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Review Article

Twenty years of changes in the definition of early chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway disease that affects the quality of life of nearly one-tenth of the global population. Due to irreversible airflow obstruction and progressive lung function decline, COPD is characterized by high mortality and disability rates, which imposes a huge economic burden on society. In recent years, the importance of intervention in the early stage of COPD has been recognized and the concept of early COPD has been proposed. Identifying and intervening in individuals with early COPD, some of whom have few or no symptoms, might halt or reverse the progressive decline in lung function, improve the quality of life, and better their prognosis. However, understanding of early COPD is not yet well established, and there are no unified and feasible diagnostic criteria, which complicates clinical research. In this article, we review evolution of the definition of early COPD over the past 20 years, describe the changes in awareness of this concept, and propose future research directions.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic heterogeneous respiratory disease characterized by persistent respiratory symptoms and progressive airflow limitation.[1] There has been growing recognition of COPD as a global public health problem that imposes not only symptoms on affected individuals, but also a significant economic burden on society.[2] In the United States, the cost of hospitalization due to acute exacerbations of COPD can be as high as 18 billion USD annually.[3] In China, COPD causes about 0.9 million deaths per year.[4] COPD is a vastly prevalent disease that afflicts 10% of the world's population and significantly reduces quality of life and life expectancy.[5,6] A report from the World Health Organization (WHO) shows that COPD ranks in the top five causes of deaths in high-income countries and is predicted to be the third leading cause of death worldwide by 2030.[7] Although the importance of studying COPD cannot be overstated, research currently focuses on middle-aged and older individuals with obvious clinical symptoms and established airflow obstruction. This limited focus of clinical research on those with advanced disease is unlikely to uncover pathogenic mechanisms that can arrest progression earlier in COPD development.

There is also growing awareness that many cases of COPD originate from early life events.[8-12] Studies of pulmonary function trajectory show that forced expiratory volume in the first second (FEV_1) declines much faster in the early stage of COPD than in the terminal stage.[13] Therefore, the concept of "early COPD" has been developed, to identify at the onset of the disease individuals at potential risk of developing overt COPD. The hope is to intervene, halt or reverse the decline in lung function and arrest disease progression.[14] The word "early" means at the initial stage of disease onset, although there remain no uniformly accepted criteria for the diagnosis of early COPD.

This review summarizes the development of the concept of early COPD over the past 20 years, from its proposal to various controversies, and finally to current perception. We also provide several feasible perspectives to refine the existing concept of early COPD and present some potential research directions, which are expected to be helpful for future clinical research.

The conceptual changes of early COPD

The proposal of GOLD Stage 0

Many pulmonologists would say that the concept of early COPD originated in the GOLD 0 stage introduced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001.[15] The classification of airflow limitation severity in COPD, which has changed significantly

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between 2001 and 2022, is based on post-bronchodilator FEV_1 value. In GOLD 2022, GOLD stage 1 is characterized by mild airflow limitation (FEV_1/forced vital capacity [FVC] <0.7, FEV_1 ≥80% predicted) and GOLD 2 by moderate airflow limitation (FEV_1/FVC <0.7, 50% ≤ FEV_1 <80% predicted). GOLD 3 is defined as severe airflow limitation (FEV_1/FVC <0.7, 30% ≤FEV_1 <50% predicted) and GOLD 4 as very severe airflow limitation (FEV_1/FVC <0.7, FEV_1 <30% predicted).[1]

However, GOLD 2001 recommended classifying COPD severity into four stages by considering both spirometry results and clinical symptoms. GOLD 0 was then proposed to be characterized by the absence of airflow limitation on spirometry but the presence of risk factors (smoking) and persisting respiratory symptoms (cough and sputum production). Hence, this stage ("stage 0, at risk") aimed to cover populations at potential risk of developing COPD later in life.[15,16]

In GOLD 2001, GOLD stage 1 was characterized by mild airflow limitation with or without chronic symptoms (cough and sputum production), similar to GOLD stage 1 of the GOLD 2022 guidelines. GOLD 2 was defined by worsening airflow limitation (FEV_1/FVC <0.7, 30% ≤FEV_1 <80% predicted) with or without chronic symptoms (cough, sputum production, and dyspnea). Of note, GOLD 2 was further divided into Stage IIA and Stage IIB based on the frequency of COPD exacerbations. Stage IIA (50% ≤FEV_1 <80% predicted) was similar to GOLD 2 of GOLD 2022, while Stage IIB (30% ≤FEV_1 <50% predicted) was similar to GOLD stage 3 of GOLD 2022. In the 2001 criteria, GOLD 3 was characterized by severe airflow limitation (FEV_1/FVC <0.7, FEV_1 <30% predicted) or the presence of respiratory failure, or clinical signs of right heart failure, which was similar to GOLD 4 of GOLD 2022. As can be seen, in terms of COPD severity classification, the cutoff values of lung function indicators have not changed significantly over 20 years. Then and now, they retain the idea that a diagnosis of COPD requires a reduced FEV_1/FVC ratio, at the fixed cutoff of 0.7.

The earlier GOLD reports also highlighted the importance of clinical symptoms as a guide to classification, although there was no perfect relationship between the presence of symptoms and the degree of airflow limitation. GOLD 0 was a novel category proposed by GOLD 2001 to identify those people at risk for COPD and to intervene before significant airflow limitation developed, however, no therapeutic interventions were recommended by the GOLD 2001 guideline for this subset. Whether GOLD 0 patients would definitely develop COPD and whether therapeutic interventions were necessary for these patients were unknown at that time.

