



Early View

Series

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What is Early COPD and Why is it Important?

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ABSTRACT

There is increasing interest on the origins of COPD, as it is envisaged that preventive efforts and treatment can modify its clinical course. The concept of early COPD is not new, but it has recently regained interest, given new population data, recent cellular and molecular advances, and insights from clinical trials. To date, many knowledge gaps in the nature of early COPD still exist, mainly because COPD has always been considered a disease of the elderly, and little attention has been paid to the pathologic changes occurring in the lungs of individuals at risk before they develop clinically evident COPD. Future studies should focus on identifying early pathologic manifestations of COPD in order to prevent its progression in susceptible individuals. In this review, we aim to summarize what is known on early COPD, from the epidemiological, cellular and clinical perspectives.

INTRODUCTION

COPD is a heterogeneous, common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that are due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. This concept implies that we expect to find the disease in patients with a certain age when the pathophysiological changes are well established, which limits our capability to modify its natural history. However, COPD pathogenesis may begin much earlier, even before birth, as passive foetal smoke exposure in utero is associated with increased adult COPD risk, with independence of either active and passive smoke exposure in childhood, adolescence or adulthood.¹ Individuals sustaining childhood respiratory impairment are also at increased risk of reduced adult lung function.² Therefore, we have a number of challenges to overcome before defining what is early COPD.³ Current definitions do not help. For instance, Martinez FJ, et al.,² define early COPD as ever-smokers (≥ 10 pack-years), younger than 50 years, and with any of these abnormalities: (1) $FEV_1/FVC <$ lower limit of normal; (2) compatible CT abnormalities (airway abnormality and/or emphysema); or (3) FEV_1 decline (≥ 60 mL/year). Regrettably, in historical cohorts and often in current patients, imaging and/or serial lung function are often unavailable.

What is clear is that early disease does not mean mild disease (**Table 1**). The severity of any disease relates to the extent of functional impairment of the target organ and, in the case of COPD, severity has traditionally been determined by the degree of airflow limitation, mainly by the FEV_1 ,⁴ or by composite measures that express respiratory impairment and prognosis, such as the BODE (BMI, airflow obstruction, dyspnoea and exercise capacity)⁵ and ADO (age, dyspnoea and obstruction)⁶ indices, among others.⁷ The definitions of “early” vs. “late” disease take as reference point the time when the disease is diagnosed or studied for the first time. Thus, the terms “early” and “late” not necessarily mirror the real time course of the disease. So far, COPD severity is indicative of the loss of lung function, whereas early relates to a timescale, and both may/may not be coincident in the same individual. Part of the confusion is that, at present, it is not possible to differentiate mild COPD of recent onset from earlier-onset COPD that has not progressed to a more severe stage of disease.⁸ Some evidence indicates that the majority of GOLD stage I patients fail to develop clinically important

COPD, even if they are persistent smokers.⁹ Furthermore, GOLD I patients present similar characteristics, in terms of respiratory symptoms and exercise capacity, to smokers with normal spirometry. In contrast, other studies suggest that the decline in lung function is much faster in the early stages than in the advanced stages of the disease, mainly among symptomatic patients.¹⁰ Recent studies of long-term cohorts have shown that the majority of patients do not progress to the most advanced phases of the disease, although the presence of mild obstruction predisposes to a more rapid fall of FEV₁. Lange et al.,¹¹ showed that the combination of low baseline lung function and rapid decline, as defined by a mean annual loss of 40 mL FEV₁ or more, results in a greater risk of development of COPD compared to subjects having only one or none of these traits; this was independently replicated in the Lovelace cohort.¹²

Articles for this Review were identified from searches of PubMed and references from relevant articles, published in English with the search terms “COPD”, “emphysema” “chronic bronchitis”, “early origins”, “lung development”, “early childhood exposures”, “low birth weight”, “intrauterine growth retardation”, “stunting”, and “foetal growth restriction”.

EPIDEMIOLOGY OF EARLY COPD

No information is available on the impact of COPD of recent onset, so data must be extrapolated from what is known for mild COPD. In Spain, the EPISCAN study on the prevalence of COPD, established that mild COPD accounted for 56% of all patients diagnosed with COPD, although 73% of subjects with COPD remained undiagnosed.¹³ In this study, the global prevalence of COPD in smokers or ex-smokers younger than 50 years old was 4.1% (2.9-5.4). Other studies yield similar figures.¹⁴ The Global Burden of Disease (GBD) study, by extrapolating data from multiple studies, identifies a large geographical heterogeneity of COPD prevalence in those younger than 50 years by country, being the highest in males in Papua New Guinea (4.99%) and United Arab Emirates (4.35%), and in females in Papua New Guinea (6.16 %) and Taiwan (6.01 %) (**Figures 1 A and B**).¹⁵

As exemplified by The Asian Network for Obstructive Lung Disease (ANOLD),¹⁶ BOLD,¹⁴ and GBD,¹⁵ there is a large international and intra-national heterogeneity in all COPD epidemiological estimators. Of interest, BOLD recently suggested that in BOLD sites, even adjusting by tobacco history, national COPD mortality rates were more strongly associated with spirometric restriction rather than obstruction, especially in

those younger than 60,¹⁷ therefore connecting stunting with lung development and early COPD and restriction.

This universal underdiagnosis, together with the lack of information about the risk of progression of the disease, makes it difficult to predict the true impact of the disease. However, patients with mild COPD and respiratory symptoms demand more health care and consume more health resources than those asymptomatic with the same degree of disease.¹⁸

Initially, epidemiologists did not include mild COPD in the epidemiological definitions of the disease, for the sake of uniformity.¹⁹ A definition of early COPD depends in part on smoking history and implies anatomical changes in the absence of airflow obstruction.

