From Gold 0 to Pre-COPD

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Abstract

Currently the diagnosis of chronic obstructive pulmonary disease (COPD) requires the demonstration of airflow limitation, defined as a post-bronchodilator $FEV_1/FVC < 0.7$, a measurement that remains methodologically robust and widely available. FEV_1 is one of the most powerful predictors of clinically relevant outcomes including symptoms, exacerbations and mortality. However, reliable data suggest that respiratory symptoms, in particular chronic bronchitis, airway abnormality and emphysema detected using modern imaging techniques such as computed tomography (CT), and certain physiologic measures including rapid decline in FEV_1 and DLCO are present among individuals who do not meet spirometric criteria for COPD. These abnormalities may help to identify individuals at increased risk for developing airflow limitation in the future. Here, we review the evidence that support the use of the term "pre-COPD" in individuals with symptoms (e.g., "Non-Obstructive Chronic Bronchitis" (NOCB)), physiologic (e.g., low DLCO) and/or imaging abnormalities (e.g. CT emphysema) but spirometry in the normal range, who are at risk of developing COPD defined by a reduced FEV_1/FVC ratio. We acknowledge, however, that further research on early disease in young individuals will be critical to develop a clinically operable definition of "pre-COPD" that demonstrates good sensitivity and specificity.

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Background

The diagnosis of chronic obstructive pulmonary disease (COPD) currently requires the demonstration of poorly reversible airflow limitation, defined as a post-bronchodilator $FEV_1/FVC < 0.7$ (1-3). While some have argued that the lower limit of normal (LLN) 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 FEV_1/FVC ratio <0.70 provides discrimination of COPD-related hospitalization and mortality that is equal to or better than other thresholds and LLN (4).

At present FEV_1/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, FEV_1 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, FEV_1 may not fully indicate the extent of disease severity and progression, which may instead be manifest by symptoms, exacerbations and increased risk of death. Further, it significant lung damage may have already occurred before abnormalities in FEV_1 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 Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) report proposed an “at risk” stage (GOLD 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).

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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 "pre"-disease status (e.g., pre-diabetes, pre-hypertension, pre-cancer or pre-eclampsia). In those disciplines, "pre-disease" 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, et al. (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 time to consider the evolution of the GOLD 0 concept to that of "pre-COPD" from a clinically relevant perspective (11). While not an official GOLD document, this manuscript was generated based on 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" spirometry 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 cohort, roughly 43% of smokers with a normal FEV_1/FVC ratio had emphysema, gas trapping or airway wall thickening on CT. Twenty-three percent of these individuals had an mMRC dyspnea score ≥ 2 compared to 4% of never smokers and 22% of individuals with GOLD stage 1 COPD

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(12). Further, 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, another NIH-funded cohort of smokers, roughly half of the smokers without airflow obstruction had a COPD Assessment Test (CAT) score ≥ 10 and exacerbation rates similar to symptomatic GOLD 1-2 subjects (15). These symptomatic individuals without spirometric 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 cohort where 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 comprise a heterogeneous group with some having dyspnea and others 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 spirometric obstruction were prescribed bronchodilators and 23% 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 Redefining Therapy in Early COPD (RETHINC) trial

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(NCT02867761) in order to examine whether symptomatic smokers without spirometric defined obstruction derive benefit from inhaled bronchodilator therapy.

Symptoms as a biomarker 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 elderly 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 while dyspnea and wheeze were significantly associated with incident COPD in men. The SAPALDIA (Swiss Study on Air Pollution and Lung Disease in Adults) cohort of over 5,000 individuals, also found that chronic bronchitis was associated with incident COPD as defined by pre-bronchodilator spirometry, rate ratio 1.23 (95% ci 1.00 to 1.51) (22).

In the Atherosclerosis Risk in Communities (ARIC) cohort, both smokers and non-smokers with any chronic respiratory symptom but pre-bronchodilator FEV_1 in the normal range had an increased risk of mortality, 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, GOLD 0 subjects had 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/year excess decline in FEV_1 ($p<0.001$), a 2.18 ml/year excess decline in FVC ($p<0.001$) and a 1.63 odds ratio for development of incident

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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/year with a stronger association noted in men (25). However, while at 15 years, 20.5% of smokers with chronic bronchitis at baseline had developed COPD, 18.5% of smokers without symptoms at baseline had also developed COPD. Further, smokers without symptoms represented the majority of individuals who developed COPD (8). The European Community Respiratory Health Survey Study (ECRHS) 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 to those without respiratory symptoms, symptomatic subjects were more likely to be current smokers, report respiratory infections before the age of five and to 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 [IRR] 1.85). Probably due to its multidimensionality and to the variety of its causes, dyspnea alone was not associated with incident disease, IRR=0.98 even after adjusting for smoking habits.

