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The Natural History of Chronic Obstructive Pulmonary Disease: Beyond Fletcher and Peto

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ABSTRACT

The landmark publication of the "British Postal Worker Study" by Fletcher and colleagues in the 1970s established that chronic obstructive pulmonary disease occurs because smoking exposure in susceptible individuals accelerates the decline of lung function that occurs physiologically with age. In the 40 years since Fletcher et al. published the results of their study, subsequent research has advanced our understanding of chronic obstructive pulmonary disease and its natural history. The current review focuses on areas where the proposal by Fletcher et al. require expansion and/or modification, including: (i) the recognition of the role of exposures other than cigarette smoking (or even in its absence where chronic obstructive pulmonary disease may be related to other conditions such as asthma); (ii) that smoking affects a larger percentage of individuals than suggested by Fletcher et al.; (iii) that the benefits of smoking cessation vary with age/disease severity; (iv) that lung function decline does not accelerate with advancing age; (v) that many can develop chronic obstructive pulmonary disease with "normal" rates of lung function decline if they have abnormal lung growth and, therefore, low lung function at early age; (vi) that the relationship between mucus hypersecretion, exacerbations, and lung function decline is more complex than suggested by Fletcher et al.; and, finally, (vii) that chronic obstructive pulmonary disease is now recognized to have extra-pulmonary manifestations that can contribute significantly to the clinical impact of the disease. **(BRN Rev. 2015;1:116-30)**

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INTRODUCTION

Results of the eight-year study of early chronic obstructive lung disease in working men in London, informally called the "British Postal Worker Study", were published as a monograph (The natural history of chronic bronchitis and emphysema) by Charles Fletcher, Richard Peto, Cecily Tinker and Frank Speizer in 1976[1]. This was followed by a summary in the British Medical Journal in 1977[2]. This was truly a landmark study that has shaped our thinking about chronic obstructive pulmonary disease (COPD) and its natural history for the subsequent four decades. The key findings of the study, as summarized by Fletcher et al.[1], were as follows.

"Our basic conclusion is that there are two distinct, but commonly associated, components of chronic obstructive lung disease.

"The obstructive disorder, due both to intrinsic disease of the airways and to emphysema, is caused by smoking, especially of cigarettes. Only a minority of cigarette smokers are affected severely enough to become disabled by it. In them, it causes more rapid loss of FEV with advancing age. This loss can be detected before it is severe enough to be disabling. If affected smokers stop smoking, their lost FEV is not restored but the rate of subsequent loss becomes normal, so that disablement may be delayed or prevented.

"The hypersecretory disorder is also caused, in susceptible subjects, by smoking and consists of chronic, excessive secretion of bronchial mucus sufficient to cause expectoration. It encourages recurrent clinical bronchial infections, which are thus a common feature of the disorder. These cause only temporary increases in expectoration. The disorder is not usually progressive and usually remits on stopping smoking. Susceptibility to it correlates with, but is distinct from, susceptibility to the obstructive disorder.

"In the preclinical stages of these disorders, which we have studied, we find no causal relationship between them, for neither mucus hypersecretion nor clinical chest illness cause accelerated loss of FEV, and reduction of FEV is a cause of neither mucus hypersecretion nor of clinical chest illnesses. The two disorders are correlated with each other only because susceptibility to one is in some way linked to susceptibility to the other. Research is still needed to discover how it is that certain cigarette smokers develop significant obstruction, whereas most do not".