Worldwide variations in the way COPD arises likely reflect differing prevalence of smoking, with which chronic cough and phlegm are closely associated, but also a combination of other exposures that interact differently during lung development (**Figure 2**),²⁰ ageing, and gender distribution.²¹ Collectively, these data indicate a strong association of smoking in early adulthood with lung function decline, and imply that the impact of smoke exposure in susceptible smokers is detectable with exposures as little as 8-10 pack-years, in their late 30s to early 40s. Importantly, an early COPD definition does not exclude previous asthma, which has been recently reported as an important risk factor for development of fixed airflow obstruction. Within the ECRHS study, early-onset asthma was observed in 26% of those diagnosed with COPD at a mean age of 37 years, which represents a 20-fold increased risk of adult airway obstruction compared with those without asthma diagnosis.²²

Smoking during adolescence reduces peak lung function values.²³ In an approximation to the “infamous” Fletcher & Peto curves, the BODE cohort demonstrated that clinical COPD patients <55 years old might have similar severity distributions (**Figure 3**) and FEV₁ decline trajectories as patients >65 years old (**Figure 4**).²⁴ Although adverse early-life exposures are common, their precise contribution to adult COPD remains unclear, merits exploration, but also needs not be considered exclusionary in an operational definition of early COPD.

Childhood stunting, a condition that is defined as height for age below the fifth percentile on a reference growth curve, affects a large percentage of the world's youth. It measures the nutritional status of children, and it is an important indicator of the prevalence of malnutrition or other nutrition-related disorders among an identified population in a given region or area. It is yet unknown the effect of stunting on lung development and eventually COPD. All in all, merging global children needs with adult respiratory epidemiology, may yield to advancing in our understanding of determinants of early COPD trends.

Other factors have been implied in rapid decline in lung function during early adulthood include emphysema on CT scan;²⁵ low DLCO,²⁶ gas trapping on inspiratory/expiratory CT scan;²⁷ or airway hyperresponsiveness.²⁸ However, a substantial part of individual variation of FEV₁ decline can be explained by routinely measured clinical variables (age, weight, smoking burden, ...).²⁹

PATHOLOGY AND MOLECULAR IMPLICATIONS

Moving to histological and molecular evidence, COPD develops slowly over decades as small airways narrow and disappear, causing lung function to decline.^{30,31} As inflammation develops in the lungs of (nearly) all smokers, sequential, stereotypical changes in distal airways happen only in a few susceptible smokers, leading to accelerated loss of lung function.³² The introduction of micro computed tomography (microCT) has made possible to show that the destruction of the terminal bronchioles is well established when the emphysematous lesions become large enough to be visualized on thoracic multidetector CT scans.³³ Importantly, one recent study showed that early

COPD is characterized by destruction and loss of the terminal and transitional bronchioles before a decline in lung function is observed, even in the absence of emphysematous destruction, whereas the surviving airways have narrowed lumens and thickened walls.³⁴ This finding has important clinical implications, as several large clinical trials targeting severe COPD may have failed because they were initiated in patients who already had “irreversible disease” characterized by parenchymal destruction and remodeling of vast numbers of terminal and transitional bronchioles (**Table 2**).

Another early effect of cigarette smoke is the epigenetic reprogramming, remodeling, and hyperplasia of airway basal cells, the stem/progenitor cells of the ciliated and secretory cells that are central to pulmonary host defense, initially without inflammatory cell infiltration.³⁵ Small airway epithelium basal/progenitor cells from COPD smokers, and to a lesser extent from smokers without COPD, are limited in their ability to regenerate a fully differentiated epithelium.^{36,37,38} In COPD, the decreased number, self-renewal, and multipotentiality of airway basal progenitor cells relates to impaired lung function, and might identify a subset of people representing an early, pre-diagnostic stage of COPD.³⁹

Little is known about the initial steps in the activation and spreading of the innate and adaptive immune systems in early COPD. It was initially postulated that the innate immune inflammation drives the mild stages of COPD, whereas in more advanced COPD adaptive T- and B-cell responses become predominant. This concept has now been called into question. The involvement of innate and adaptive immune responses might not be sequential,⁴⁰ but might occur at the same time early in life as a result of individual susceptibility to several factors apart from active cigarette smoking, such as

air pollution, maternal smoking, asthma and infections in childhood, determining the development of airflow obstruction at a young age.⁴¹ The destructive remodelling processes observed in both bronchiolar and alveolar tissue in COPD, are associated with the infiltration of macrophages, CD4 and CD8 cells, and B cells, combined with increased formation of tertiary lymphoid organs as the disease progresses,⁴² indicating that innate and adaptive immune systems act simultaneously during the entire onset and progression of COPD. Also, dendritic cells (DCs) serve as bridge between innate and adaptive immune responses and have emerged as key players in both pathological processes from the earliest to the later stages of COPD pathogenesis (**Table 3**).⁴³

