Focus on Early COPD: Definition and Early Lung Development

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Abstract: Chronic obstructive pulmonary disease (COPD) is a disease with high incidence rate and mortality rates worldwide. It is the third leading cause of death in the world. Nevertheless, little progress has been made in treating and preventing the disease. Under these circumstances, the concept of “early COPD” was proposed. Although this concept is not new, most health-care workers do not fully understand early COPD and tend to confuse it with mild COPD. In this review, we mainly discuss the definition of early COPD and the developmental trajectory of lung function. Although patients with early COPD have no symptoms, their lung function is already lower than that of normal people. A relatively complete definition is needed to identify this group of people. Reduced lung function is the diagnostic criterion for COPD, but lung development is a long-term dynamic process. In addition to smoking and air pollution, we should pay more attention to prenatal and childhood risk factors, for example, parents smoking, birth weight, preterm birth, mode of delivery, childhood respiratory infections and childhood asthma. Health-care workers need to be fully aware of early COPD, to reduce the morbidity of COPD and take effective measures to prevent these risk factors.

Keywords: early COPD, definition, early lung development

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with high incidence and mortality rates worldwide that is caused by airway and alveolar abnormalities, and is characterized by irreversible airflow limitation.¹ Furthermore, COPD is expected to be a leading cause of death worldwide by 2030.² With the increase in air pollution and the speed of aging worldwide, COPD is expected to become the main economic burden of human chronic diseases in the future.³ Worryingly, COPD is more common in younger populations. Previous studies have identified that tobacco and fine particulate matter are the major risk factors for COPD,⁴ which mainly affects adults. However, such is not the case. Early life events are getting more attention, also affecting those under the age of 18.

Lung development is a complicated process, that is influenced by many factors.⁵ Exposure to risk factors often occurs decades before abnormal lung function, respiratory symptoms and forced expiratory volume in 1 second (FEV₁) decline.⁶ COPD usually presents with small airway obstruction in the early stage, and it takes decades to develop slowly from small airway obstruction to the stage of FEV₁ decline.⁷ These pathological changes may begin in the fetus and manifest in adulthood. First, this review discusses some of the controversies surrounding the

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definition of early COPD. Second, but importantly, we focus on the risk factors associated with an early natural history of COPD.

Search Strategy and Selection Criteria

We searched “early COPD”, “COPD”, “genetics”, “maternal smoking”, “low birth weight /very low birth weight”, “preterm birth”, “maternal nutrition”, “mode of delivery”, “vitamin D deficiency”, “childhood smoking”, “air Pollution”, “childhood respiratory infections”, “childhood asthma”, “manual working class and overcrowding”, “risk factors”, “definition”, “lung development” and the different combinations of them on PubMed and Web of science before August 30, 2021. All articles were published in English and related to COPD or early COPD. We excluded some articles whose resources were not available. We reviewed the reviews and original researches in this area, then cited relevant articles.

The Definition of Early COPD

The definition of early COPD has been around for a long time, and a major controversy has been the unclear distinction between “mild COPD” and “early COPD”. “Early” means the time of disease progression is early, while “mild” refers to the degree of disease, and there is no complete overlap between “mild COPD” and “early COPD”. The definition of early COPD is similar to that of “early diabetes”, “early Parkinson’s”, “early cardiovascular disease” and other early diseases. “Early” represents the pathophysiological changes occurring in the early stage of the natural history of disease, aiming to provide effective prevention strategies for the further development of the disease and reduce the fatality rate of the disease.

There is still no consensus on the definition at home and abroad. COPD is complex and heterogeneous, which means that each individual has an independent natural history.^{8,9} Genetics, environment, smoking, air pollution and early life events. These risk factors complicate the description of disease definition.