The graphic representation from the 1977 summary of the results published in the British Medical Journal (Fig. 1 A), commonly known as the Fletcher-Peto curve, is by far the best-known graphic in the COPD literature. Initially proposed as a conceptual model, the Fletcher-Peto curve has often been taken as a representation of "the" natural history of COPD, despite the accompanying discussion that alternate natural histories were possible (Fig. 1 B). Yet, the fundamental concept of a single natural history, which was central in the clinical epidemiology of the 1960s and 70s, is currently insufficient and inconsistent with more recent studies that have identified a number of areas where the findings of Fletcher et al. require expansion and/or modification. These include:

– Recognition of the role of exposures other than cigarette smoking, and that smoking affects a larger percentage of individuals than suggested by Fletcher et al.;

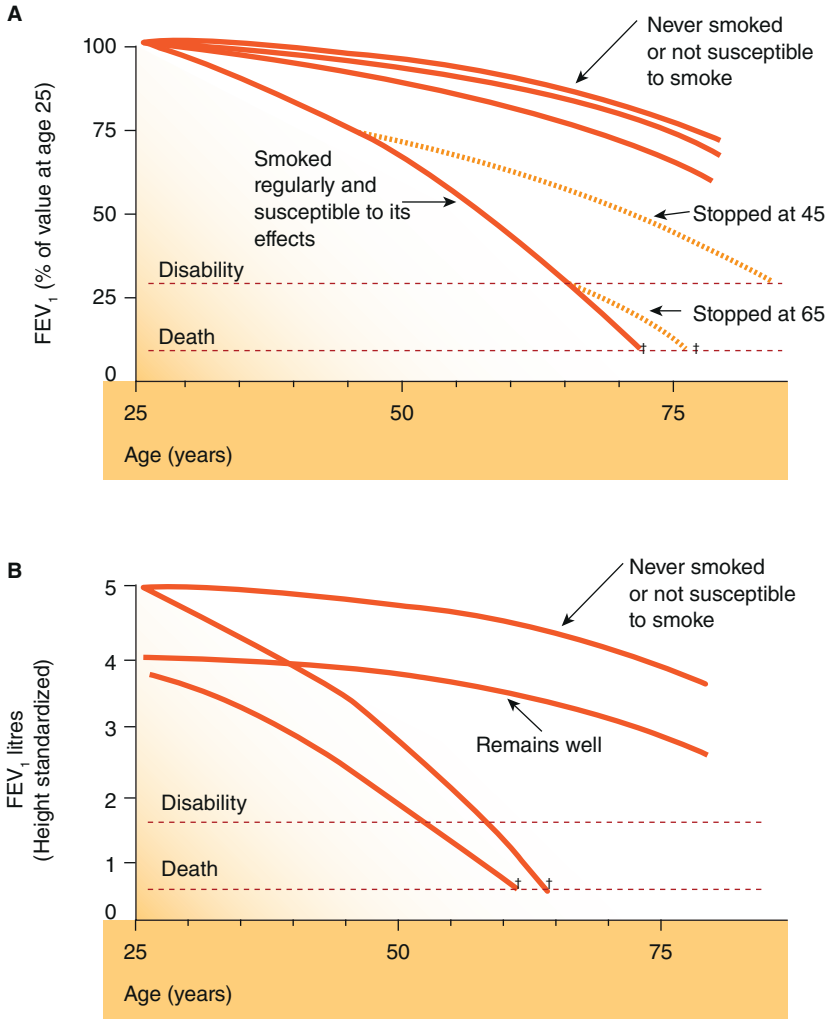

Figure 1. The Fletcher-Peto Curve. **A:** the classic Fletcher-Peto Curve. Reproduced from their 1977 publication, this figure represents a conceptual progression of the natural history of COPD. It was based on extrapolation of the data from the British Postal Workers Study. It emphasizes the importance of accelerated lung function decline in susceptible smokers. **B:** this is figure 2 in Fletcher and Peto's 1977 publication and indicates alternate natural histories. Current data suggest that those with accelerated decline and those with normal decline may be similar in numbers. See text for details *(reproduced with permission from Fletcher et al.[2]).*
FEV_1: forced expiratory volume in one second.