A loss of peripheral tolerance to self-antigens is another important early event contributing to lung parenchymal destruction in smokers with emphysema.⁴⁴ Ever-smokers with emphysema present autoreactive T cells in their peripheral blood long after smoking cessation, and the degree of activated T cells correlates with loss of lung function.⁴⁵ Auto-antigens to lung components such as elastin appear during either abnormal lung development or abnormal tissue repair process. Active smokers with increased cytokine responses to self-antigens have a higher rate of emphysema progression. This could induce a host response that prevents the lung from developing normal maximal flows in and out of the lungs by age 25, thus representing a risk factor for the development of early COPD. Regulatory T cells (Treg) are subsets of CD4+ T cells with immunoregulatory functions, which inhibit autoimmunity and suppress inflammation. Smokers with COPD have a loss of Tregs in lung parenchyma and in bronchoalveolar lavage compared with smokers without COPD.^{46,47} Also, in COPD, Tregs are highly suppressive and T effector cells express an exhausted phenotype, with a dysregulation of immune checkpoint axes leading to excessive T-cell inflammation as

a consequence of acute infection, which may be an additional cause for T-cell dysfunction. Importantly, the frequency of highly suppressive Tregs has a direct relationship with lung function of patients with COPD (**Table 3**).⁴⁸

Increased number of B cells, either aggregated or scattered in lymphoid follicles, is found in the parenchyma and in both small and large airways from patients with emphysema-predominant COPD.^{49,50,51} A transcriptomics study reported an enrichment in B cell-related genes in patients with COPD with high-resolution CT-defined emphysema that was absent in chronic bronchitis.⁵² However, to date, the presence of B cells and lymphoid follicles is regarded as a late event in the pathogenesis of COPD and there is a lack of studies linking the presence of B cells with the early onset of COPD. Innate immune lymphoid cells (ILCs) have recently been detected in human lung tissue.⁵³ Specific subsets of ILCs deliver potent innate immune stimuli to promote Th1 responses and activate CD4, CD8, and B cells without the requirement for antigen presentation.⁵⁴ Interestingly, the appearance of COPD is associated to the colonization of the bronchial tree by potentially pathogenic microorganisms from its early stages, and a decline in microbial diversity is associated with emphysematous lung destruction.⁵⁵ Thus, the susceptibility of some smokers to develop early onset COPD might be explained if ILCs stimulation induced a specific Th1 response to microbial antigens in early stages of the disease. This also suggests a direct effect of the lung microbiome on the onset and progression of COPD (**Table 3**). A blunted innate and/or adaptive immune system contributes to recurring infections in COPD. COPD alveolar macrophages have impaired phagocytosis of *S. pneumoniae* and a selective defect in uptake of opsonized bacteria, but these defects are mostly associated with COPD exacerbation frequency.⁵⁶ On the other hand, infections in the early age (e.g. respiratory syncytial virus) increase the susceptibility to cigarette smoke or biomass exposure,

directly contributing to early onset of COPD. Thus, it is still unclear whether a primary deficit in the innate/adaptive immune system development and function precedes the microbial colonization, infections, and the development of the inflammatory process in COPD, or vice versa (**Table 3**).

One important unanswered question is why some smokers develop COPD at early age whereas others develop lung cancer. Interestingly, the incidence of lung cancer appears lower in younger patients with GOLD III-IV COPD compared with older patients with GOLD I-II COPD.^{57,58} One hypothesis is that the dysfunctional activation of the immune system by noxious stimuli such as cigarette smoke becomes a double-edged sword: in some individuals, the immune system is hyperactivated, thus leading to the severe stages of COPD, emphysematous destruction and autoimmunity. In others, immune escape mechanisms prevail,⁵⁹ in order to evade COPD, thus facilitating the development of cancer. Anti-inflammatory therapies attempting to modify COPD progression might also suppress key protective functions of our body system and thus should be approached carefully.

Genetic factors might contribute to the development of COPD in young individuals, but knowledge gaps in their exact role in early COPD still exist. There is a dose-dependent relationship between telomere length and pack-years of smoking.⁶⁰ Also, cigarette smoke alters mitochondrial structure and function especially in airway epithelial cells.^{61,62,63} However, as the development of the persistent airflow limitation characteristic of COPD is not always a result of accelerated decline in FEV₁, but can be due to an abnormal lung development in childhood, aging may not always be a pathogenic mechanism in those individuals who develop COPD early in life.⁶⁴

CLINICAL IMPLICATIONS

Diagnosis of COPD of recent onset

Spirometry is considered the fundamental tool for the diagnosis of COPD according to the Global Initiative on Obstructive Lung Disease (GOLD).⁴ However, despite being “normal” according to GOLD, smokers with normal spirometry but low DLCO are at significant risk of developing COPD with obstruction to airflow.⁶⁵

To date, no other markers of the disease are known to predict which patients with COPD of recent onset will progress to a greater severity/worse prognosis of the disease. The ECLIPSE study identified a subgroup of patients with an accelerated loss of lung function,⁶⁶ which can be considered as an indirect marker of activity. Similarly, an increase in symptoms or frequent exacerbations^{67,68} could be considered as indirect markers of activity.

Therefore, the search for signs of disease activity is especially relevant in patients with COPD of recent onset. For this reason, we propose a strategic view of the concept of COPD of recent onset (**Table 1**):

Prevention and treatment of COPD of recent onset

Of the many causes of COPD, cigarette smoking is by far the most important. Smoking cessation is the main intervention in order to prevent the development of COPD. If achieved early enough, smoking cessation reduces the incidence of respiratory morbidity and incident COPD.⁶⁹ There are several studies showing that intervention in phases of lesser COPD severity can have an impact on the evolution of the disease (**Table 4**), although none of these phases would fit the definition of early COPD. The Lung Health Study showed that an intensive smoking cessation program was associated with improvements in lung function at 5 years in patients with mild and moderate COPD ($FEV_1 > 50\%$).⁷⁰ A recent clinical trial in patients with COPD GOLD stages I and II using tiotropium vs. placebo demonstrated a modest improvement in FEV_1 decline.⁷¹ Other clinical trials with post hoc analysis focused in GOLD II patients such

as UPLIFT,⁷² or TORCH,⁷³ also demonstrated a significant effect of the pharmacological intervention on lung function and exacerbations. Moreover, the secondary analyses of COPD patients less than 50 years old in UPLIFT suggested an effect of the pharmacological intervention on lung function and symptoms.⁷⁴