Prior to 2006, the guidelines of GOLD included a “GOLD 0” category, which mainly included people with high risk factors such as long-term smoking and air pollution.¹⁰ A large proportion of smoking patients did not progress from “GOLD 0” to “GOLD 1”; however, the classification was removed in 2007. Even to date, most studies confuse the concept of “mild” and “early”. Early

COPD is usually considered GOLD1–2, which could lead to biased results. For “mild COPD”, the GOLD was clearly defined as follows:¹¹ 1) $FEV_1/FVC < 70\%$ (inhalation of bronchodilator); and 2) $FEV_1 \geq 80\%$ of the predicted values. At present, “ $FEV_1/FVC < 70\%$ ” is used as the GOLD standard in the international guidelines for the diagnosis of COPD.⁵ FEV_1 and forced vital capacity (FVC) decline with age, and FEV_1 declines faster than FVC.¹² Since the international guidelines failed to correct for age, the elderly are over-diagnosed and the younger population is underdiagnosed.¹³ Nonetheless, there are no clear diagnostic criteria for early COPD. In 2017, Martinez proposed that diagnosis of early COPD should include (Table 1) 1) age < 50 years and smoking quantity > 10 packs/year; and 2) meeting any of the following criteria: 1) $FEV_1/FVC < LLN$ (post-bronchodilators); 2) chest computer tomography (CT) scan showed small airway obstruction or thickened airway walls; and 3) lung function decreased rapidly, with decline in $FEV_1 > 60\text{mL/year}$.¹⁴ The definition excluded other chronic lung diseases except asthma. In 2020, Yunus Colak conducted a study based on Martinez’s definition showing that less than 24% of young adults in the general population with early COPD develop clinical COPD 10 years later, depending on the amount of smoking exposure, suggesting that smoking exposure should be redefined because there is less tobacco exposure in the young population.¹⁵

Martinez et al proposed the definition of “early COPD”, which focused on smokers but ignored the group of non-smokers and effects of early life events. They have noted the effects of early life events in his article, while failed to add them in definition. The followings point out the shortcomings of Martinez’s definition and provide directions for future definition (Table 2). 1)

Table 1 Definition of Mild COPD and Early COPD

Mild COPD	Early COPD
1) $FEV_1/FVC < 70\%$ (post-bronchodilators) 2) $FEV_1 > 80\%$ predicted value	1) > 50 year of age and smoking > 10 packs/year 2) Meet any of the following: $FEV_1/FVC < LLN$ (post-bronchodilators); Chest CT showed small airway obstruction or thickened airway walls; Lung function reduced rapidly; with the decline in $FEV_1 > 60\text{mL/year}$

Note: Other known chronic lung diseases were excluded except for asthma.

Abbreviations: FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; COPD, chronic obstructive pulmonary disease; CT, computer tomography.

Table 2 Disadvantages and Future Directions for Early COPD

Early COPD	Disadvantages	Future
1) <50 year of age and smoking >10 packs/year	<ul style="list-style-type: none"> • Age < 50 years should be adjusted earlier. • Smoking exposure should be redefined. • 25–45% with COPD are non-smokers, resulting in missed diagnosis in some patients. 	<ul style="list-style-type: none"> • Adjust the range of age and number of cigarettes smoked. • Antenatal and childhood risk factors should be added in early COPD.
2) Meet any of the following:		
FEV ₁ /FVC < LLN (post-bronchodilators);	<ul style="list-style-type: none"> • LLN is the value before the inhalation of bronchodilators. 	<ul style="list-style-type: none"> • Change post-bronchodilators to prebronchodilators.
Chest CT showed small airway obstruction or thickened airway walls;	<ul style="list-style-type: none"> • The threshold for CT scan abnormalities are not clear. 	<ul style="list-style-type: none"> • More studies are needed to clarify thresholds.
Lung function reduced rapidly; with the decline in FEV ₁ > 60mL/year;	<ul style="list-style-type: none"> • FEV₁ can also decrease with acute pulmonary inflammation, but it can later return to normal. • The majority of adult COPD patients progress without accelerated decline in lung function. • Symptomatology is an important basis of COPD. 	<ul style="list-style-type: none"> • The duration of FEV₁ decrease by 60mL/year should be specifically defined. • The symptoms (cough or sputum production) should be considered.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; COPD, chronic obstructive pulmonary disease; CT, computer tomography.

