEV₁ ($P < 0.001$) and a 2.18-ml/yr excess decline in FVC ($P < 0.001$) as well as a 1.63 OR for development of incident obstruction Cough-related symptoms in particular were associated with a 1.56 OR for development of visually assessed emphysema on Year 25 CT scans

Definition of abbreviations: adjHR = adjusted HR; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CB = chronic bronchitis; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CT = computed tomography; ECRHS = European Community Respiratory Health Survey; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; MRC = Medical Research Council; OR = odds ratio; SAPALDIA = Swiss Study on Air Pollution and Lung Disease in Adults; TESAOD = Tucson Epidemiological Study of Airway Obstructive Disease; UK = United Kingdom.

0.98), even after adjusting for smoking habits.

The MRC National Survey of Health and Development was a prospective cohort of over 5,000 individuals within the United Kingdom (19). Chronic bronchitis symptoms at the ages of 36 and 43 years were associated with subsequent risk for incident airflow obstruction, with ORs of 3.70 and 4.11, respectively. Among smokers, symptoms before age 36 were not associated with incident airflow limitation. However, among nonsmokers, symptoms at most ages were associated with incident airflow limitation by ages of 60–64 years. The longer individuals had symptoms, the greater the rate of FEV₁ decline. Reporting of chronic bronchitis on at least one occasion between 43 and 60–64 was associated with an additional 4.5-ml/yr decline in FEV₁.

TESAOD (Tucson Epidemiological Study of Airway Obstructive Disease) examined over 1,400 participants aged 21–80 in the southwestern United States. Among adults <50 years of age with over 24 years of follow-up, 42% of those with chronic bronchitis developed airflow obstruction, versus 23% of those without chronic bronchitis (20). The presence of chronic bronchitis was also

associated with increased mortality (HR, 1.31) among subjects less than 50 years of age but not among subjects 50 years of age or older.

Taken together, these studies provide compelling evidence for a relationship between chronic cough and phlegm, in particular, and the subsequent development of airflow limitation. However, there is only a subset of individuals who experience disease progression, and this subset does not even include the majority (8, 25). Some of the variability in the data with respect to respiratory symptoms, particularly dyspnea alone, may relate to greater variation in their etiology from comorbid conditions such as cardiac disease and obesity. The contribution and potential confounding effect of such factors as comorbidities to the relationship between respiratory symptoms and the development of COPD has not been fully addressed by most studies to date.

Physiologic Measurements as Biomarkers of Disease Progression

The measurement of lung function as a tool to determine the presence or absence of respiratory health has been central to

diagnosis, prognosis, and response to interventions in the field of COPD. Recent evidence from cohorts of children followed over time with sequential spirometry show that those who belong to the lower quartiles of predicted FEV₁, even if the values are still within the normal range for their age, are more likely to meet spirometric criteria for a diagnosis of COPD during early adulthood (28, 29). In the Lovelace prospective study of ever-smokers, low-normal FEV₁ without obstruction at baseline combined with “rapid” decline as defined by a loss of FEV₁ greater than 40 ml/yr (normal rate of loss after the third decade of life is <25 ml/yr) over 18 months was associated with a 36-fold risk of developing COPD over the time of observation, as compared with those with high baseline lung function without rapid decline (30).

The single-breath DL_{CO} test is another measurement that identifies individuals at increased risk for COPD. In one small New York City study, follow-up of active smokers over 45 months found that among those with normal spirometric findings/normal DL_{CO}, 3% developed GOLD-defined COPD, whereas in those with normal spirometric findings/low DL_{CO}, the incidence was 22% (31). These studies support the use of lung function as a

Table 2. Association between Lung Function and Incident COPD in Smokers without Airflow Limitation

Study	Outcome
Lovelace smokers cohort (30)	<ul style="list-style-type: none"> • These nonobstructed subjects aged between 40 and 50 yr who had a normal FEV₁ (75% predicted) in the lower quartile of lung function in the cohort and who lost >40 ml/yr of function in 18 mo of observation had a 36-fold risk of developing GOLD spirometric stage 2 COPD over 42 mo of observation compared with subjects with high normal FEV₁ and no FEV₁ decline. • At baseline, these nonobstructed subjects had worse health-status scores measured with the SGRQ questionnaire. • They also had higher mMRC dyspnea scores than the reference group with high normal FEV₁ %.
New York smokers cohort (31)	<ul style="list-style-type: none"> • From a cohort of 1,570 smokers in the New York City metropolitan area with normal spirometric results, two groups were randomly selected: normal spirometric results/normal DL_{CO} (n = 59) and normal spirometric results/low DL_{CO} (n = 46). They were followed over 41 mo. • In the normal spirometric results/normal DL_{CO} group, 3% developed GOLD-defined COPD. In the normal spirometric results/low DL_{CO} group, the incidence was 22% (P = 0.001).