The Medical Research Council (MRC) National Survey of Health and Development (NSHD) was a prospective cohort of over 5,000 individuals within the UK (19). Chronic bronchitis symptoms at age 36 years 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 non-smokers, symptoms at most ages were associated with incident airflow limitation by ages 60-64

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years. The longer individuals had symptoms, the greater the rate of FEV_1 decline. Reporting of chronic bronchitis on at least one occasion between 43 and 60-64 was associated with an additional 4.5 ml/year decline in FEV_1.

The Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD) examined over 1,400 participants aged 21-80 in the southwestern US. 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 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, this is only a subset of individuals who experience disease progression, and not even 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.

Physiological measurements as biomarkers of disease progression

The measurement of lung function as a tool to determine presence or absence of respiratory health has been central to the 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 FEV_1, even if the

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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 FEV_1 without obstruction at baseline combined with "rapid" decline as defined by a loss of FEV_1 greater than 40 ml/year (normal rate of loss after the third decade of life is <25 ml/year) over 18 months was associated with a 36-fold risk of developing COPD over the time of observation as compared to those with high baseline lung function without rapid decline (30).

The single breath diffusion capacity for carbon monoxide (DLco) 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 spirometry/normal DLco, 3% developed GOLD-defined COPD while in those with normal spirometry/low DLco, the incidence was 22% (31). These studies support the use of lung function as useful, practical tools to identify subjects at risk for incident COPD development (Table 2). Other physiologic measures besides FEV_1/FVC that may also prove helpful in this regard include forced oscillation technique, 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). While not currently standard of care for COPD, CT is widely available in many countries and routinely used in lung cancer screening programs. Incorporation of quantitative CT imaging into several recent, large cohort

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studies provides a wealth of information regarding imaging abnormalities and their relationship to disease progression.

Emphysema is identified on CT imaging either based on the percentage of lung with low density [-910 Hounsfield Units (HU) and -950 HU have both been used as thresholds] or using the "Perc15" that measures the HU representing the lowest 15th percentile for lung density (the lower the Perc15, the lower the distribution of lung density for an individual patient). While two small studies failed to find a relationship between CT emphysema and FEV_1 decline among unobstructed individuals (35, 36), results from larger studies are more definitive. In the NELSON trial, a population-based CT screening program for lung cancer in men, smokers without baseline airflow obstruction who developed spirometric obstruction at follow-up had significantly lower mean Perc15 scores at baseline, -934.2 HU versus -930.2 HU, $p<0.001$ (37). Participants with upper lobe-predominant emphysema also had greater loss in lung function at follow-up compared with those with lower lobe emphysema distribution, independent of total emphysema extent (38). Individuals with a 10 Hounsfield Unit lower Perc15 at baseline had an odds ratio of 1.46 ($p<0.001$) for the development of airflow obstruction. In a separate US 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 a percent emphysema above the upper limit of normal (ULN) (40). In adjusted models, percent emphysema >ULN was associated with increased odds of incident airflow limitation (OR 4.38) with similar results seen using percent emphysema 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

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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 odds ratio of 2.45 ($p<0.001$). In MESA, a greater Pi10 was associated with a 9% faster FEV_1 decline ($p=0.012$) and incident COPD (odds ratio, 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 inner diameter <2 mm are thought to represent a "quiet" zone at early stages of disease progression where pathologic abnormality 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 non-emphysematous gas trapping, presumed to be small airway abnormality (44, 45). Histologic studies in lung tissue with severe disease have since confirmed significant small airway abnormality in these regions (45). Using PRM in COPDGene, a wide range of PRM small airways abnormality (PRM^{SAD}) was seen among "at risk" current and former smokers and was associated with subsequent excess FEV_1 decline. Individuals with the highest PRM small airway abnormality quartile (≥16%) demonstrated an FEV_1 decline of 49.2 ml/year as compared to those in the lowest quartile, 35.4 ml/year. 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