The concept of COPD as an inflammatory disease led to explore anti-inflammatory drugs. However, all of them failed to modify the natural course of the disease. The European Respiratory Study on Chronic Obstructive Pulmonary Disease (EUROSCOP),⁷⁵ failed to demonstrate a benefit of budesonide in individuals with post-bronchodilator FEV₁ >50% predicted and FEV₁/FVC <70% who continued smoking. Similarly, the Copenhagen City Heart Study;⁷⁶ or the Lung Health Study II,⁷⁷ or the ISOLDE trial⁷⁸ did not show a beneficial effect of inhaled corticosteroids on the rate of decline in FEV₁ in patients with mild-moderate disease.

FUTURE INVESTIGATIONS

Determinants of disease progression are still unknown and efforts should be made in order to understand the main factors that contribute to disease activity from early stages. The role of asthma and COPD overlap,^{79,80} or the potential ethnic differences in COPD expression and progression,⁸¹ are uncharted territories that will require new research efforts on early COPD.

Several trials are ongoing in order to study cohorts of young patients with COPD such as the British Lung Foundation Early COPD Development study in the UK (ClinicalTrials.gov Identifier: NCT03480347) or the study of Determinants of Onset and Progression of COPD in Young Adults (EARLY COPD) in Spain (ClinicalTrials.gov Identifier: NCT02352220). From a therapeutic point of view, the effects of early treatment in the early stages of COPD or even in symptomatic patients without airflow limitation are still unknown. A clinical trial using indacaterol/glycopyrronium versus placebo in symptomatic smokers with FEV₁/FVC>0.70 is currently recruiting patients (RETHINC: REdefining THERapy In Early COPD for the Pulmonary Trials Cooperative. ClinicalTrials.gov Identifier: NCT02867761). Finally, the interaction between early COPD and the development of comorbidities needs to be investigated from the clinical and biological points of view.

Opposite to the topic of this review, just as we have late-onset asthma, we may have late-onset COPD in individuals 80 years and older, an age near the median life span in both genders in many countries;⁸² hence how this phenomenon is in contrast to early-

onset stable and early-onset progressive COPD are concepts that might be further explored.

CONCLUSIONS

COPD has always been considered a disease of the elderly, and little attention has been paid to the clinical and pathologic features of COPD in younger individuals. Current evidence suggests that early COPD is associated with poor clinical outcomes and it makes sense to think that early detection, diagnosis, and maintenance treatment of COPD, alongside smoking cessation and exercise, may help to provide the best symptom control, disease progression and outcomes in COPD.

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LIST OF TABLES AND FIGURES:

Figure 1. Geographical variability of COPD prevalence in those younger than 50 years in A) Males and B) Females (according to GBD2017)

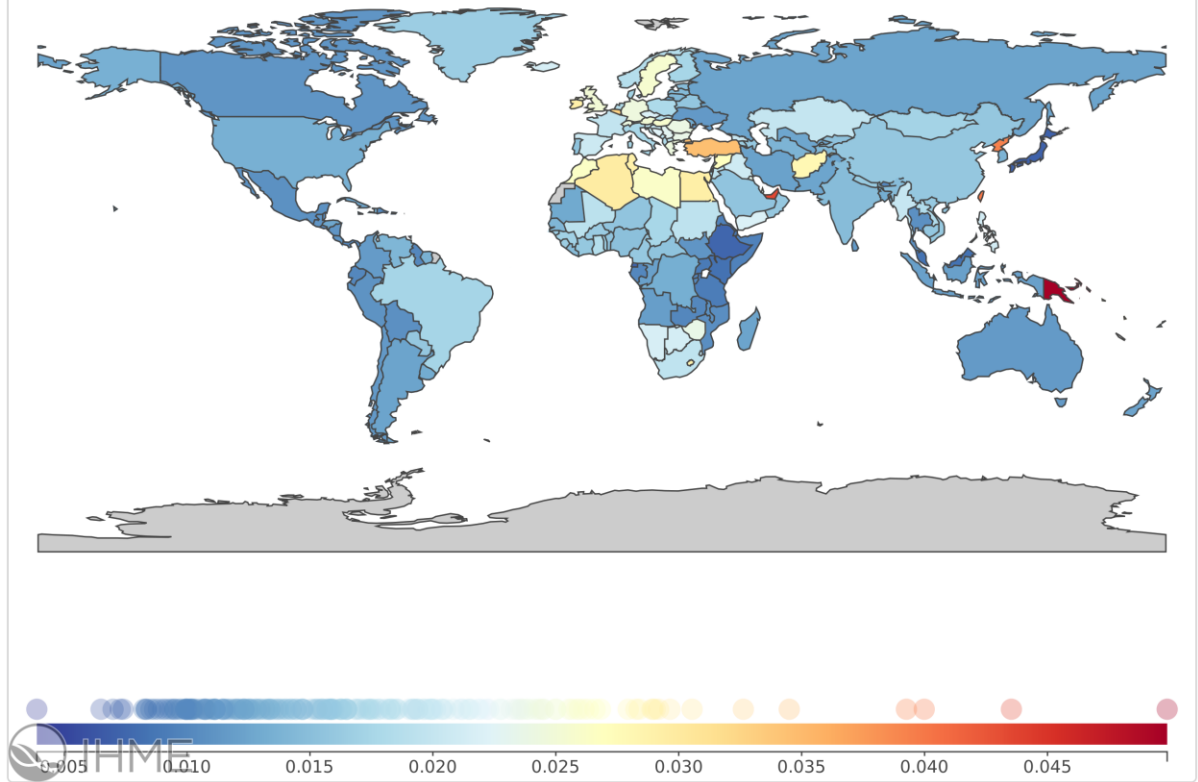
Figure 2. Graphic representation of the risk factors for chronic obstructive pulmonary disease during the different stages of life [from reference 17, permission obtained, attached]