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.

useful, practical tool to identify subjects at risk for incident COPD development (Table 2). Other physiologic measures besides FEV₁/FVC that may also prove helpful in this regard include the forced oscillation technique, the multiple-breath nitrogen washout, and new spirometry-derived indices (32–34).

Imaging Biomarkers of Disease Progression

Imaging is another way to identify patients with pathology who may be at risk for developing spirometrically defined airflow obstruction (Table 3). Although not currently the standard of care for COPD, CT is widely available in many countries and is routinely used in lung cancer screening programs. Incorporation of quantitative CT imaging into several recent, large cohort studies provides a wealth of information regarding imaging abnormalities and their relationship to disease progression.

Emphysema is identified on CT imaging either on the basis of the percentage of lung with low density (–910 Hounsfield

units [HU] and –950 HU have both been used as thresholds) or by using the HU that represents the lowest 15th percentile lung density value (Perc15; the lower the Perc15, the lower the distribution of lung density for an individual patient). Although two small studies failed to find a relationship between emphysema as demonstrated by CT-defined emphysema and FEV₁ decline among unobstructed individuals (35, 36), results from larger studies are more definitive. In the NELSON trial (Dutch–Belgian Lung Cancer Screening trial), a population-based CT screening program for lung-cancer in men, smokers without baseline airflow obstruction who developed spirometrically defined obstruction at follow-up had significantly lower mean Perc15 scores at baseline (–934.2 HU vs. –930.2 HU; P < 0.001) (37). Participants with upper lobe–predominant emphysema also had greater loss in lung function at follow-up than those with lower-lobe emphysema distribution, independent of total extent of emphysema (38). Individuals with a 10-HU lower Perc15 at baseline had an OR of 1.46 (P < 0.001) for the development of airflow obstruction. In a separate U.S.-based study

examining lung-cancer screening CT scans, visually detected emphysema was also associated with incident airflow obstruction (HR, 5.14) (39). In the MESA (Multi-Ethnic Study of Atherosclerosis) Lung Study population sample, 5.4% of subjects had an emphysematous lung percentage above the upper limit of normal (40). In adjusted models, the emphysematous lung percentage greater than the upper limit of normal was associated with an increased odds of incident airflow limitation (OR, 4.38), with similar results seen using the emphysematous lung percentage as a continuous measure or using a fixed threshold of 5%.

The segmental and subsegmental airways can also be directly measured using CT imaging and may also provide insights into COPD. In NELSON, Pi10 (a standardized measure of airway wall thickness) was also significantly (and independently from Perc15) associated with development of airflow obstruction (41). A 1-mm greater Pi10 equated with an OR of 2.45 (P < 0.001). In MESA, a greater Pi10 was associated with a 9% faster FEV₁ decline (P = 0.012) and incident COPD (OR, 2.22; P < 0.001) at 5-year follow-up (42). Greater Pi10 was also associated with a 57% higher risk of hospitalization or mortality related to chronic lower respiratory disease.

The small airways with an inner diameter <2 mm are believed to represent a “quiet” zone at the early stages of disease progression, in which pathologic abnormalities may accumulate before the development of spirometrically detected airflow obstruction (43). Parametric response mapping (PRM) combines data from inspiratory and expiratory images to distinguish emphysema from nonemphysematous gas trapping, presumed to be a small-airway abnormality (44, 45). Histologic studies in lung tissue with severe disease have since confirmed significant small-airway abnormalities in these regions (45). Using PRM in COPDGene, a wide range of PRM small-airway abnormalities (PRM^{SAD}) were seen among at-risk current and former smokers and was associated with subsequent excess FEV₁ decline. Individuals within the highest quartile of PRM^{SAD} (≥16%) demonstrated an FEV₁ decline of 49.2 ml/yr as compared with those in the lowest quartile, who