– The benefits of smoking cessation vary with disease severity;

– Lung function decline does not simply accelerate with advancing age;

– Many individuals can develop COPD with normal rates of lung function decline if they have abnormal lung growth and, therefore, low lung function at early age (Fig. 2 A);

– COPD may develop in the absence of obvious exposures and may be related to other conditions such as asthma;

– The relationship between mucus hypersecretion, exacerbations, and lung function decline also appears to be more complex than suggested by Fletcher et al.; and, finally

– COPD is now recognized as having extrapulmonary manifestations.

All these novel findings will have to be incorporated into any new model(s) describing the natural history (or histories) of COPD. Importantly, research strategies, particularly those designed to improve the outcome for COPD patients, have been, in large part, based on the narrow view of the COPD natural history reflected in the Fletcher-Peto curve (Fig. 1 A). The current BRN review will discuss the current broader understanding of COPD natural history, particularly with regard to implications for future studies.

DEFINITION AND HETEROGENEITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Airflow limitation that cannot be fully reversed by bronchodilators, which serves as the defining feature of COPD, can result from several histologic lesions[3,4]. These include destruction of alveolar wall with loss of lung elastic recoil, the characteristic lesion of emphysema, narrowing and loss of small airways, and, likely, narrowing of larger airways together with accumulation of inflammatory exudate and mucus within the airway lumen. Each of these lesions can result from several different etiologic factors and pathobiological mechanisms. Some causes of fixed airflow limitation have been excluded from COPD definitions, e.g. cystic fibrosis. Nevertheless, because the diagnosis of COPD is based on a single physiologic feature –the ratio between forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)– and there are many causes that can affect this ratio, COPD is inherently heterogeneous. Moreover, cigarette smoke can cause all of the histologic lesions that contribute to airflow limitation, albeit to varying degrees in different individuals. In addition, their simple definition greatly facilitated epidemiologic studies that could be based on relatively simple assessments of large populations.

Over time, however, it has become increasingly recognized that etiologies other than cigarette smoke play important roles in the pathogenesis of COPD[4]. Many, such as particulate air pollution, may activate similar pathogenic mechanisms to those activated by cigarette smoke. However, air pollution appears to be a risk factor in both smokers and non-smokers, suggesting that pathogenic mechanisms are not identical[5]. More importantly, the recognition that multiple risk factors, discussed below, can contribute to the development of COPD, and that a given individual may have COPD as a result of several distinct but interacting pathogenic processes has emphasized the heterogeneity and complexity of COPD. Finally, the observation made by Fletcher et al. has been amply confirmed that there is tremendous individual variation in susceptibility to exposures such as smoking and air pollution. Genetic differences undoubtedly account for some of this variation, and a number of "susceptibility" genes have been identified[6,7]. None of them, however, have large effects, other than $alpha_1$-antitrypsin

deficiency, which is relatively rare. Thus, it is likely that many genes with small effects will interact to account for some of the interindividual variability in susceptibility. To what degree other factors such as diet account for variable susceptibility remains to be determined[8].

It has also become clear that COPD has more manifestations that can be measured by assessing airflow limitation alone. Within the lung, for example, cough and sputum production, susceptibility to exacerbations, dynamic hyperinflation, and compromise of the pulmonary circulation with abnormal gas exchange and reduction of cardiac output are all very loosely related to altered airflow, but can be clinically relevant features of COPD[3,4]. Importantly, COPD is also associated with extrapulmonary manifestations in many organ systems that are often a major clinical issue in individual patients[9,10]. Interestingly, these extrapulmonary manifestations appear to be features of specific COPD patient subsets[11,12]. In any case, each of these features is likely to have a natural history that may be quite independent of that of airflow limitation. Indeed, current evidence suggests that there are multiple disease trajectories that can lead to COPD[43]. Moreover, as disparate pathogenic processes may be active in a given individual, a single patient may manifest multiple natural histories. All these are concepts that are not addressed by the classic Fletcher-Peto paradigm.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE TRAJECTORIES