Age < 50 years should be adjusted earlier, a study indicates that 4% to 13% of early adults show lung function decline.¹⁶ 2) 25–45% with COPD are non-smokers, resulting in missed diagnosis in some patients. 3) lower limit of normal (LLN) is the value before the inhalation of bronchodilators, but the definition just the opposite. 4) The duration of FEV₁ decrease by 60mL/year should be specifically defined. For example, FEV₁ can also decrease with acute pulmonary inflammation, but it can later return to normal.¹⁷ 5) The majority of adult COPD patients progress without accelerated decline in lung function.^{18,19} Therefore, the use of reduced lung function as a diagnostic criterion also misses some patients. 6) COPD is a clinical diagnosis. Martinez's definition relies on lung function and CT but ignores symptomatology, which is an important basis for diagnosing COPD,²⁰ therefore, symptomatology should be added in the definition of early COPD. Even with its many shortcomings, the definition is still valuable, as screening people with early COPD in large cohort studies regardless of their lung function status and excluding individuals unlikely to develop clinical COPD later in life is effective.²¹

The Early Development of Lung Function

Lung development is a continuous process throughout life. The development of the bronchial tree begins with the

formation of lung buds at 21–28 days of gestation, followed by the formation of a complete bronchial tree at 3–17 weeks.²² Lung function peaks at approximately 20 years of age.²³ The plateau (lung function remains roughly constant) is a special stage of lung development that occurs at approximately 20–25 years of age, and then lung function slowly declines with age.^{24,25} Smoking is considered to be a major factor in the decline of lung function during this period.²⁶ Of course, individuals with different risk factors experience different changes in lung function, such as reduced lung growth, reduced maximum lung function, episodic accelerated loss of lung function and late accelerated loss of lung function.²³

Lung development is usually determined by genetic and environmental factors, such as asthma, childhood respiratory tract infection, nutrition and maternal smoking.²⁷ Complete lung function is largely dependent on early life.²⁸ Smoking, genetics and air pollution were suggested as the main risk factors for COPD in a previous study,⁴ apparently, early events of life were neglected. In 1991, Barker pointed out that low birth weight affects lung development, intrauterine growth irreversibly affects airway development and childhood respiratory disease further reduces lung function.²⁹ Afterward, several studies have suggested that early events of life (maternal smoking,^{30,31} low birth weight,³² preterm birth^{33,34}) are also risk factors in the process of COPD, which may explain why more than 50% of COPD patients

are nonsmokers. In summary, lung development is a dynamic and multifactorial process. The following sections describe in detail the various stages of lung development and their risk factors (Figure 1). This section aims to explain the early risk factors for lung function and the importance of understanding early COPD.

Genetics

Genetic factors play an important role in the development of COPD and determine the beginning of lung development. In the 20th century, researchers realized the connection between α 1-antitrypsin Deficiency (AATD) and COPD. The mechanisms including antiproteinase theory, Chemotactic mediators and A1AT polymerization. Studies have shown that AATD deficiency increases the incidence of COPD and exacerbates airway obstruction in smokers.³⁵ At present, AATD is the only confirmed genetic risk factor for COPD and asthma,³⁶ while there is a lack of research on whether AATD enters COPD earlier than those without

AATD. Costa believes screening for AATD is necessary to facilitate early diagnosis and treatment.³⁷ Intravenous augmentation appears to be a therapy to delay AATD, but corresponding evidence-based information is scarce.³⁸ Gene and Stem cell therapies are the direction of future research.

Other related genes include ADAM33, SOX540 and TNS1.³⁹ These genetics ultimately lead to reduced lung function in adulthood by airway hyperactivity, lung growth and repair damage and airway remodeling.⁴⁰ These genes are considered to be high-risk genes for COPD. Prevention and treatment of “genetic COPD” is the focus of future research.