Table 3. Association between Imaging Features and Outcomes among Individuals at GOLD Stage 0

Study	Outcome
NELSON (37, 38, 41)	<ul style="list-style-type: none"> • Among male smokers in a lung cancer screening trial, participants without baseline airflow obstruction who developed obstruction at follow-up had significantly lower mean Perc15 at baseline, -934.2 HU vs. -930.2 HU ($P < 0.001$), suggesting that greater presence of emphysema at baseline can help identify patients who will go on to develop emphysema. • Participants with upper lobe-predominant emphysema had greater loss in lung function at follow-up than those with lower-lobe emphysema distribution, independent of total emphysema extent. • Of those with no airflow limitation at baseline, a 1-mm greater Pi10 (measure of airway wall thickness) equated with an OR of 2.45 ($P < 0.001$), and a 10-HU lower Perc15 had an OR of 1.46 ($P < 0.001$) for the development of airflow limitation at follow-up.
New York lung cancer screening cohort (39)	<ul style="list-style-type: none"> • In a small, United States-based study examining lung cancer screening CT scans among 521 participants, the presence of moderate to severe emphysema based on visual assessment was associated with incident airflow obstruction (HR, 5.14).
MESA Lung (40, 42)	<ul style="list-style-type: none"> • Examining only participants without prior diagnosis of chronic lower respiratory disease or use of inhaled corticosteroids or bronchodilators, a greater Pi10 was associated with a 9% faster FEV₁ decline ($P = 0.012$) and incident COPD (OR, 2.22; $P < 0.001$) at 5-yr follow-up. • Greater Pi10 was associated with a 57% higher risk of hospitalization or mortality related to chronic lower respiratory disease. • In this study, 5.4% of subjects had an emphysematous lung percentage above the upper limit of normal, and this was associated with increased odds of incident airflow limitation (OR, 4.38), with similar results seen using the emphysematous lung percentage as a continuous measure or using a fixed threshold of 5%.
Korean cohort (35)	<ul style="list-style-type: none"> • This Korean cohort study of 628 healthy volunteers without known respiratory disease or abnormal PFT results at baseline demonstrated that those with emphysema (defined as $\geq 10\%$ low-attenuation area based on a -950-HU threshold) had the fastest decline in FVC (-33.9 vs. -18.8 ml/yr; $P = 0.02$), but emphysema was not associated with incident airflow limitation at follow-up (35). • Although the presence of emphysema was associated with a greater rate of FEV₁ decline, the difference was not statistically significant.
Pooled DLCST and ECLIPSE data (36)	<ul style="list-style-type: none"> • Data pooled from DLCST and ECLIPSE found that among 687 current and former smokers without airflow obstruction, no significant relationship existed between Perc15 and FEV₁ decline, whereas these relationships were evident in participants at GOLD stages 2 and 3.
COPDGene (44-46)	<ul style="list-style-type: none"> • CT-identified small-airway abnormalities defined using PRM^{SAD} were associated with excess FEV₁ decline at 5 yr among at-risk smokers without airflow obstruction at baseline. • Individuals within the highest PRM^{SAD} quartile ($\geq 16\%$) demonstrated an FEV₁ decline of 49.2 ml/yr as compared with those in the lowest quartile (35.4 ml/yr). • Additional longitudinal CT analyses suggest that over time, voxels with PRM^{SAD} among at-risk smokers progress to voxels with emphysema.
Pooled data from MESA, CanCOLD, and SPIROMICS (48)	<ul style="list-style-type: none"> • Comparing the highest to the lowest quartile for mean airway-to-lung ratio in MESA, the COPD incidence rate ratio was 8.12 (95% CI, 3.81-17.27); there was no difference in FEV₁ decline. • Comparing the highest to the lowest quartile for mean airway-to-lung ratio in CanCOLD, the COPD incidence rate ratio was 3.33 (95% CI, 1.89-5.85); there was no difference in FEV₁ decline.