The classic Fletcher-Peto curve assumes that individuals start with similar maximally attained lung function and that COPD develops as a result of accelerated lung function loss in adulthood. Further, the way the curve was drawn, the rate of loss was assumed to increase with progressive ageing (Fig. 1 A). Fletcher et al. recognized that this model was an oversimplification and suggested that COPD could also result from individuals who started with reduced maximally attained lung function in adulthood who then declined at a normal rate (Fig. 1 B). There may be, moreover, several different models (Fig. 2) for compromised lung development and for accelerated lung loss[13,14]. Current concepts of COPD natural history, therefore, are best considered in the context of the natural history of lung function throughout the life of an individual, from earliest development to old age, as events at any of these times can impact COPD natural history[15,75].

Lung development. The human lungs develop from the embryonic foregut as buds from the laryngo-tracheal *sulci* at 26 days of gestation[16]. The lung buds then undergo dichotomous branching, forming approximately 18 generations of airways through 16-26 weeks of gestation. The epithelium of the airway progressively thins during this process, as does the intervening mesenchyme. This results in very thin epithelial layers separated by an attenuated mesenchyme containing blood vessels and structures that will become respiratory bronchioles. At this point, dichotomous airway branching is believed to cease, although the process completes at different times at different parts of the lung. Alveolar walls form by a separate process of septation in which epithelial cells grow into the airspace lumen. Several generations of this process account for the acinar structure of the human lung. Three to five generations of alveolar walls form in a