Footnote of Figure 2. Risk factors are shown for in utero and perinatal life (upper left corner), early childhood (lower left corner), and adulthood (lower right corner). General risk factors are also shown (upper right corner). COPD=chronic obstructive pulmonary disease.

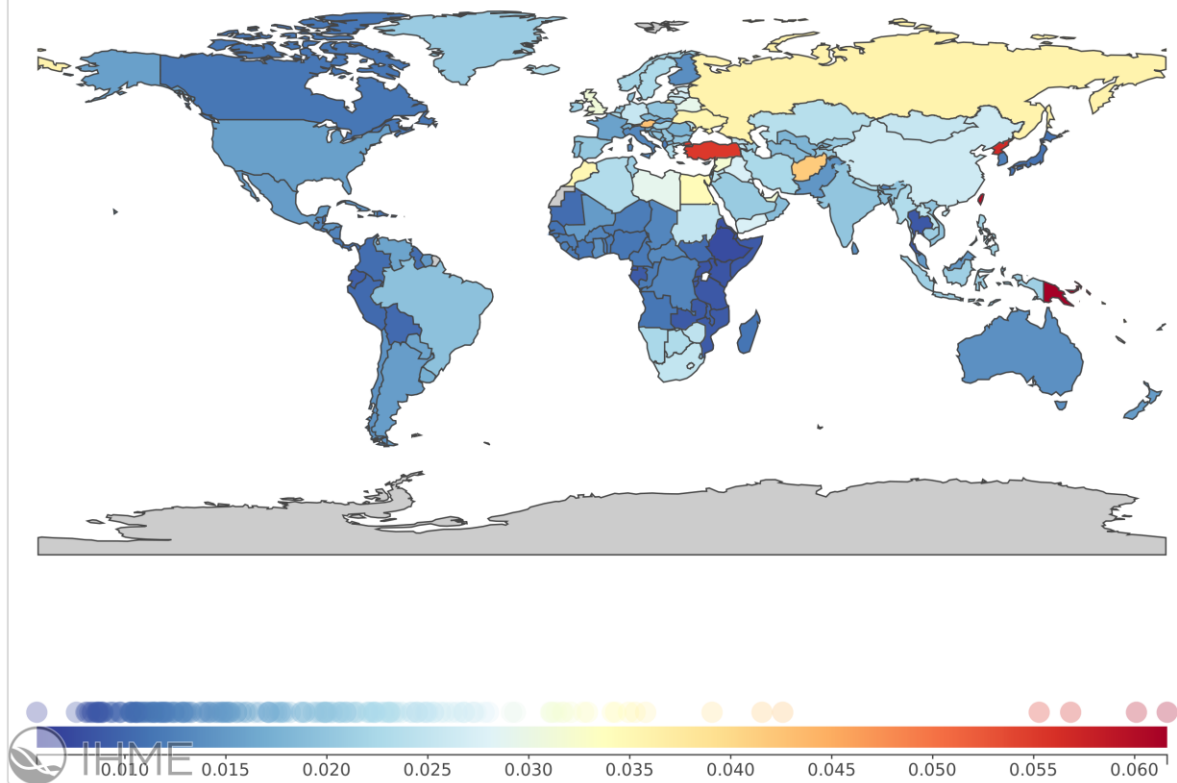
Figure 3. Distribution in mean annual changes in lung function in the BODE COPD cohort by age group, A) younger than 55 years; B) older than 65 years. [adapted from reference 28, ERJ permission not needed]

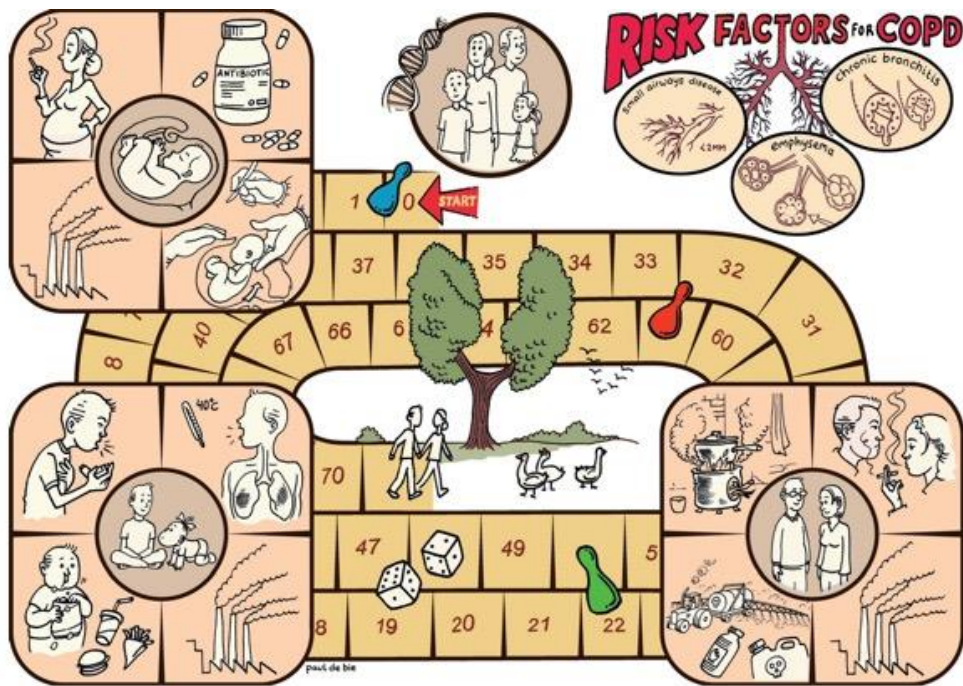
Figure 4. Lung function progression expressed as FEV₁ % predicted, stratified by GOLD) grades (1, 2 and 3+4) and by age group, compared with the curve from FLETCHER and PETO for smokers (FP). [adapted from reference 28, ERJ permission not needed]