Controversies about GOLD stage 0

GOLD 0 has been controversial since it was first proposed.[16-19] Controversies were mostly in two areas, definition and clinical relevance. Patients with GOLD 0 were defined as having chronic respiratory symptoms with normal lung function, however, the earlier definition of COPD required evidence of both impaired lung function and respiratory symptoms.[20] Therefore, there was doubt whether patients with normal lung function could really have so-called "chronic obstruction" and clinical symptoms. However, analyses of data from the Third National Health and Nutrition Examination Survey (NHANES III) revealed that among subjects with low lung function (FEV_1/FVC <0.7, FEV_1 <80% predicted), 66.1% claimed to have at least one respiratory symptom, compared with only 34.4% of subjects with normal lung function.[21] These individuals met the criteria of GOLD 0, which was taken to confirm the authenticity and necessity of the GOLD 0 definition.

The symptoms used to define GOLD 0 were also controversial. GOLD 2001 required the presence of cough and sputum production, without specifying duration. Some authors favored the classical definition of chronic bronchitis (chronic cough productive of sputum in the morning or during the day for at least three months every year), while others used a more sensitive definition of recent respiratory symptoms (cough, sputum production, wheeze, breathlessness, or dyspnea).[16,22] At the time, there were no prospective data to favor either definition.

In terms of clinical relevance, opinions on GOLD 0 varied from "of little help in identifying subsequent airway obstruction" to "the same high demand for medical assistance as COPD" to "an increased mortality risk among male smokers".[16,18,19] For example, using surveys from the Copenhagen City Heart Study, Vestbo et al[16] suggested that the GOLD 0 definition was not suitable to identify those at risk of developing COPD in the general population, even among smokers. By contrast, analyzing data from the European Community Respiratory Health Survey, Marco et al[18] demonstrated that the overall prevalence of GOLD 0 in high-income countries was 11.8% (95% CI: 11.3% to 12.3%) and that those in GOLD stage 0 utilized a significantly higher percentage of healthcare resource than healthy subjects, as true for other GOLD stages.

Importantly, Aronsson et al[19] showed that GOLD 0 was associated with an increased mortality risk among smoking men (HR: 1.65, 95% CI: 1.32–2.08), of similar magnitude as GOLD 2 (HR: 1.41, 95% CI: 1.31–1.70) and significantly higher risk than GOLD 1 (HR: 1.13, 95% CI: 0.98–1.29). Their results supported symptoms of chronic bronchitis as a marker for increased all-cause mortality risk among middle-aged smokers.[19]

Such studies, particularly prediction of adverse outcomes such as mortality despite normal lung function, suggested that GOLD 0 did really exist and mattered.[17] However, several questions remained. What was the probability of GOLD 0 patients progressing to COPD? Did GOLD 0 already represent a subtype of COPD? And could the quality and duration of life be improved by interventions on those in GOLD stage 0?

The demise of the concept of GOLD stage 0

Due to the lack of compelling evidence that individuals "at-risk" would necessarily progress to GOLD Stage 1, in the 2006 GOLD staging system GOLD 0 was no longer included.[23] In that system, the spirometric classification of COPD severity comprised four stages: stage 1, mild; stage 2, moderate; stage 3, severe; and stage 4, very severe, consistent with the 2022 guidelines. Nevertheless, it was recognized that respiratory symptoms such as cough and sputum should not be considered normal and scientists were encouraged to uncover the underlying causes.[24]

In 2016, the American Thoracic Society (ATS) organized a debate on whether GOLD 0 should return to the COPD classification. Proponents argued to include GOLD 0, based on data for acute respiratory events, activity limitation, and abnormal high resolution computed tomography (HRCT) findings in ever-smokers with respiratory symptoms despite normal lung function.[25,26] They also stressed that use of a fixed FEV_1/FVC ratio to define airflow restriction had significant rates of false positivity in the elderly, and false negativity in those <45 years of age.[11] Across the whole population, the GOLD criteria based on fixed ratio caused a false positive rate of up to 60%.[27] Therefore, moving the diagnosis and treatment of COPD to early life stage may in the future be a breakthrough in managing and preventing COPD.

Opponents of reinstating GOLD 0 presented several arguments. Only a quarter of individuals with FEV_1 ≤80% predicted by age 40 developed COPD 22 years later.[12] The classification of GOLD 0 was unstable, with up to 40% symptom-free after five years. Hence, while smoking remains a major risk factor for COPD, labeling all smokers with normal spirometry as "at-risk" had limited predictive value for developing COPD.[16] In addition, chronic cough and sputum production were common in or precursors of many chronic respiratory diseases. Treating those with chronic cough and sputum in the absence of airflow limitation exclusively as GOLD 0 could limit inquiry and potentially delay the diagnosis of other lung diseases.

Since 2016, whether GOLD 0 should return to the COPD staging system has continued to generate debate. Several large studies have shown that individuals with spirometry within the normal range can suffer recurrent acute exacerbations, structural lung changes, and other abnormalities of lung function.[25,26,28] GOLD 2017 referenced two articles as key studies. One was an observational study from the

Subpopulations and Intermediate Outcome Measures in COPD (SPIROMICS) cohort, which involved 2736 current or former smokers and control subjects.[26] Results showed that half of the ever-smokers in this cohort with normal post-bronchodilator spirometry (FEV_1/FVC ≥0.7, and FVC above the lower limit of normal [LLN] range) had significant respiratory symptoms (scores on the COPD Assessment Test [CAT] ≥10). Compared with asymptomatic current or former smokers and non-smoking control subjects, these symptomatic ever-smokers had significantly higher respiratory exacerbation rates, greater limitation of activity, and slightly reduced FEV_1, FVC, and inspiratory capacity. On HRCT, they also had greater airway-wall thickening without emphysema. Of note, 42% of these participants used bronchodilators, and 23% used inhaled corticosteroids (ICS), despite absence of an evidence base for therapy in this non-obstructed group.[26] Hence, chronic respiratory symptoms and acute respiratory events typical of exacerbations of COPD can occur in some smokers without overt airflow obstruction. Whether these individuals will develop obstruction over time is the subject of study in the second phase of SPIROMICS.