Definition of abbreviations: CanCOLD = Canadian Cohort Obstructive Lung Disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COPDGene = Genetic Epidemiology of COPD; CT = computed tomography; DLCST = Danish Lung-Cancer Screening Trial; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; HU = Hounsfield units; MESA = Multi-Ethnic Study of Atherosclerosis; NELSON = Dutch-Belgian Lung Cancer Screening trial; OR = odds ratio; Perc15 = 15th percentile point; PFT = pulmonary function test; Pi10 = the square root of the wall area of a theoretical airway with a lumen perimeter of 10 mm; PRM^{SAD} = parametric response mapping small-airway abnormalities; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study.

demonstrated a decline of 35.4 ml/yr. Additional longitudinal CT analyses suggest that over time, voxels with PRM^{SAD} among at-risk smokers progress to voxels with emphysema (46). Diffusion-capacity abnormalities correlate with PRM^{SAD} in mild to moderate COPD (47), suggesting PRM^{SAD} might detect airways transitioning to early emphysema, with resulting impaired gas exchange. Finally, in an analysis of the MESA, CanCOLD, and SPIROMICS cohort studies, the airway-to-lung ratio (dysanapsis; i.e., the geometric mean of airway-lumen diameters at standard anatomic locations divided by the cube root of lung volume) was associated with airflow-limitation severity, COPD prevalence, and COPD incidence, suggesting that lung development early in life conditions the risk of developing COPD and susceptibility to airborne noxious components (48).

In summary, CT-detected small-airway abnormalities, airway wall thickening, and emphysema may all be helpful in identifying patients at increased risk for disease progression to COPD, but the sensitivity and specificity for exact thresholds of CT abnormalities in particular have not yet been well defined. Variations in CT acquisition protocols as well as visual assessment and quantitative methods likely also contribute to heterogeneity in study findings and the complexity of clinical implementation.

Patterns of Progression: Lung Function Trajectories

The pattern of progression to airflow limitation is variable. Some individuals have lung function in the normal range in early adulthood but decline more rapidly, whereas others, whether because of genetic predisposition and/or early life exposures, never reach peak adult lung function and develop COPD despite normal age-related rates of lung function decline (49). There are also individuals who may initially have supranormal lung function but suffer significant lung damage and still have technically normal spirometric findings at the age of 60–70 because of their high starting point (10). Furthermore, although we have traditionally assumed that most patients pass from normal spirometric results through to GOLD stages 1 and 2, data from COPDGene suggests that some patients with restrictive physiology, defined

as Preserved Ratio Impaired Spirometry (PRISm; an FEV₁/FVC > 0.70 and FEV₁% predicted < 80), also progress to classically defined GOLD COPD (50). In COPDGene, among subjects with PRISm at baseline, 22.2% transitioned to normal spirometric results, whereas 25.1% progressed to GOLD stages 1–4 at the Year 5 visit. Subjects with PRISm at baseline also had higher rates of all-cause mortality than those with normal spirometric results, although these rates were lower than that those of participants at GOLD stages 1–4. It has been further suggested by COPDGene that those who progress via the PRISm pathway may have more “airway-dominant” disease and that those who progress from normal spirometric results have more of an “emphysema-dominant” disease, although these are somewhat loose distinctions. In the Rotterdam population-based study, 15.7% of PRISm subjects transitioned to normal spirometric values, whereas 49.4% developed airflow obstruction after 4.5 years (51).

Variability in patterns of progression is further highlighted by a separate recent analysis of COPDGene data using machine learning on CT images captured at baseline and at 5 years. They identified two trajectories of disease progression, one in which 70.4% of subjects developed small-airway abnormalities and emphysema before developing larger segmental-airway abnormalities and one in which 29.6% of the cohort demonstrated a reverse pattern, with large-airway abnormalities being present first (52). If further confirmed, these data would help to explain why airway wall thickening, excess mucin production, and symptoms of chronic bronchitis do appear to relate to COPD development but do not identify the majority of those who progress.

Putting It All Together?

Conceptually, one step forward would be to combine symptoms, lung function, and CT assessments to try to stage people with respect to risk for COPD development. A recent publication from the COPDGene research group suggests exactly this and puts forward a new proposed disease-classification scheme for COPD (53). According to this proposal, individuals can be classified using a combination of symptoms, abnormal spirometric results, and abnormal CT features as possible,

probable, and definite COPD. It should be noted that this system would both classify some individuals without spirometrically defined obstruction as having possible or probable COPD while reclassifying others with spirometrically defined obstruction into possible COPD. At this point, however, the clinical utility of classifying patients in this manner is unknown. Further prospective data will be needed to understand disease evolution from these respective categories as well as response to therapies.