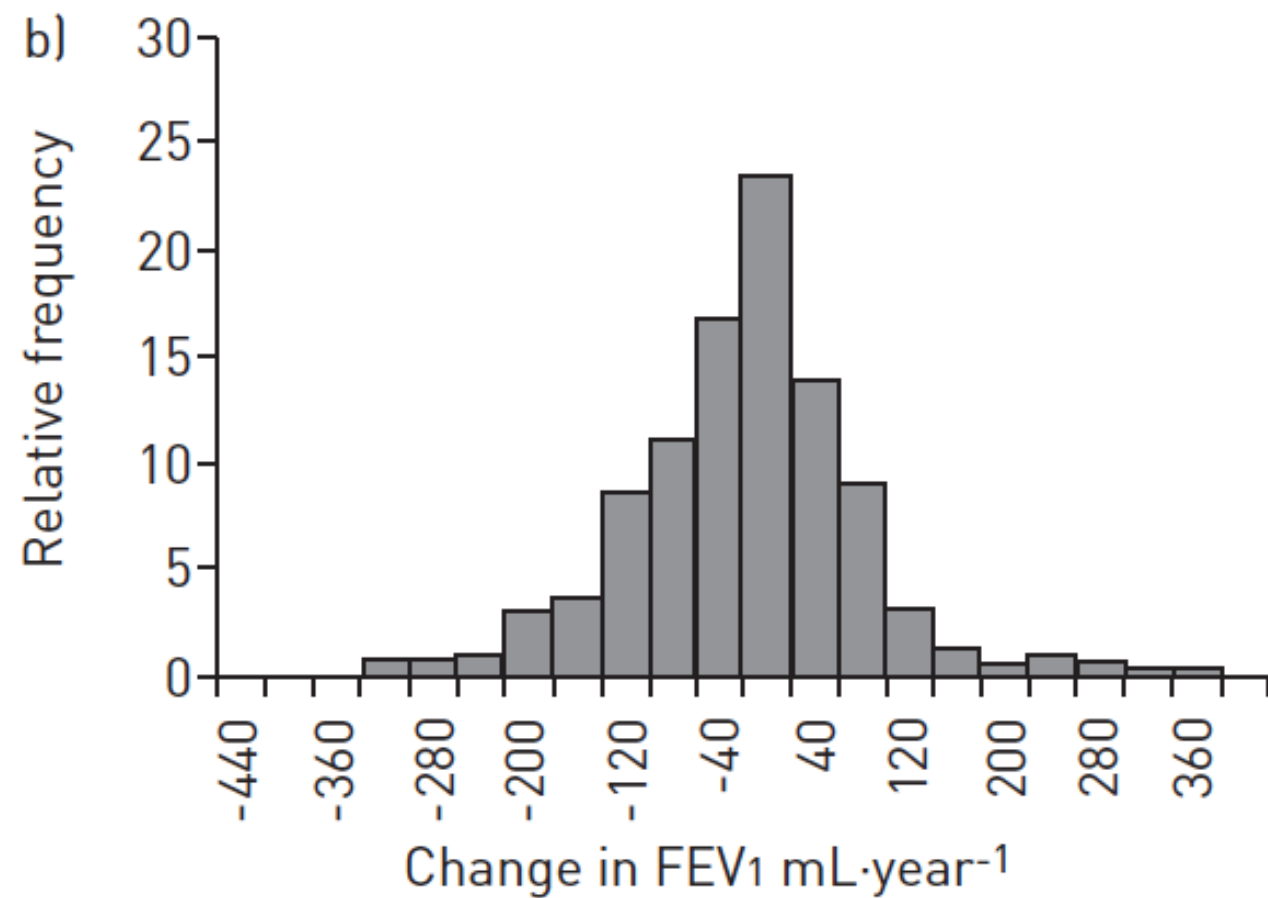
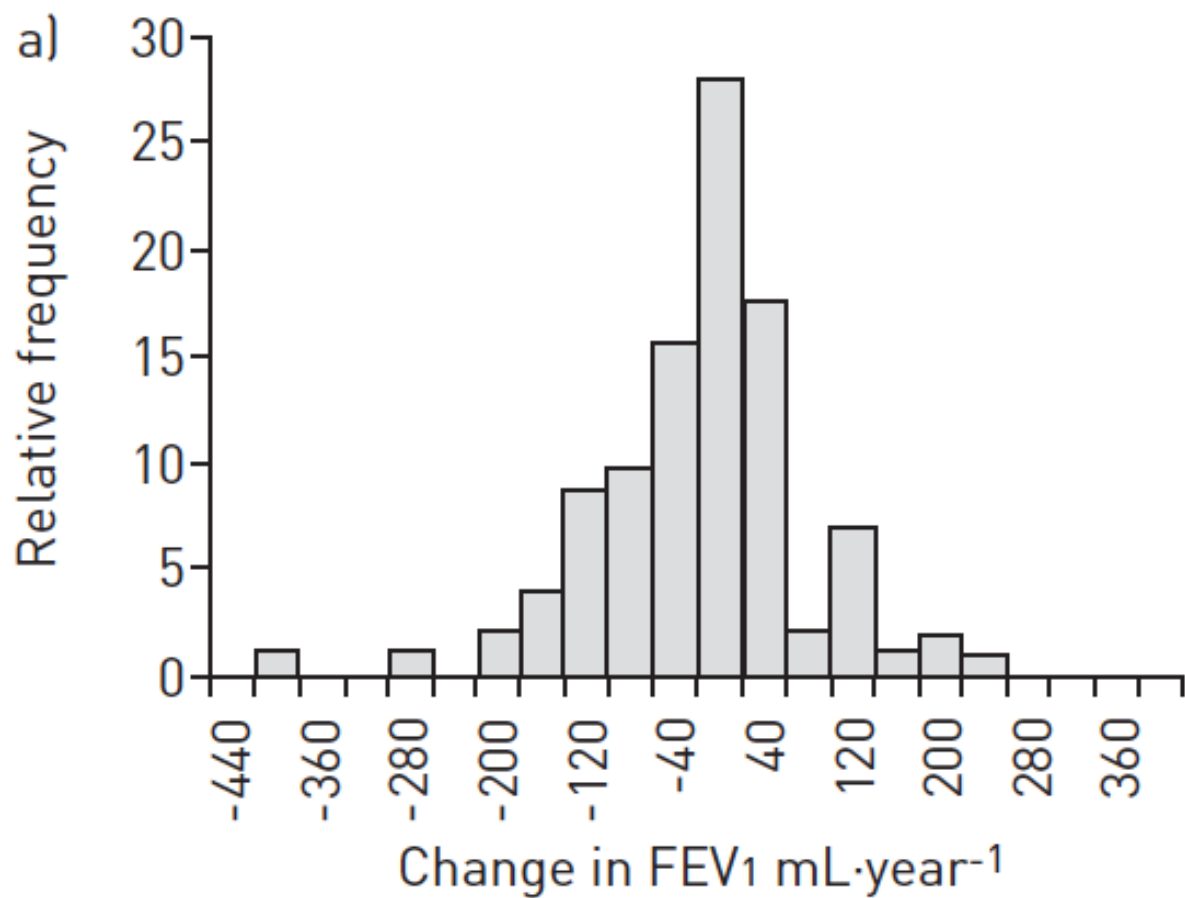
Chronic obstructive pulmonary disease
Males, 15-49 years, 2017, Percent of total prevalent cases