Antenatal Risk Factors

Lung development begins when the fetus is in the womb. From week 4 to week 7 (embryonic), the main bronchus is formed. From week 7 to week 16 (pseudoglandular stage), the bronchus continues to subdivide into terminal bronchioles. From the week 16 to the week 27 (tubule stage), the

Figure 1 Natural history of lung function and risk factors at different stages. This figure shows the developmental trajectory of lung function, which is influenced by prenatal and postnatal factors. Reprinted with permission from Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. *Lancet*. 2015;385(9979):1778–1788. Copyright 2015 Elsevier Ltd. All rights reserved.²³

Abbreviations: FEV₁, forced expiratory volume in 1 second; LBW, low birth weight.

airway branch is completed, and the primitive balloon is formed. At this stage, with the increase in interstitial peripheral vasculature, the cuboid epithelial cells in the sac differentiate into Type I and Type II pulmonary cells. From week 27 (cystic phase), preacinar airway growth, additional respiratory bronchiole development and acinar formation are observed.²⁷ Then, the alveoli begin to develop; at 29 weeks of gestation, 30 million alveoli gradually develop to 150 million at term.^{41,42} In this stage, lung development can be affected by maternal smoking, low birth weight, maternal nutrition, preterm birth and other factors,²⁷ which seriously impair lung function, promoting the progression of COPD.

Maternal Smoking

Maternal smoking is considered to be the primary risk factor in early events of life affecting lung function and is strongly associated with low birth weight.⁴³ In 2006, Sam Pattenden reviewed the health and parental tobacco exposure of 53,897 children at 12 centers and found that maternal smoking was independently associated with wheezing, asthma and allergic rhinitis in children and that asthma was the most closely associated with maternal smoking.⁴⁴ Beyer et al recruited 288 patients diagnosed with COPD from 2003 to 2004 and collected information on parental smoking status and occupational exposure. They suggested that maternal smoking was a risk factor for reduced FEV₁ in COPD. Maternal smoking may increase the risk of asthma and reduce lung function and lung development in teenagers. The effect was more pronounced among girls than boys.⁴⁵ Li et al conducted a case-control study on 338 children diagnosed with asthma in the first 5 years of life in southern California and 570 healthy children, suggesting that grandmaternal smoking may increase the risk of childhood asthma.⁴⁶ This result suggested that maternal smoking could damage lung development in grandchildren, but the specific mechanism remains unclear.

Intrauterine hypoxia, reduced utero-placental blood flow due to nicotine, placental toxicity, or toxic growth limits of multiple toxins in tobacco smoke are considered the main pathological mechanisms of maternal smoking.⁴⁷ The harmful substances in cigarettes (nicotine and carbon monoxide) are released into blood circulation, which leads to the above changes. Furthermore, nicotine can easily pass through the placental barrier, affecting fetal lung development continuously.⁴⁸ In a study of 19 infants who were

diagnosed with sudden infant death syndrome (SIDS), prenatal smoking was found to be a risk factor for airway change in infants, and the change was mainly airway stenosis, which contributed to reduced lung function in neonates.⁴⁹ Maternal smoking was also associated with airway hyperresponsiveness (AHR),⁵⁰ and AHR is a major mechanism of asthma. The detailed mechanism needs further study.

Low Birth Weight, Preterm Birth

Low birth weight (LBW) is defined as a birth weight of the baby <2500 g, which can be caused by maternal malnutrition or other diseases. In a retrospective study of 164 pairs of observers conducted by J W Matthes in 1995, there was no correlation between LBW and reduced lung function in adolescents.⁵¹ Subsequently, S O Shaheen came to the same conclusion.⁵² However, D A Lawlor conducted in a meta-analysis and found that after adjusting for age, height and smoking, birth weight was moderately positively correlated with lung function.⁵³ Thereafter, many studies have identified LBW and preterm birth as risk factors for COPD.^{54–56} A retrospective cohort study from China indicated that LBW may increase the risk of adult reduced lung function in China, and there was a positive correlation between LBW and FEV₁, FVC and peak expiratory flow (PEF).⁵⁷ Maternal smoking is also a risk factor for LBW and preterm birth.⁵⁸ The effects of maternal smoking should be considered when studying the effects of LBW and preterm birth.