Second, a cross-sectional analysis of ongoing Genetic Epidemiology of COPD (COPDGene) observational study similarly showed that the GOLD 0 group had one or more respiratory-related impairments, worse quality of life, and a lower 6-minute walk distance than never-smokers.[25] Additionally, 42.3% of the GOLD 0 group already had CT evidence of emphysema or airway thickening despite absence of spirometric airflow obstruction.[25] These data support the concept that spirometry alone is insufficient to capture all smokers with lung pathology.

Accordingly, using data from the COPDGene cohort, Lowe et al[29] proposed expanding the definition of COPD itself through an integrated approach including environmental exposure, clinical symptoms, chest CT imaging abnormalities, and abnormal spirometric criteria. All individuals were then classified as NO COPD, Possible COPD, Probable COPD, and Definite COPD. This proposed revision of the diagnostic criteria for COPD was considered an initial attempt that would undergo revision as more data were available.

Rather than resurrecting the original, purely spirometric definition of GOLD 0, more recent attempts have been made by many groups to incorporate it into the concept of "early COPD", the subject of the next section.

How to define early COPD

Current understanding of early COPD

The concept of early COPD was actually proposed in 1994 by Petty et al[30] in relation to pulmonary rehabilitation. Because the clinical impact of airflow limitation began natural in the early history of those ultimately diagnosed with COPD,[31] Petty advocated early intervention in interrelated pathogenic pathways well before advanced airflow obstruction developed. Thus, "early COPD" is analogous to the "early disease" concept in many other medical disciplines, including "early diabetes", "early Parkinson's", and "early cardiovascular disease". In these disciplines, early status does not imply inevitable disease development but instead refers to early stages in the underlying pathophysiological processes.[32,33]

In an attempt to avoid confusion and to facilitate future studies, the 2022 GOLD statement clarified the concept of "early COPD".[34] It stated that the word "early" means "near the beginning of a process", which was proposed only to discuss "biological early" when appropriate.[1] The goal is to facilitate the development of effective preventive interventions to block these processes and thereby to reduce the risk of COPD-related mortality.[35] Hence, early COPD denotes the time period in the natural disease history, either before COPD develops or when it has not yet reached its full effects, including spirometric airway obstruction and typical clinical manifestations.[11,36] It is worth noting that the concept of "early COPD" has not been updated in the latest release of GOLD 2023.[37] The "biological early" remains our primary focus. The milestones in the evolution of the early COPD concept are shown in Fig. 1. However, determining the true duration of the "early stage" and exactly when the earliest changes of COPD begin in vulnerable individuals was considered to be difficult.

Understanding the concept of early COPD is facilitated by recognizing the longitudinal progression of COPD.[38] Rennard et al[11] divided the natural history of lung function attainment into five stages: (1) fetal development: the bronchial tree gradually forms and fully develops at week 17 of gestation; (2) childhood: when airway length and diameter increase and alveoli continue to form; (3) adolescent lung growth: during which lung volume and maximal airflow continue to increase along with growth of the thorax, reaching a peak around the age of 20; (4) adult plateau phase: after lung development ceases in early adulthood, lung function remains roughly constant during this period in healthy individuals, for approximately 10 years; (5) decline: thereafter, lung function is gradually lost due to either normal ageing or a pathological process.[11,39-43] Thus, the effect of early disease is specific to each stage, with reduced lung growth during fetal development, childhood, or adolescence; shortened plateau or accelerated lung function loss during adulthood; and episodic loss of lung function without full recovery in any phase.[11,14]

From this viewpoint, pathogenic processes at any stage of life could eventually lead to COPD, so the beginning of an abnormal lung function trajectory in any of these stages can be referred to as "early". Hence, early COPD could be seen as occurring at any age. A 45-year-old woman with an FEV_1 of 50% predicted undoubtedly has significant airflow limitation, but if she reached this level of lung function due to decline over a very short period of time, in terms of her lifetime, she might still be considered in the early stage of disease. Similarly, a 75-year-old man with an FEV_1 of 70% predicted has mild disease. If this degree of lung function impairment had persisted unchanged for many years, it would not be considered early disease in this viewpoint. By contrast, if his lung function decline had occurred recently, it might also be termed early.[44] Therefore, individual lung function trajectories must be considered if the development of overt COPD is to be minimized therapeutically. In this regard, both the Probable COPD and Possible COPD categories of the COPDGene 2019 criteria might be seen as having similar connotations to early COPD, depending on subsequent trajectory, though the intent of these criteria was to develop a framework to expand the diagnosis of actual COPD.[29] Unfortunately, this trajectory-dependent framework of conceptualizing early COPD is hard to operationalize for use in clinical trials, as in most cases it can only be appreciated with confidence retrospectively.

Dilemma in defining early COPD

The importance of studying early COPD is undeniable. In May 2020, *Nature* published a review article recommending a redefinition of COPD and the development of new diagnostic criteria.[45] The primary rationale for this advocacy came from observations in the COPDGene cohort that some participants had chronic respiratory symptoms and significant airway inflammation (airway wall thickening) or structural lung destruction (emphysema) on chest CT, but their lung function did not meet current diagnostic criteria for COPD. Of note, after five years, nearly 40% of participants progressed to late-stage disease.[12] Smokers who develop COPD can have rapid decline in FEV_1, which can increase from 30 mL/year to ≥60 mL/year, and the clinical symptoms generally worsen as the disease progresses.[46,47] Therefore, early diagnosis and intervention is the key to COPD prevention and management, the rationale for attention to early COPD.