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limitation severity, COPD prevalence and 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 abnormality, 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 in particular CT abnormalities 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 while others, whether due to 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 supra-normal lung function but suffer significant lung damage yet still have technically normal spirometry at the age of 60-70 due to their high starting point (50). Further, while we have traditionally assumed that most patients pass from normal spirometry through to GOLD 1 and 2, data from COPDGene suggests that some patients with restrictive physiology, defined as PRISm (Preserved Ratio Impaired Spirometry defined as $FEV_1/FVC>0.70$ and FEV_1% predicted<80), also progress to classically defined GOLD COPD (51). In COPDGene, among subjects with PRISm at baseline, 22.2% transitioned to normal spirometry while 25.1% progressed to GOLD 1-4 at the Year 5 visit. Subjects with PRISm at

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baseline also had higher rates of all-cause mortality as compared to those with normal spirometry, although lower than GOLD 1-4 participants. 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 spirometry 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 spirometry while 49.4% developed airflow obstruction after 4.5 years (52).

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 five years. They identified two trajectories of disease progression in which 70.4% of subjects developed small airway abnormality and emphysema prior to larger segmental airway abnormality whereas 29.6% of the cohort demonstrated a reverse pattern with large airway abnormality being present first (53). 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 (54). According to this proposal, individuals can be classified using a combination of symptoms, abnormal spirometry and abnormal CT features as possible, probable and definite COPD. It should be noted that this system would both

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classify some individuals without spirometric obstruction as having possible or probable COPD while re-classifying others with spirometric 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 FEV_1/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, 55) 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 studies reviewed here, such individuals are likely to demonstrate either 1) respiratory symptoms including cough with sputum production, 2) physiologic abnormality including low-normal FEV_1, DLco and/or accelerated FEV_1 decline and/or 3) radiographic abnormality including airway abnormality and emphysema. By expanding beyond the GOLD 0 concept that identified at-risk individuals based on 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 a clear form of pre-COPD for several reasons: *(1)* these symptoms are the most strongly associated with progression to COPD; *(2)* an underlying pathobiological feature has been identified, i.e., increased mucin production (16); and, *(3)* this subgroup exhibit particular morphologic abnormalities, i.e., airway

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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 Medical Research Council over 55 years ago and label these non-spirometrically obstructed individuals as "*Non-Obstructive Chronic Bronchitis*" (NOCB) (56). 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 spirometric obstruction never develops (14). Yet, it is clear that patients with NOCB represents only a subset of those at risk for ultimate disease progression, this is, pre-COPD. We also acknowledge there may be other phenotypic subsets of individuals - yet to be defined, that may or may not develop airflow obstruction but are clinically relevant subtypes due to 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 spirometric 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 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 pre disease states, such as pre-diabetes and pre-hypertension (57, 58). Identification of such individuals could also accelerate conduction of early intervention, disease modification trials.

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In thinking about COPD pathogenesis, we know that airway abnormality can accumulate without spirometric abnormality and that this "silent" period could be considered "pre-COPD" (55). 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, 59). Hence in thinking about pre-COPD versus COPD, symptoms, structural abnormality and causation are similar with the key difference being function, which in this case is 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 identifying spirometric COPD. Here we go beyond the original GOLD 0 definition that focused on symptoms alone. One of the problems with GOLD 0 is that it only identified a fraction of individuals who ultimately progressed to COPD. By additionally 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 little data on the sensitivity or specificity for any individual metric or combinations of metrics to accurately identify those individuals. Further, as highlighted by the recent perspective by Martinez, et al. on the pathogenesis of early COPD, it is also highly likely that age and multi-morbidity confound the relationships between symptoms, CT abnormality and lung function decline, which cannot fully be considered until additional data is acquired in younger individuals (9). We also have significantly less data on COPD that arises among non-smokers. 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

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screening or case finding measures in place to identify even 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 FEV_1/FVC ratio is highly specific for the disease we call COPD, but as the data we show here suggests, it is perhaps not sensitive to the breadth of abnormality we may see earlier in the disease process. Not only are such patients at increased risk for disease progression, but in some cases also experience significant morbidity in the absence of a reduced FEV_1/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 FEV_1/FVC ratio. A particular subtype of pre-COPD is NOCB. Clearly symptoms in this pre-COPD patient population are associated with morbidity, regardless of whether individuals with NOCB ultimately develop spirometric obstruction. Hence they are worthy of formal recognition by regulatory bodies such as the FDA and EMA, particularly given evolving data to support a unique pathologic abnormality. We acknowledge, however, that more data on disease in younger individuals is critical to develop and validate a clinically operable definition of "pre-COPD" with good sensitivity and specificity that can be clinically implemented with confidence.