A birth weight <1500 g is considered as very low birth weight (VLBW). Many studies have shown that VLBW is related to an increased risk of COPD.^{59–61} Since VLBW usually leads to bronchopulmonary dysplasia (BPD), the major pathological changes of BPD are reduced pulmonary alveolar septation, reduced microvascular cross-sectional area and airway injury.⁶² These changes result in potential airflow limitation and abnormal lung volume.⁶³ VLBW, preterm birth and smoking during pregnancy are risk factors for BPD.⁶⁴

Preterm birth refers to infants whose gestational age is less than 37 weeks. Eva Berggren Brostrom followed preterm babies and compared them with normal fetuses. The risk ratios of obstructive respiratory disease and asthma for babies born before 32 weeks gestation were 2.77 and 5.67 respectively, suggesting that preterm birth is a hazardous factor for obstructive pulmonary disease.⁵⁶ In 2011, a cohort study in Sweden suggested

that the gestational age of infants born between 23 and 27 weeks was related to an increased incidence of asthma in adulthood, while there was not effect for infants born between 28 and 32 weeks or 33 and 36 weeks.⁶⁵ Reduced lung volume is usually caused by preterm birth, which affects lung function in adolescents.

Other Maternal Factors

Similarly, other prenatal factors such as maternal nutrition,⁶⁶ mode of delivery,⁶⁷ and vitamin D deficiency⁶⁸ were also identified as high-risk factors of lung development. A study from the Dutch Famine collected lung function and IgE from 726 subjects at that time, suggesting that poor maternal nutrition is connected with the high incidence of asthma in adults, especially in early pregnancy.⁶⁹ The association of cesarean section with lung development requires further research.

Childhood Risk Factors

As mentioned above, lung development after growth can be divided into three stages: lung development before the age of 20 (rising stage), roughly unchanged lung function between the ages of 20 and 25 (plateau stage), and slow decline after that (declining stage). Childhood smoking, fine particulate matter, childhood respiratory infections,

asthma and manual working class and overcrowding are major hazardous factors at these stages (Table 3).^{28,70–72}

Childhood Smoking

Tobaccos is a recognized hazardous factor for COPD and other lung diseases. Tobacco exposure shortens the plateau stage duration of FEV₁.²⁵ Lung function damage usually occurs in adolescents, because it is not fully developed at that time. FEV₁/FVC ratios were significantly reduced in adolescent smokers and were associated with increased peripheral airway resistance.⁷³ A recent cohort study from Europe showed that smoking-related lung function damage occurs in early life and is completely unresponsive to bronchodilators, suggesting that lung function damage is long-term and irreversible.⁷⁴ In 2007, a study was performed in Spain, on the influence of smoking on lung function in adolescents aged 16–20 years. FVC, FEV₁, FEV₁/FVC and PEF < MEF_{25–75%} were lower in the passive and active smoking groups than in the nonsmoking group, and women were worse than men.⁷⁵ Concerningly, while the percentage of adolescents who smoke has declined in recent years, a large percentage of the teen population still uses e-cigarettes, and they are used at an earlier age.⁷⁶ E-cigarettes have many advantages over cigarettes, but they still contain nicotine, which can cause lung and cardiovascular diseases.⁷⁷ The use of e-cigarettes is more likely to induce the incidence of smoking.^{78,79} Therefore, the prevention of smoking among adolescents, especially among women, should be considered.