At present, however, no definition of early COPD is universally accepted by academics at home and abroad. The principal reasons are inability to define precisely what constitutes "early", the heterogeneity of COPD, and the lack of sensitive tests to assess the initiation of this stage.[48-51]

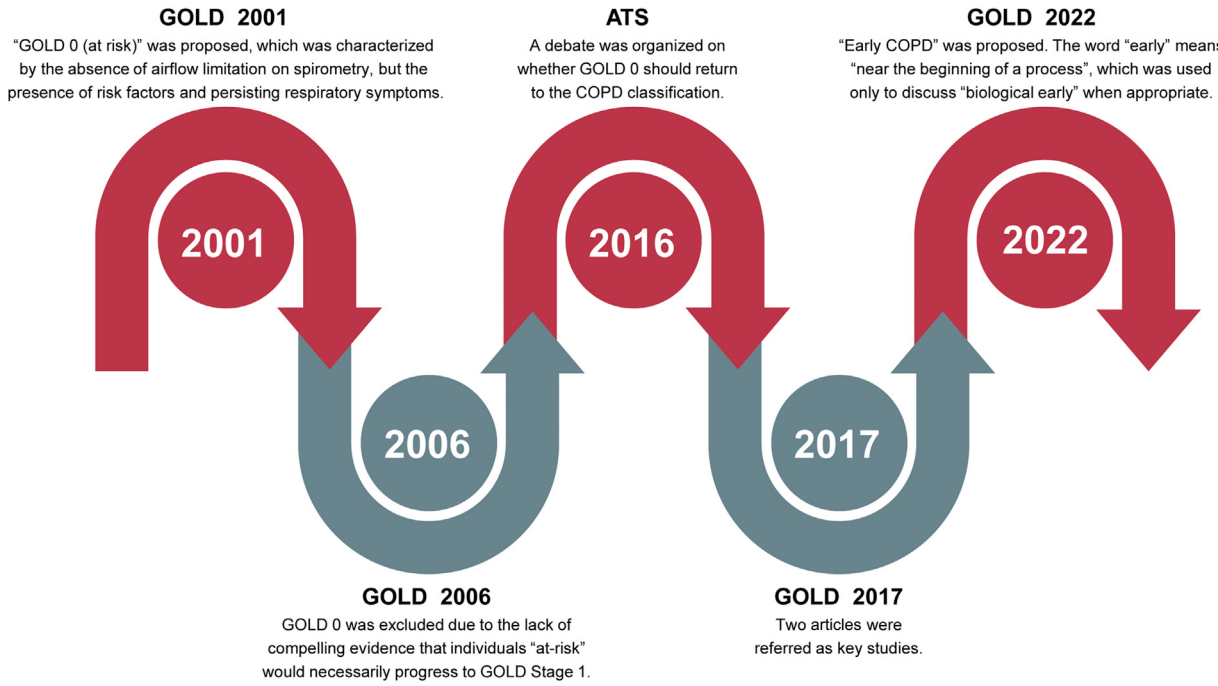

Fig. 1. Milestones in the evolution of the early COPD concept. ATS: American Thoracic Society; GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: Chronic obstructive pulmonary disease.

Appreciation of this last point is aided by considering limitations of spirometry, especially using a fixed FEV_1/FVC value, as a screening tool. Although both FEV_1 and FVC decline with age, FEV_1 declines more rapidly; hence the normal FEV_1/FVC ratio theoretically should change with age. A recent cross-sectional study of Chinese individuals by Liu's group contrasted the new LLN reference equation versus the traditional 0.7 fixed-ratio criteria.[52] Their results showed that the detection rates for COPD were generally consistent between the two methods, with 0.9% of participants under-diagnosed and 1.1% over-diagnosed using LLN as the reference diagnostic criterion. Of note, under-diagnosed participants were younger, with greater symptoms, more reduced lung function and exercise capacity, and rapidly declining FEV_1, while the elderly over-diagnosed subjects differed little from the normal group. These results differ from those of Hardie et al,[53] who found that approximately 35% of elderly healthy Norwegian never-smokers (age >70 years) had an FEV_1/FVC% of <70%, a percentage that increased with participant age. The difference likely relates to the much younger age of the Chinese cohort (mean age 50.51 ± 13.2 year). Thus, LLN appears to perform better at reducing the risk of under-diagnosis in young adults and especially over-diagnosis in the elderly, and is thus more appropriate to detect airflow limitation in those with suspected early COPD.[54] However, perhaps the more important take-home point, considering the evidence from the large North American cohorts cited above, is that spirometry is inadequate as the sole criteria to diagnose COPD.

Possible ways to identify early COPD patients

To identify people at risk for COPD as early as possible and to refine the concept of early COPD, several aspects should be considered, including risk factors, early pathophysiological changes and clinical manifestations.