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Table 1. Association Between Symptoms and Lung Function Decline among GOLD 0 individuals

Study	Prevalence of Symptoms	Outcome
Copenhagen City Heart (8, 25)	Baseline prevalence chronic bronchitis 7.1% of men and 4.8% of women	• After 5 and 15 years, COPD developed in 13.2% and 20.5% of smokers with GOLD 0 at enrollment, respectively. • 11.6% and 18.5% of smokers without respiratory symptoms also were GOLD Stage 1 or worse at 5 and 15 years, respectively. • Symptoms in GOLD 0 were associated with excess loss of 19 ml/yr in addition to the FEV_1 decline seen in unobstructed smokers without these symptoms.
ECRHS (26, 27)	At baseline, 9.2% subjects reported chronic cough and phlegm.	• Incidence of COPD in subjects who confirmed the presence of chronic cough and phlegm at the end of the follow-up (9.4 cases/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/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/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/1,000/yr; 95% CI, 1.9–3.0).
Northern Swedish Cohort (17)	At baseline, 41.9% of subjects reported chronic productive cough.	• 10-year 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 while dyspnea and wheeze were significantly associated with incident COPD in men.

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SAPALDIA Cohort (22)	At baseline, among those without airflow obstruction, 8.1% of subjects reported chronic bronchitis symptoms	• Chronic bronchitis associated with incident COPD as defined by pre-bronchodilator spirometry, rate ratio 1.23 (95% CI 1.00 to 1.51
UK MRC Cohort (19)	Among smokers, chronic bronchitis prevalence escalated between ages 36 and 43 from 7.6 to 13.0%.	• Symptoms associated with a higher risk of subsequent airflow limitation (odds ratio, 3.70 and 4.11, respectively). • The longer chronic bronchitis was present across three occasions (ages 43, 53, and 60–64 yr), the greater the concurrent FEV_1 decline, corresponding to an additional decrement of 3.6 ml/yr per occasion that chronic bronchitis was present ($p = 0.005$).
TESAOD (20)	CB present in 6.9% (majority current or former smokers).	• Incident airflow obstruction among those with CB, 1.37 p=0.07. • Mortality risk stronger among smokers (adjHR 1.50) than non-smokers (0.80) and among subjects <50 years of age (2.22) vs >50 years of age (0.96).
ARIC (23)	Prevalence GOLD 0 14.5% in a population-based cohort based on pre-bronchodilator spirometry and any respiratory symptom including cough, phlegm, wheeze and breathlessness. Overall 20% of those with normal spirometry reported symptoms.	• HR 1.6 for death among GOLD 0 participants as compared to unobstructed individuals without symptoms

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Oslo Norway Cohort (24)	Prevalence GOLD 0, 8.1% in a population-based cohort of men in Oslo Norway. Overall, 9.7% of those without airflow obstruction demonstrated respiratory symptoms.	• GOLD 0 subjects using a modified definition (pre-bronchodilator spirometry and any respiratory symptom including dyspnea and phlegm) had increased risk for mortality, HR 1.35
CARDIA Cohort (18)	Prevalence of any respiratory symptom in population based cohort at baseline and Year 2, 43.9%.	• 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 Years 5 to Year 30. • Report of any symptom was associated with a 2.71 ml/year excess decline in FEV_1 ($p<0.001$) and a 2.18 excess decline in FVC ($p<0.001$) as well as a 1.63 odds ratio 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.

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Table 2. Association between lung function and incident COPD in smokers without airflow limitation

Study	Outcome
Lovelace Smokers Cohort (30)	• These non-obstructed subjects aged between 40 and 50 years, with a normal FEV_1 (75% predicted) in the lower quartile of lung function in the cohort, who lost >40 ml/year of function in 18 months of observation had a 36 fold risk of developing GOLD spirometric stage II COPD over 42 months of observation compared with subjects with high normal FEV_1 and no FEV_1 decline. • At baseline, these non-obstructed 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 FEV_1%
New York Smokers Cohort (31)	• From a cohort of 1570 smokers in the New York City metropolitan area with normal spirometry, two groups were randomly selected. Normal spirometry/normal DLCO (n=59) and normal spirometry/low DLCO (n=46). They were followed over 41 months. • In the normal spirometry/normal DLCO group 3% developed GOLD-defined COPD. In the normal spirometry/low DLCO group, the incidence was 22% ($p = 0.001$).