From GOLD Stage 0 to Pre-COPD

It is clear that some persons with risk factors for COPD experience respiratory morbidity but have an FEV₁/FVC ratio in the normal range. Like COPD, this population is markedly heterogeneous, as is their risk of developing persistent airflow limitation. Yet, conceptually, we believe the term “pre-COPD” (11, 54) should be useful to identify individuals in whom spirometry is unable to detect airflow limitation but in whom the disease is likely to progress, resulting in overt airflow obstruction without further intervention. From the studies reviewed here, such individuals are likely to demonstrate 1) respiratory symptoms, including cough with sputum production; 2) physiologic abnormalities, including low-normal FEV₁, DL_{CO}, and/or accelerated FEV₁ decline; and/or 3) radiographic abnormalities, including airway abnormalities and emphysema. By expanding beyond the GOLD stage 0 concept that identified at-risk individuals on the basis of symptoms alone, we should be able to identify a larger majority of individuals who will develop COPD.

In particular, patients with chronic cough and phlegm stand apart as having a clear form of pre-COPD for several reasons: 1) these symptoms are the most strongly associated with progression to COPD, 2) an underlying pathobiologic feature has been identified (i.e., increased mucin production) (16), and 3) this subgroup exhibits particular morphologic abnormalities (i.e., airway wall thickening on CT). Historically, the term “chronic bronchitis” has been used rather loosely to identify these patients. However, to avoid confusion and stress the clinical importance of this condition, we propose to return to the

specific classification proposed by the MRC over 55 years ago and label these nonspirometrically obstructed individuals as having “nonobstructive chronic bronchitis” (NOCB) (55). This group is worthy of identification for the purposes of risk reduction and further research so that appropriate treatments can be developed and studied, even if spirometrically defined obstruction never develops (14). Yet it is clear that patients with NOCB represent only a subset of those at risk for ultimate disease progression (i.e., pre-COPD). We also acknowledge there may be other phenotypic subsets of individuals, yet to be defined, who may or may not develop airflow obstruction but represent clinically relevant subtypes because of significant symptoms, exacerbations, or increased mortality.

We believe that the introduction of the concept of pre-COPD would provide greater awareness within the medical community and general public of the fact that by the time spirometrically defined obstruction develops, significant airway damage has already occurred (Figure 1). We realize that a tighter definition for pre-COPD is desirable and would facilitate early-

intervention and disease-modification trials, but present evidence does not allow further refinement of the concept. However, we acknowledge that drawbacks to defining a pre-COPD population include conferring disease status on a potentially large number of individuals who under current guidelines are not considered to have a respiratory disease diagnosis, who may never progress, and for whom there is no evidence-based treatment apart from risk-reduction measures. However, risk reduction is the current approach for other conditions with well-defined predisease states, such as prediabetes and prehypertension (56, 57). Identification of such individuals could also accelerate conduction of early-intervention, disease-modification trials.

In thinking about COPD pathogenesis, we know that airway abnormalities can accumulate without spirometrically identified abnormalities and that this “silent” period could be considered pre-COPD (54). In the 1980s, J.D. Scadding proposed that disease be defined by four key characteristics, including 1) clinical description, 2) disorder of structure, 3) disorder of function, and 4) causation

(11, 58). Hence, in thinking about pre-COPD versus COPD, symptoms, structural abnormalities, and causation are similar, with the key difference being function, which, in this case, is defined by the presence or absence of spirometrically defined airflow obstruction.