Risk factors

As described above, attainment of lung function can be classified into five stages over a lifelong continuum from fetal development to the phase of loss-of-function. At disparate life stages, various toxic exposure can lead to distinct changes of lung function in different individuals.[11] Foremost are the genetic factors involved in lung development, as COPD results from complex interaction between genes and the environment.[1] The most well-documented genetic risk factor for COPD is severe hereditary deficiency of alpha-1 antitrypsin (AATD).[55,56] AATD individuals with the protease inhibitor ZZ (PiZZ) genotype who smoke had a significantly lower life expectancy, more severe FEV_1 decline, and greater airway obstruction than PiZZ individuals who do not smoke.[57-59] Costa et al[60] suggested that early diagnosis and screening for AATD might facilitate smoking cessation to maintain lung function. A recent systematic review estimated the prevalence of the PiZZ genotype in 20 European countries and found a PiZZ/COPD ratio of 0.12% (range 0.08–0.24%).[61] However, in China, only the protease inhibitor SS (PiSS) genotype (0.06%) could be found, with an estimated number of 457 individuals with deficiency alleles, while the PiZZ genotype was practically absent.[62,63]

Other potential genetic risk factors include polymorphisms in serpin family E member 2 (*SERPINE2*), transforming growth factor beta 2 (*TGFB2*), hedgehog interacting protein (*HHIP*), patched 1 (*PTCH1*), the matrix metalloproteinase (MMP) family, and several others.[64-69] These genes eventually cause reduced lung function with abnormal lung development, airway remodeling, transient early wheeze, and the *HHIP* risk variant impaired immunity.[70,71] McCloskey et al[72] demonstrated that smoking siblings of patients with severe COPD had a significant familial risk of airflow limitation, indicating that, together with environmental exposure, genetics plays a vital role in susceptibility.[72] Evidence is lacking to prove whether these genes affect the early or late entry of patients into the COPD disease progress, but targeting "genetic COPD" could be a possible way to identify and intervene early in COPD development.[73]

In addition to the genome, transcriptomic changes in some genes may similarly be involved in the progression of early COPD. It is generally recognized that inflammation and oxidative stress are crucial pathogenic contributors to the progression of COPD. While interleukin 1 (IL1) and tumor necrosis factor alpha (TNFα) are necessary for the initiation and maintenance of inflammation, the enzyme epoxide hydrolase 1 (EPHX1) may alleviate increased oxidative stress in the lungs caused by cigarette smoke (CS).[74] Therefore, molecules regulating

these phenotypes may serve as diagnostic biomarkers for early COPD. For individuals with normal lung function, previous research has observed an increased level of sputum matrix metalloproteinase-8 (MMP-8) in symptomatic smokers compared with asymptomatic smokers and non-smokers, indicating a potential diagnostic role of MMP-8 in early COPD.[75,76] Similar results have also been reported for cathepsin S and cystatin C.[77] There is still a considerable amount of research and validation required before biomarkers for the detection of early COPD can be implemented into clinical practice. However, the studies that have been described thus far are encouraging. In addition to alterations in the genome and transcriptome, a previous study has also identified changes in the microbiome of the small airways in COPD patients, which deserves further in-depth investigation.[78]

Cigarette smoking has been the most well-studied and leading environmental risk factor for COPD, which was once considered exclusively a smoking-induced disease in the elderly.[1] Exposure to tobacco smoke, whether active or passive smoking during pregnancy, childhood, or adulthood, is associated with an increased risk of COPD.[79,80] However, among 4291 never smokers from 14 countries in the Burden of Obstructive Lung Disease (BOLD) study, 6.6% met the criteria for mild COPD and 5.6% for moderate to very severe COPD. Even using the LNN threshold, 20.5% of those in this population-based cohort who met spirometric criteria for COPD (≥GOLD 2) were never-smokers.[81] In the prospective Copenhagen General Population Study, never smokers with COPD tended to have fewer symptoms, milder disease, and lower levels of systemic inflammation.[82] Conversely, however, not all smokers necessarily develop COPD; at least 50% of heavy smokers will not progress to COPD during their lifetime, which appears not be explained simply by competing risks of death.[83] Therefore, risk factors other than genetics and smoking must also be involved in the risk of developing COPD.

Multiple studies have confirmed that COPD pathogenesis can even start before birth and that early life events have huge impacts on ultimate adult lung function.[8,84,85] During the antenatal period, maternal smoking, low or very low birth weight, preterm birth, maternal nutrition imbalance, premature delivery, and vitamin D deficiency are all risk factors for COPD in adulthood.[86-93] In childhood, air pollution, childhood smoking, and several diseases, including respiratory infections and asthma, can lead to disordered lung development, reduced lung function, and airflow obstruction.[94-99] Some risk factors are common, while also noteworthy, including sex, socioeconomic status, and longer life expectancy. These risk factors may partly explain COPD in non-smokers, and so should also be considered when defining early COPD.

Early pathophysiological changes

Pathologically, COPD is characterized by persistent respiratory symptoms and chronic airflow limitation resulting from variable degrees of small airway disease (SAD) and emphysema.[1,100] Although clinical and pathological phenotypes of COPD patients vary, most have airflow restriction in addition to chronic bronchitis and emphysema.[101] Some patients present with symptoms of chronic bronchitis, emphysema, or even asthma, while others present with significant lung pathology (e.g., emphysema, chronic bronchitis, or both) in the absence of airflow limitation that requires further evaluation to prevent progression to established COPD.[1] In contrast to emphysema detected by CT scans and airflow obstruction detected by spirometry, which are indicative of late or moderate-to-severe disease, SAD is the pathological characteristic of early COPD.[100,102,103]

In the 1960s, Hogg et al[104] demonstrated that by using the retrograde catheter technique to partition airway resistance, small airways (< 2 mm in diameter) were found to be the major site of obstruction in the human airways. In healthy lungs, small airway resistance contributed to only 25% of total peripheral resistance, while increasing up to 40 times in excised emphysematous lungs, due to mucus plugging, narrowing and obliteration. Since then, researchers utilizing multidetector CT have discovered that small conducting airways shrink and disappear before onset of emphysematous deterioration, which explains the higher peripheral airway resistance in COPD.[100] They also showed that both terminal bronchioles and transitional bronchioles were damaged and their numbers decreased in patients with GOLD 1 and 2 stage COPD. Of note, by the time a smoker progressed to GOLD 1, their number of small airways decreased by 40%. These pathological changes were significantly correlated with lung function decline.[105] A study by Labaki et al[106] showed that areas of SAD gradually evolved into emphysema during COPD progression. These results imply that identifying and interrupting SAD early might halt disease progression.