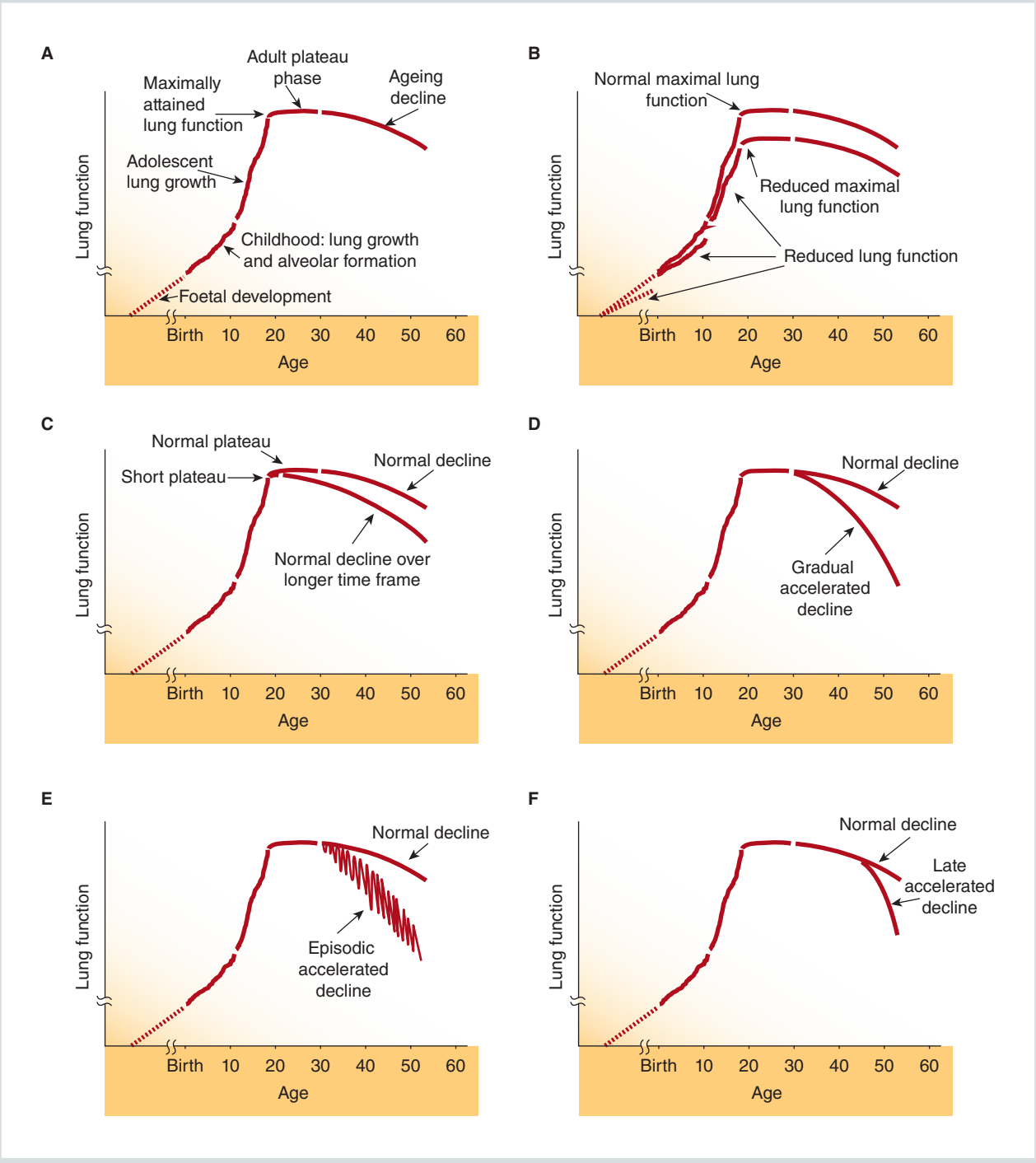

FIGURE 2. Potential trajectories for COPD natural history. **A:** schematic representation of lung function growth and development through the human lifespan. **B:** Reduced maximally attained lung function in young adulthood could result from compromised foetal or childhood development when lung structures are forming or from compromised lung growth at any time. **C:** A reduction in the duration of the plateau phase of maximal lung function will lead to an earlier decline and, consequently, lower than normal lung function with age. Accelerated lung function could begin in early adulthood and be gradual **(D)**, episodic **(E)** or could begin in late life **(F)**. None of these trajectories are exclusive. See text for details *(modified with permission from Rennard[72]).*
FEV_1: forced expiratory volume in one second.

process that continues through childhood and forms most of the lung surface area.

Following formation of alveolar units, the lungs grow in size and surface area as the thorax grows in childhood and adolescence. Maximal lung function is attained in young adulthood and, in the majority of normal individuals, remains constant for a period of 10 years or so[17,18]. Following this plateau phase, lung function begins to decline. The mechanism(s) for this decline is not known, nor is it clear whether this represents "normal" ageing or reflects the response of normal individuals to the multiple insults inherent with breathing (Fig. 2 A).

Pathogenic processes that can lead to COPD may occur at any phase of this lung health cycle (Fig. 2 B-F). Insults occurring during gestation can compromise lung development. The studies of Barker et al., which related birth weight to health outcomes in later life, established that being born small had a measureable effect on lung function and increased COPD risk[19], although the anatomic basis for this effect remains undetermined. Subsequent studies have also established a role for prematurity[20], maternal smoking[21,22], and maternal nutrition[15,23] as early life determinants of lung function that could contribute to COPD risk. These risk factors may explain the correlation between poverty and observed mortality rates from COPD and other lung diseases, including COPD in non-smokers[24].

In childhood, both passive[22] and active[25-27] cigarette smoking can compromise lung growth, leading to reduced maximally attained lung function. Lung function growth is also compromised among children who developed broncho-pulmonary dysplasia[20,28]. Similarly, both reactive airways[27], while controversial, and childhood infections[19,29-31] also appear to compromise lung growth. A potential mechanism is suggested by studies in an early childhood model of asthma in the rhesus macaque. In this model, the development of asthma led to a reduction in the number of airway branches[32], a feature that is also present in human patients with COPD[33]. Whatever the mechanisms, a variety of factors can result in reduced maximally attained lung function, which can increase the risk for COPD (Fig. 2 B).