Air Pollution

Air pollution exposure is a risk factor of COPD and decreased lung function.^{80–82} These pollution particles, mainly including in PM_{2.5}, NO_x, O₃ and others, are considered to have diameters <2.5 μm. Saeha Shin conducted a 15-year cohort study collecting the incidence of COPD and asthma among subjects who were exposed to air pollution. Air pollution is a risk factor of COPD, not asthma.⁸³ Long-term exposure to these polluted particles induces airway inflammation and oxidative stress in bronchial epithelial cells, which may contribute to the development of COPD. Anais Havet et al believed that the decreased lung function caused by air pollution was related to small airway obstruction.⁸⁴ Unfortunately, air pollution is more likely to threaten children and increase the risk of respiratory infections.⁸⁵ Furthermore, childhood exposure to pollution

Table 3 Risk Factors for Lung Development at Different Life Stages

The Stage of Life	The Risk Factors for Lung Function
Genetics	α1-antitrypsin deficiency
	ADAM33, SOX5, TNSI
Antenatal period	Maternal smoking
	LBW/VLBW, Preterm birth
	Maternal nutrition
	Mode of delivery Vitamin D deficiency
Childhood	Childhood smoking
	Air Pollution
	Childhood respiratory infections
	Childhood asthma Manual working class and overcrowding

Abbreviations: LBW, low birth weight; VLBW, very low birth weight.

particles is associated with poor lung function in adolescents. Similarly, exposure to air pollution during pregnancy can adversely affect fetal lung function.⁸⁶ It has also been suggested that maternal exposure to air pollution may alter the trajectory of lung development, making children more susceptible to respiratory disease later in life.⁸⁷ The mechanism may be due to the transmission of pollution particles through the placental barrier, causing a series of pathological changes.⁸⁸

A cohort study of 7071 adults 45 to 84 years of age was conducted between 2000 and 2018 in six large cities of the US. It focused on the association of lung development in people chronically exposed to air pollution. The results showed that PM_{2.5}, O₃, NO_x and black carbon in the environment were obviously related to the increase in the percentage of emphysema every 10 years, and O₃ was correlated with the decline in FVC.⁸⁹ The risk of COPD caused by indoor pollution particles is higher than that caused by outdoor particles. This may be due to spending much more time indoors than outdoors each day. Indoor environment optimization is easier to carry out, reducing indoor pollution particles should be considered, and it is more urgent in children and pregnant women.

Childhood Respiratory Infections

Respiratory infections are common diseases in childhood, and affect the most critical stage of lung development and immunity. The pathogenesis are mainly respiratory syncytial virus (RSV), adenovirus and coronavirus, among which the most common is RSV.⁹⁰ At present, there are different opinions on the impact of childhood respiratory infections on lung development. The mainstream view is that childhood respiratory infections are related to adult lung function. However, some studies suggest that the evidence is insufficient.^{91,92}

In the 1990s, S O Shaheen considered the association between childhood respiratory infections and COPD to be difficult to test. However, in Hertfordshire and Derbyshire, England, pneumonia before 2 years of age was associated with a reduced mean FEV₁ after adjustment for age and height.⁹³ In a multicenter study from Europe, childhood respiratory infection or lung disease was associated with asthma in adulthood, with lower FEV₁, FVC, and FEV₁/FVC than in adults without a history of respiratory infection.⁹⁴

In a study from 10,192 adult smokers in the US, an early history of respiratory infections by questionnaire, and lung function scans and chest CT scan were measured. Childhood pneumonia was found to be related to COPD,

reduced FEV₁ and FVC in adult smokers, and increased airway wall thickness in these populations on CT scans.⁹⁵ However, the study failed to explain the correlation between childhood pneumonia and nonsmokers with COPD. Peter suggested that severe respiratory illness in childhood is associated with reduced FEV₁ in middle age, based on changes in lung function at age 14 and 49 to 51 years.⁹⁶ Childhood pneumonia may reduce maximum FEV₁ rather than decreased the rate of declined FEV₁.⁹⁷

In contrast, Agnes E Marossy conducted a large cohort study of 1158 adults born in the United Kingdom in 1958. Spirometry measurements were collected at 35 and 45 years of age. Subjects were divided into asthmatic, asthmatic bronchitis, and normal categories. The mean reduction in FEV₁ was 35 mL/year, but the rate of decline was not associated with early respiratory disease. It was clear that a history of whooping cough was not related to FEV₁ and FVC in adulthood.⁹² Subsequently, a birth cohort study by Geir Haland showed that respiratory infections before age 2 did not affect lung function before age 10,⁹¹ while it failed to track lung function until adulthood. The main goal of subsequent research should be to determine whether respiratory infections cause reduced lung function and the stage of reduction.