The proximate cause of SAD is currently believed to be smoking-induced epigenetic changes of airway epithelium, which lead to inflammation and progressive SAD.[107] Normal airway epithelium consists of numerous cell types, including ciliated, mucus-producing goblet, and secretory (club) cells, all of which originate from self-renewing basal cells. However, cigarette smoking reprograms these progenitors epigenetically, resulting in hyperplasia of basal and goblet cells, loss of club and ciliated cells, and ciliary injury. These alterations weaken the immunological defenses of the small airways and increase mucus secretion.[107] Due to the decreased number of ciliated cells, it is difficult to clear the increased mucus with altered physical properties, resulting in a thickening mucus layer. Analysis of induced sputum samples from the SPIROMICS cohort revealed that sputum mucin concentrations are significantly associated with forced expiratory flow at 25% and 75% of pulmonary volume (FEF25-75%) and annualized rates of exacerbations,[108] suggesting that agents that reversed mucus hypersecretion might arrest COPD development or progression.

In addition, the absence of host defense molecules contributes as much as or more to the pathogenesis of SAD. Laucho-Contreras et al[109] confirmed that club cell secretory protein-16 (CC16), a key secreted product of airway club cells, plays a protective role in the development of COPD. CC16 was dramatically decreased in the airways of human smokers, COPD patients, and in a murine model of COPD caused by CS. By stimulating the nuclear factor-κB (NF-κB) signaling pathway, CC16 deficiency exacerbated emphysema formation and airway pathology in CS-exposed mice.[109] Loss of secretory immunoglobulin A (IgA) translocation into the airway lumen is another significant pathophysiological alteration induced by smoking.[107] In normal small airways, dimeric IgA is translocated into the mucosal lumen by the polymeric Ig receptor (pIgR). This process reduces airway inflammation by binding to bacteria and their products to facilitate their elimination. However, diminished pIgR expression in response to smoking leads to a shortage of secretory IgA in individual small airways, resulting in bacterial invasion and adhesion, chronic inflammation, and airway wall remodeling.[110] Early identification and intervention of SAD may be a promising strategy to halt the progression of early COPD.

Clinical manifestations

Early COPD may present with or without symptoms, hence whether symptoms should be used to diagnose the condition, or even to identify those at higher risk remains controversial. When present, symptoms can include chronic cough and phlegm, with dyspnea appearing only on greater loss of lung function. Previous studies highlighted the dynamic changes of symptoms in smokers, with individuals showing persistent symptoms having faster FEV_1 decline and greater risk of developing COPD than asymptomatic individuals.[25,26] However, data from the Copenhagen City Heart study showed that in a general population, most individuals who eventually develop spirometrically-defined COPD do not initially report cough or sputum production.[111]

More recent compelling evidence supports that the persistence of clinical symptoms is associated with COPD progression. Analysis of the North West Adelaide Health Cohort Study (NWAHS) revealed that, in both smokers and non-smokers, persistent respiratory symptoms (cough ± sputum) helped to identify people with a significant subsequent lung function decline, and psychologic and metabolic morbidity.[112] Simi-

larly, a study by de Marcos et al[113] identified a subgroup of young adults with a high risk of developing COPD with the presence of chronic cough/phlegm, which was an independent, significant predictor (incidence rate ratio: 1.85; 95% CI: 1.17–2.93).[113] Data from a nationally representative British cohort revealed that chronic mucus hypersecretion between ages 36 and 43 years was associated with a higher risk of airflow obstruction in later life. The longer chronic mucus hypersecretion was present, the greater the FEV_1 lost.[114] A study by Kesimer et al[108] confirmed the harmful effects of mucus hypersecretion. Smoking cessation was usually followed by the resolution of smoking-related chronic mucus hypersecretion.[114]

Therefore, although there is no absolute association between early COPD and the presence of clinical symptoms, those at risk for early COPD (based on the exposures cited above) should be advised that development of pronounced symptoms may indicate a poor prognosis. Whether and what kind of therapeutic interventions should be performed when early COPD patients develop symptoms deserves our further consideration and resolution.

Differences between early COPD and mild COPD

Unfortunately, previous therapeutic trials have used spirometrically mild COPD in older individuals as a surrogate for early COPD.[115-117] While this is understandable, as early COPD is difficult to define accurately, differences between the two concepts should be recognized. Early COPD is the point in COPD development before frank spirometric airway obstruction or typical clinical manifestations appear. Patients with early COPD may not meet the current diagnostic criteria for COPD (e.g., accelerated FEV_1 decline in a short period that still remains in the normal range), but emphasis is on the concept of time (realizing that definition of duration remains controversial, as discussed below). Importantly, some early COPD patients start their FEV_1 progression trajectory from a reduced maximal attained lung function due to early life events affecting lung growth.[118]

Thus, early COPD is not synonymous with mild COPD, which is clearly defined by the GOLD criterion as GOLD 1 stage, regardless of age, based on post-bronchodilator spirometry using the fixed ratio definition.[1,119] Such mild COPD might not progress over time, [9] especially in the elderly. Hence, equating mild COPD with early COPD has hampered investigation of the real pathological mechanism responsible for progressive lung damage, and thus the development of actual disease-modifying agents.