The challenge at hand, however, is developing a set of clinically implementable thresholds able to identify groups at risk of developing fully identifiable spirometric COPD. Here, we go beyond the original GOLD stage 0 definition that focused on symptoms alone. One of the problems with GOLD stage 0 is that it only identified a fraction of individuals who ultimately progressed to COPD. By in addition examining a range of physiologic and radiographic abnormalities, we have the potential to hopefully identify the majority of individuals who will progress. Yet we acknowledge that at the present time, pre-COPD is difficult to fully operationalize from a clinical standpoint. We currently have few data on the sensitivity or specificity for any individual metric or combinations of metrics to accurately identify those individuals. Furthermore, as highlighted by the recent perspective by Martinez and colleagues on the pathogenesis of early COPD, it is also highly likely that age and multimorbidity confound the relationships among symptoms, CT abnormalities, and lung function decline, which cannot fully be considered until additional data are acquired in younger individuals (9). We also have significantly fewer data on COPD that arises among nonsmokers. Finally, we also acknowledge that even among patients who meet spirometric criteria for COPD, despite studies being published for methodologies to find such individuals, most health systems do not have robust screening or case-finding measures in place to identify these individuals. Hence, more research on implementation of such programs will clearly be needed to understand how to find earlier disease.

Conclusions

The term “COPD” clearly includes a spectrum of physiologic and histologic abnormalities. Our current definition of COPD based on the FEV₁/FVC ratio is highly specific for the disease we call

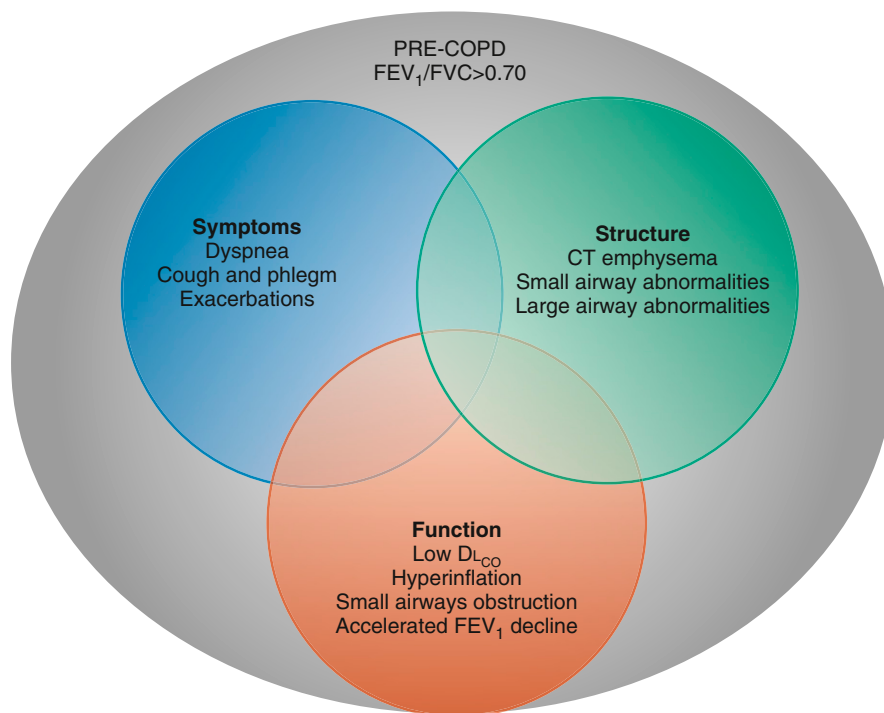


Figure 1. Conceptualized understanding of the relationships among symptoms, structure, and function with respect to pre-COPD. COPD = chronic obstructive pulmonary disease; CT = computed tomography.

COPD, but as the data we show here suggest, it is perhaps not sensitive to the breadth of abnormalities we may see earlier in the disease process. Not only are such patients at increased risk for disease progression, but, in some cases, such patients also experience significant morbidity in the absence of a reduced FEV₁/FVC ratio. Hence, we propose that the term pre-COPD should be used to refer to individuals in whom spirometry is unable to detect airflow obstruction but

who are at risk of subsequently developing COPD with a reduced FEV₁/FVC ratio. A particular subtype of pre-COPD is NOCB. Clearly, symptoms in this patient population with pre-COPD are associated with morbidity, regardless of whether individuals with NOCB ultimately develop spirometrically defined obstruction. Hence, they are worthy of formal recognition by regulatory bodies such as the Food and Drug Administration and European Medicines Agency, particularly given

evolving data to support a unique pathologic abnormality. We acknowledge, however, that more data on disease in younger individuals are critical to develop and validate a clinically operable definition of pre-COPD that has good sensitivity and specificity and that can be clinically implemented with confidence. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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