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

Study	Outcome
NELSON (37, 38, 41)	• 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 versus -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 compared with 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 odds ratio of 2.45 (p<0.001) and a 10 Hounsfield Unit lower Perc15 had an odds ratio of 1.46 (p<0.001) for the development of airflow limitation at follow-up.
New York Lung Cancer Screening Cohort (39)	• Small, US 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)	• 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 FEV_1 decline (p=0.012) and incident COPD (odds ratio, 2.22; p<0.001) at 5-year follow-up • Greater Pi10 was associated with a 57% higher risk of hospitalization or mortality related to chronic lower respiratory disease. • 5.4% of subjects had a percent emphysema above the upper limit of normal and was associated with increased odds of incident airflow limitation (OR 4.38) with similar results seen using percent emphysema as a continuous measure or using a fixed threshold of 5%.

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Korean Cohort (35)	• Korean cohort of 628 healthy volunteers without known respiratory disease or abnormal PFTs at baseline demonstrated that those with emphysema (defined as ≥ 10% low attenuation area based on a -950 Hounsfield unit threshold) had fastest decline in FVC (-33.9 versus -18.8 ml/year, p=0.02) but emphysema was not associated with incident airflow limitation at follow-up (35). • While the presence of emphysema was associated with a greater rate of FEV_1 decline, the difference was not statistically significant.
Pooled Danish Lung Cancer Screening Trial (DLCST) and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) (36).	• Data pooled from DLCST and ECLIPSE, found that among 687 current and former smokers without airflow obstruction, no significant relationship between Perc15 and FEV_1 decline, whereas these relationships were evident in GOLD 2 and 3 participants.
COPDGene (44-46)	• CT small airway abnormality defined using Parametric Response Mapping (PRM^{SAD}) demonstrated association was associated with excess FEV_1 decline at 5 years among at risk smokers without airflow obstruction at baseline. • Individuals with the highest PRM^{SAD} quartile (≥16%) demonstrated an FEV_1 decline of 49.2 ml/year as compared to those in the lowest quartile, 35.4 ml/year. • 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)	• Comparing highest to lowest quartile for mean airway to lung ratio in MESA, COPD incidence rate ratio 8.12 (95% CI 3.81 to 17.27); no difference in FEV_1 decline • Comparing highest to lowest quartile for mean airway to lung ratio in CanCOLD, COPD incidence rate ratio 3.33 (95% CI 1.89 to 5.85); no difference in FEV_1 decline

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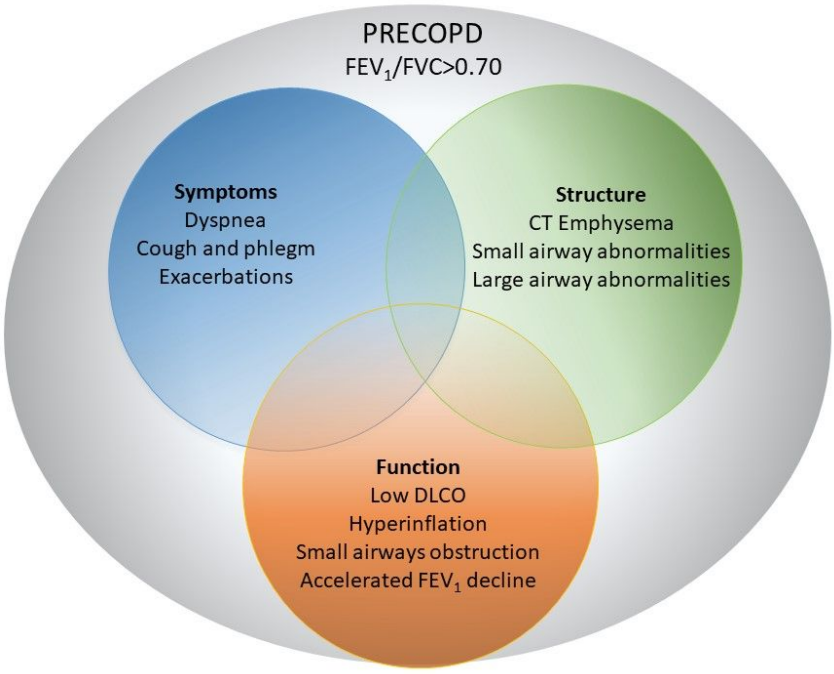
Figure 1. Conceptualized understanding of the relationships between symptoms, structure and function with respect to pre-COPD.



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