Diagnostic criteria of early COPD in different clinical studies

Several research teams have defined early COPD for enrollment in clinical trials. In 2018, a large group of international experts led by Martinez proposed the most widely used definition, based on operational and practical considerations.[107] The diagnosis was to be made in individuals aged under 50 years with ≥10 pack-years smoking history who fulfilled at least one of the following criteria: (1) evidence of early airflow obstruction: FEV_1/FVC below the LLN (post-bronchodilators); (2) compatible chest CT abnormalities, including visual emphysema, gas trapping, or bronchial thickening; or (3) known accelerated FEV_1 decline: annual decline rate of FEV_1 ≥ 60 mL/year. Other chronic lung diseases, including interstitial lung diseases, but not asthma, were exclusionary. Thus, this definition was based on age, smoking exposure, and a relaxed definition of impaired lung function, or radiographic evidence of anatomic lung derangement.

Although this empiric definition is applicable to clinical trials and academic research, some points merit discussion, especially with regard to its use in non-European populations. The first is the diagnostic criteria of age. As mentioned above, early COPD can conceptually occur at any age. The strict age limit (<50 years of age) was designed to avoid inclusion of individuals with late mild COPD, which could dilute treatment effects in trials of novel therapies. However, it has the acknowledged potential to exclude individuals whose disease commences at an older age. This consideration may be more important for asthma–COPD overlap (ACO), which will clearly require separate criteria.

Second is the threshold of smoking volume and indeed the exclusive focus on cigarette smoking exposure. The cumulative smoking threshold was based on data from the Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort, which identified 10 pack-years as both the minimum exposure resulting in lung function decline in early adulthood and also the point at which accelerated lung function decline can be detected.[12,120] Examination of these age and pack-year criteria in the Copenhagen General Population Study identified early COPD in 15%.[54] However, a recent analysis from the same cohort showed that among 5497 individuals aged <50 years at baseline with FEV_1/FVC ≥0.70, prevalences of early COPD differed minimally by smoking history: 4%, 3%, and 2% in smokers with ≥10 pack-years, smokers with <10 pack-years, and never-smokers, respectively.[121] In this cohort, fewer than 24% of those who met the age and pack-year criteria proposed by Martinez et al[107] developed COPD 10 years after their initial evaluation. These results lead Çolak et al[121] to comment on the difficulty of predicting progression to overt disease in younger individuals, while pointing out the very high negative predictive value (97%) of the criteria proposed by Martinez et al.[107]

Moreover, although smoking was included as the most commonly encountered risk factor for COPD in industrialized nations and urban populations worldwide, non-smokers account for 25–45% of all COPD patients.[122,123] From a clinical viewpoint, other important risk factors, such as exposures to biomass fuel combustion, to air pollution (both outdoor and indoor), and resulting from specific occupations, should also not be neglected. Investigating these exposures also represents a promising target for unique research opportunities in China.

The secondary diagnostic criteria can also be examined. Reflecting the concept reviewed above that strict reliance on a fixed ratio spirometric definition of COPD is too restrictive, especially in early disease, CT scan abnormalities including airway wall thickening and small airway abnormality were also included in the definition.[107] However, this inclusion requires refinement of age-specific thresholds of imaging data.[124,125] Because such thresholds are incompletely defined at present, more studies will be needed. Nor is there consensus on the duration or magnitude of the criterion of FEV_1 decrease. Considering that acute pulmonary inflammation could lead to transient decline in FEV_1 followed by improvement, this definition also requires standardization.[126] The concept of lung function trajectory merits specific consideration. A substantial proportion of adults with overt COPD do not experience an accelerated FEV_1 decline in the progression of COPD.[12,127] However, because the goal of the criteria proposed by Martinez et al[107] was to facilitate the development of disease modifying-therapies, their definition did not include this group, who are in the absence of such decline will mostly develop late mild COPD. Lastly, whether clinical symptoms should be included as a secondary criterion of early COPD is an open question. It is being investigated in the new SOURCE cohort of the SPIROMICS network (clinicaltrials.gov identifier NCT05033990) and also by follow-up of symptomatic smokers with respiratory symptoms in the absence of airflow obstruction in SPIROMICS.[25,26]

In response to these concerns, Soriano et al[14] proposed an expanded concept of early COPD to identify subgroups that are more likely to progress to worse disease outcomes. Their criteria for age and smoking exposure were identical (though they also proposed that an equivalent biomass exposure history could be substituted, without defining how to estimate such exposure). Their definition differed in including reduced FEV_1/FVC ratio as either <LLN or <0.70 (rather than only as <LLN) and not considering radiographic evidence of lung pathology, which might reduce resource utilization in case-finding at the expense of sensitivity [Table 1]. The noteworthy addition of this definition was to distinguish early COPD with low versus high disease activity, based on symptoms (modified Medical Research Council score [mMRC] <2 versus ≥2, exacerbations <2 versus ≥2 annually), and diffusing capacity of the lung for

Table 1
Early COPD diagnosis criteria as proposed.

Reference	Diagnosis criteria
Martinez et al[107]	Required diagnosis
	Age <50 years
	Smoking history ≥10 pack-years
	One or more of the following
	FEV_1/FVC less than LLN
	Compatible CT abnormalities
	Evidence of accelerated FEV_1 decline (≥60 mL/year)
Soriano et al[14]	Required diagnosis
	Age <50 years
	Smoking exposure >10 pack-years
	FEV_1/FVC less than LLN/0.7
	Early COPD with low disease activity
	FEV_1 >50% predicted
	mMRC <2
	DL_{CO} ≥80% predicted
	No frequent exacerbations
	Early COPD with high disease activity
	FEV_1 <50% predicted
	mMRC ≥2
	DL_{CO} <80% predicted
	And/or ≥2 exacerbations per year

COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; LLN: Lower limit of normal; mMRC: Modified Medical Research Council score; DL_{CO}: Diffusing capacity of the lung for carbon monoxide.

carbon monoxide (DL_{CO}) ≥80% versus ≤80% predicted. Whether all or only some of these additional criteria were required was not specified.