Chronic obstructive pulmonary disease
Females, 15-49 years, 2017, Percent of total prevalent cases







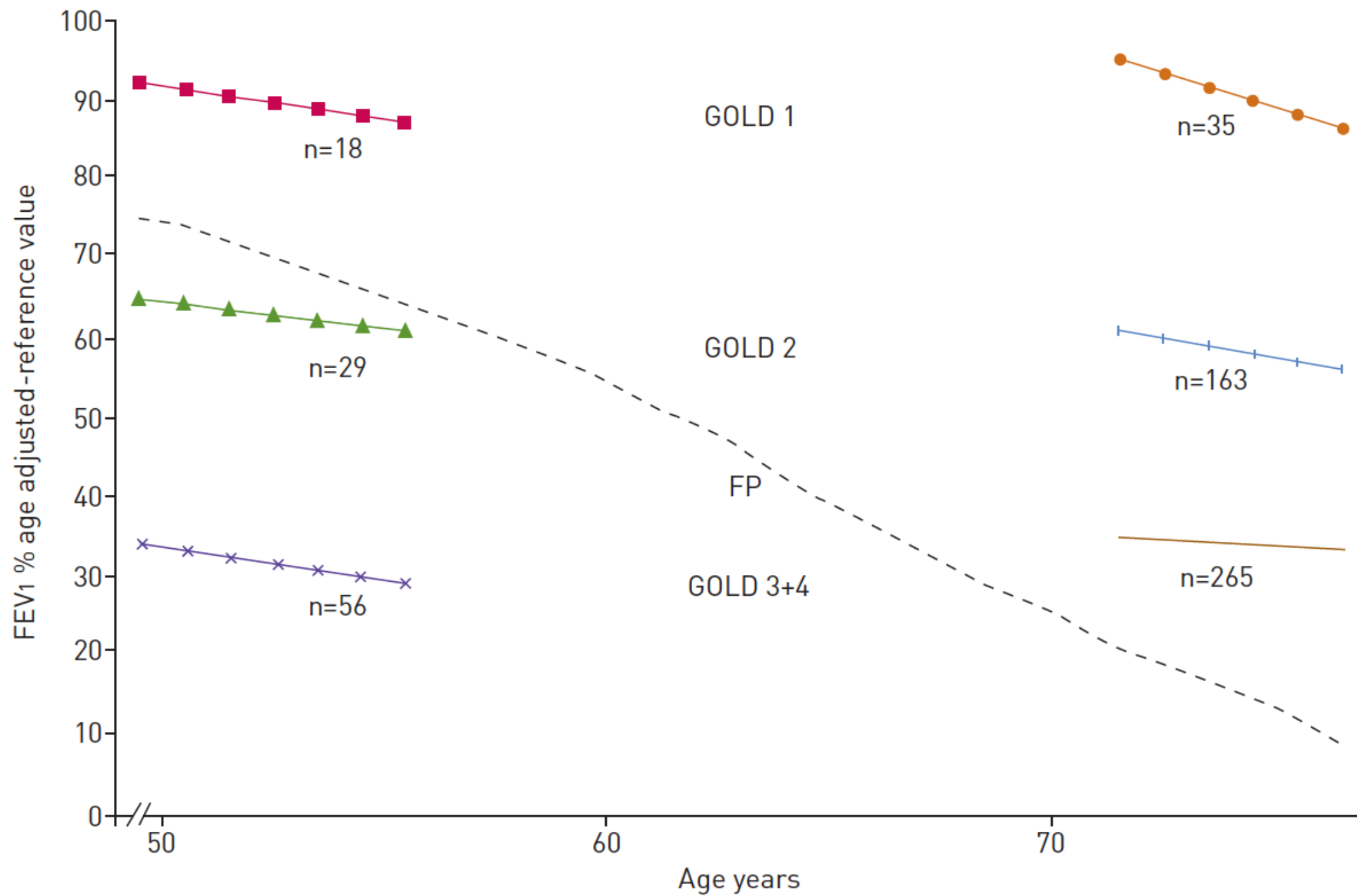


Table 1. Proposed functional definitions of Early COPD and activity

Mild COPD	Early COPD
<ul style="list-style-type: none"> • FEV₁/FVC <0.70 (or <LLN) • FEV₁ ≥80%, at any age 	<p>Early COPD with low disease activity:</p> <ul style="list-style-type: none"> • <50 year old patients • smoking exposure >10 pack years • FEV₁/FVC <0.70 (or <LLN) • FEV₁>50%, mMRC<2 and no frequent exacerbations • DLCO≥80%
	<p>Early COPD with high disease activity:</p> <ul style="list-style-type: none"> • <50 year old patients • smoking exposure >10 pack years • FEV₁/FVC<0.70 (or <LLN) • FEV₁ <50%, mMRC≥2 and/or 2 or more exacerbations per year • DLCO <80%.

Footnote: All spirometry values are post-bronchodilator; Smoking exposure>10 pack years refers also to an equivalent biomass exposure; LLN: lower limit of normal

Table 2. Risk factors of Early COPD, by age

Prenatal	Perinatal	Childhood and early life
<ul style="list-style-type: none">• Maternal smoking• Family history of COPD and/or asthma/atopy• Atopy• Genetic factors• Anatomic variations of the lung: bronchopulmonary dysplasia• Malnutrition	<ul style="list-style-type: none">• Parental smoking and/or exposure to pollution• Antibiotic use• Non-vaginal birth• Preterm birth• Undernourishment/stunting• Low lung function at birth and/or ARDS at birth• Low birth weight	<ul style="list-style-type: none">• Second-hand smoke exposure• Active smoking during childhood/adolescence• Lower respiratory tract infections (especially respiratory syncytial virus)• Indoor/outdoor air pollution• Childhood asthma• Bronchial hyper-responsiveness• Occupational exposures• Emphysema on CT scan• Gas trapping on inspiratory/expiratory CT scan• Psychosocial stress