We believe that the differences between the two viewpoints are mainly related to the following aspects: 1) it is difficult to exclude the influence of intrauterine development factors and the postnatal environmental when studying the association with respiratory infections and lung development; 2) most studies collect information based on parental recall, with large bias and unreliable data and conclusions; 3) many studied subjects came from families with low socioeconomic status, and most of the studies did not exclude the effect of the low socioeconomic status from lung function. 4) it is possible that only some pathogens impair lung function, but most studies have not examined respiratory tract etiology.

Childhood Asthma

The definition of early COPD does not exclude asthma because asthma is a risk factor for irreversible airway obstruction. A number of long-term cohort studies now suggest that childhood asthma increases the risk of COPD in adulthood, and independent of smoking, childhood asthma could be considered an independent risk factor for COPD.^{98–100} Airway remodeling is the main mechanism, and histological features include inflammatory cell infiltration (macrophages and lymphocytes), proliferation of fibroblasts and myofibroblasts, angiogenesis, connective tissue fibrosis, and tissue destruction.¹⁰¹ Interestingly,

many adults with a history of childhood allergic asthma or aspirin exacerbated respiratory disease show irreversible airway obstruction.^{102,103}

Manual Working Class and Overcrowding

Manual working class and overcrowding may also be called socioeconomic status, reflecting the unequal distribution of socioeconomic resources, which is common in the groups of middle and low income countries. It usually represents low income levels, low education and poor nutrition. Manual social class and home overcrowding accelerate FEV₁ reduction after adulthood, suggested in a prospective study by Allinson.⁷² Kanervisto concluded that poor socioeconomic status not only reflected the low income, education and malnutrition, but also increased the risk of asthma and COPD.¹⁰⁴ Although people are aware of the detriment of socioeconomic status, little preventive measures are taken.

Conclusion

Early COPD is not a novel concept, but many health-care workers fail to realize its importance, confusing its definition with mild COPD. Lung function in early life is most vulnerable to risk factors. A study from Mexican shows that 13.7% of COPD patients are asymptomatic,¹⁰⁵ while this group reaches 35.3% in China.¹⁰⁶ Therefore, we think asymptomatic early COPD should also be paid to receive increased attention. It is easier to understand asymptomatic early COPD in terms of lung function development, people with reduced lung function (do not reach FEV₁/FVC < 0.7) but no respiratory symptoms, the future definitions of early COPD should focus on this group.

A large proportion of people with COPD are nonsmokers. Martinez failed to identify this group, and antenatal and childhood risk factors should be added in early COPD, at the same time, while adjusting the range of age and number of cigarettes smoked. Early life events and genetics are risk factors of COPD. We suggest that making rating scale to describe early life events, the duration of air pollution exposure and times of childhood respiratory infections should be considered in rating scale, while there is a lack of relevant studies, further study should aim to quantify early life events. Early life events contribute to the identification of COPD in nonsmokers, while individual differences in early life experiences add to the difficulty of defining this group.

COPD continues to have increasing morbidity and mortality globally, yet we still lack effective means to prevent and reduce it. We need to understand that the

development of COPD is a long-term cumulative process, and lung function development begins in the embryonic stage. Lung development is affected by many risk factors, and these factors could result in decreased lung function, while further cohort studies should focus on the occurrence of early COPD rather than lung function injury. Therefore, it is necessary to recognize the dynamic process of lung development to diagnose early COPD, and monitoring lung function changes regularly in people with early risk factors could help with early prevention and reduce the incidence of COPD.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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