Siafakas et al[128] suggested that the preclinical stage of COPD (GOLD 0) or the definition of "at-risk to develop COPD" should be re-established and that early symptoms, including chronic cough and sputum expectoration, should be considered inclusionary, even without spirometric abnormality. Although they noted the ability of imaging to detect subclinical disease, they did not advocate including them in the definition of early COPD, which they equated with GOLD 0 and advocated reintroducing.

Importantly, none of these definitions has been validated in longitudinal cohort studies, nor has any been accepted by regulatory agencies for product development. There is no universally acknowledged definition.

Potential treatments in early COPD

There are currently a variety of clinical treatments for COPD, including smoking cessation, inhaled bronchodilator and steroid therapy, phosphodiesterase-4 inhibitors, macrolides and N-acetylcysteine (NAC), vaccination, and pulmonary rehabilitation.[37] However, there is a distinct lack of literature on clinical trials concerning early COPD, despite the fact that the vast majority of the studies on COPD treatment have concentrated on the established disease. While bronchodilator therapy can alleviate COPD symptoms, it is unclear whether or not this can also confer benefits in early COPD. NAC was found to be more beneficial in chronic bronchitis patients with normal lung function, which generally precedes the development of a spirometric diagnosis of COPD.[129] In addition, a systematic review of pulmonary rehabilitation in patients with mild COPD revealed indications of improvement in the 6-min walk test and exercise capacity.[130] These results might point to the potential benefits of NAC and pulmonary rehabilitation even in the early stages of COPD. However, more research is needed to explore the treatments for early COPD.

Future research directions

Research on early COPD is still in its infancy, and many questions need to be addressed. A crucial one is the dimension of "time", on which there is not consensus. Though a single pathway to COPD is unlikely, a frequent pattern is silent development of SAD after a significant period of toxic exposure; this process could begin in a lung that has attained normal adult function, or in one that did not, with the latter situation predisposing to earlier progression to overt COPD. Next are lung structural changes that may precede or be accompanied by symptoms, and finally demonstrable airflow limitation.[131-133] Depending on how long a time frame is allowed within the definition, any of these factors such as lung function, lung structural changes and symptoms, could be included within early COPD. Truncating the definition based on a specific time-frame would yield a range of individuals with different clinical characteristics available for studies. Hence, the challenge or research is to pick practical, objective means of selecting potential participants.

Doing so will require careful consideration of research goals. Although genetic factors are clearly important, at present it would be infeasible to genotype individuals before enrollment; however, that may change as sequencing costs decrease, and examining genetic risk could become essential for the application of precision treatments, which have revolutionized treatment of diseases of other organs.[64-69] Deciding to study other risk factors will also depend on what is hoped to be learned. For example, there is great need for research on early COPD induced by biomass fuel inhalation, which will require vastly different recruitment strategies from those for smoking-induced disease. Comprehensively identifying which risk factors impact pulmonary function trajectory would best be solved by birth cohorts, which require decades-long funding commitments. SAD can be identified by parametric response mapping, which requires radiation, or endobronchial optical coherence tomography (EB-OCT), an invasive procedure that also permits bronchoscopic tissue sampling for mechanistic studies.[134-136] However, given the key role that SAD appears to play in early COPD, at least in smokers, less invasive methods, perhaps including impedance oscillometry or molecular markers would be highly desirable. Does the presence of SAD mean we should start intervening early, and if so, how? All these questions, which have tremendous implications for healthcare utilization and public health, need to be answered by evidence from large observational cohort studies or randomized clinical trials (RCTs). Therefore, the question of how to conduct clinical studies in early COPD should urgently be addressed.

In addition to the rational design of clinical studies, there are many other aspects worth exploring in the future. As mentioned above, apart from the genome, the transcriptome and microbiome are similarly altered in the early stages of COPD. Therefore, large multicenter prospective disease cohorts should be integrated with multi-omics, including genomics, transcriptomics, proteomics, microbiomics, metabolomics, and radiomics, to identify diagnostic and prognostic biomarkers for early COPD. Moreover, individualized intervention and treatment strategies also need to be considered, for example, how to administer drug therapy to early COPD patients with different clinical characteristics? How to choose biomarkers for individualized diagnosis and treatment? We should scientifically develop individualized diagnosis and treatment regimens for patients based on their epidemiological, clinical characteristics and endotypes.

Conclusion

Early COPD is the initial stage of COPD. It is a concept long proposed but often not fully appreciated by clinicians, who may confuse it with mild COPD. Over the past 20 years, the perception of early COPD has changed, evolving from the GOLD stage 0 concept to the current focus on considering life-stage, lung function trajectories, and potentially silent pathological changes. Identification, management, and hopefully prevention of early COPD should be an important focus of medical practice, particularly in the primary care setting, and should include whole-course management, and personalized treatment. At present, proven interventions consist chiefly of removing toxic inhalational exposures, minimizing respiratory infections through immunizations, and perhaps

improving nutrition, especially before adulthood. Such timely interventions are expected to prevent lung function decline that leads to full-blown COPD, thereby improving the prognosis of the patients. Many unresolved questions about early COPD need to be explored in long-term cohort studies.

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Conflicts of interest

Dr. Curtis participated in the following COPD-relevant industry-sponsored activities: AstraZeneca PLC, consultant, AstraZeneca Respiratory Advisory Council, 09/16/2020–12/31/2021, $1362, paid to University of Michigan; CSL Behring, LLC 199240, consultant, Virtual Nebulized Immunoglobulin (NebIg) Advisory Board, 02/01/2021–2/23/2022, $2500, paid to University of Michigan.

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