Table 3. Pathologic and immunologic events leading to Early COPD

	Step 1	Step 2	Step 3
Pathologic events	Loss of the terminal and transitional bronchioles	Emphysematous destruction	Loss of lung function
	Narrowing of airway lumens and thickening of airway walls		
	Epigenetic reprogramming, remodeling, and hyperplasia of airway basal cells	Abnormalities in airway epithelial junction formation of the small airway epithelium	
immunologic events		Infiltration of B cells	Formation of lymphoid follicles
	Innate lymphoid cells inducing Th1 responses		
	Blunted immune tolerance		
	Infiltration of alveolar macrophages, dendritic cells, CD4 and CD8 T cells		
	Progressive decrease in lung microbial diversity		
	Innate immune deficit in bacterial opsonization and phagocytosis		

Table 4. Different trials exploring mild stages of COPD

Study (year)	Sample size	Duration	Mean age	FEV₁	Intervention vs. placebo	Main result
Lung Health Study (1994)	5887	5 years	48.6 years	75%	Smoking cessation (SC)/ipratropium	SC reduced FEV1 decline
EUROSCOP (1999)	1277	3 years	52 years	77%	Budesonide	No long term effect on lung function
City of Copenhagen Health Study	290	3 years	59 years	86.2%	Budesonide	No effect on lung function or exacerbations
Lung Health Study II (2000)	1116	40 months	56.2 years	68.5%	Triamcinolone	No effect on lung function. Reduce exacerbations in FEV1<50%
ISOLDE (2000)	751	3 years	63 years	61%	Fluticasone	No effect on exacerbations/patient/year but reduced exacerbations requiring oral corticosteroids
TORCH (2008) GOLD II	2156	3 years	64.9 years	58.8%	Salmeterol/ Fluticasone	Improved FEV1
UPLIFT (2008) GOLD II	2739	4 years	65 years	59%	Tiotropium	Reduced FEV1 decline, SGRQ and exacerbations
Tie-COPD (2017)	841	2 years	63.9 years	73%	Tiotropium	Improved FEV1 and reduced post-bronchodilator FEV1 decline