After attaining a maximum in young adulthood, in most individuals, lung function remains constant for about 10 years, after which it slowly declines[17,18,34]. In cigarette smokers, the duration of the plateau phase is reduced and the decline begins earlier[17,18,35] (Fig. 2 C). Some non-smokers also experience a shortened plateau phase, although the risk factors for this are unknown[17]. A shortened plateau phase should result in compromised lung function at an earlier age and increase the risk for COPD.

NATURAL HISTORY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN ADULTS

In clinical practice, COPD is most often diagnosed in smokers who complain of dyspnoea during activities of daily living, most commonly between the ages of 50-70 years. Although treatment is often started based on clinical impression, definitive diagnosis requires spirometric confirmation of the presence of poorly reversible airflow limitation, which can guide treatment[3,36]. Given that the latter can influence the clinical features, evolution, and prognosis of these patients, it

seems appropriate to discuss separately the "natural history" of COPD in the adult before and after the diagnosis of COPD has been established and treatment started.

Natural history of chronic obstructive pulmonary disease prior to diagnosis

While a landmark, the study by Fletcher et al.[1] was limited by its relatively small sample size (792 healthy male postal workers from London, aged 30-59 years) and a relatively short follow-up time (eight years). The effects of smoking cessation included in the figure, and often cited as fact, were speculation, albeit supported by the subsequent Lung Health Study[37].

A more recent analysis of the Framingham Offspring Cohort (FOC) revisited these issues in a larger cohort of men and women (n = 4,391) with a wider age range (13-71 years) followed for a longer period of time (median follow-up time of 23 years)[38]. Key results of this study include: (i) healthy never-smoker females achieve full lung growth earlier than males, and their rate of lung function decline with age is slightly lower than that of males (Fig. 3); (ii) as shown by Fletcher et al.[1], smoking indeed increases the rate of lung function decline, both in males and in females, and there is a range of susceptibility to the effects of smoking, as they suggested. Interestingly, the presence of respiratory symptoms at baseline and/or a respiratory diagnosis during follow-up appears to identify a group of susceptible smokers[39-41], although a significant proportion of adults without symptoms will also be at high risk[42]; and (iii) quitting smoking has a beneficial effect at any age, but it is more pronounced in earlier quitters, resulting in a modified Fletcher-Peto curve (Fig. 3).

A subsequent analysis by Lange et al. of three cohorts (the FOC, the Copenhagen City Heart Study, and the Lovelace Smoker cohorts) has investigated the natural history of COPD patients in a larger number of subjects and over longer time frames, and has shown that different lung function trajectories can lead to incident COPD in adulthood[43]. In particular, as shown in figure 4, approximately 50% of individuals with COPD in adulthood fit the Fletcher-Peto model (Fig. 1 A) as they have normal lung function before 40 years of age and develop COPD through an accelerated FEV_1 decline (53 ± 21 ml/year). By contrast, the other 50% of individuals with COPD in adulthood already had low FEV_1 in early adulthood, indicating abnormal lung development, (Fig. 1 B) and a much lower subsequent rate of decline in FEV_1 (27 ± 18 ml/year; $p < 0.001$), despite similar smoking exposure (Fig. 4)[43]. That low lung function in early life is an important risk factor for the development of COPD in adulthood is further supported by the observation that 26% of participants with abnormal lung function before 40 years of age develop COPD after 22 years of observation, whereas only 7% of those with normal FEV_1 in early life did so ($p < 0.001$). These cohorts are not all population-based samples, and thus cannot determine the prevalence of COPD trajectories in the general population[44]. Nevertheless, the study by Lange et al. clearly illustrates that low lung function in early adulthood is important in the genesis of COPD. While the possibility of different trajectories was clearly stated by Fletcher et al. (Fig 1 B), the Fletcher-Peto curve has become a type of dogma for the COPD Natural History that needs to be abandoned.

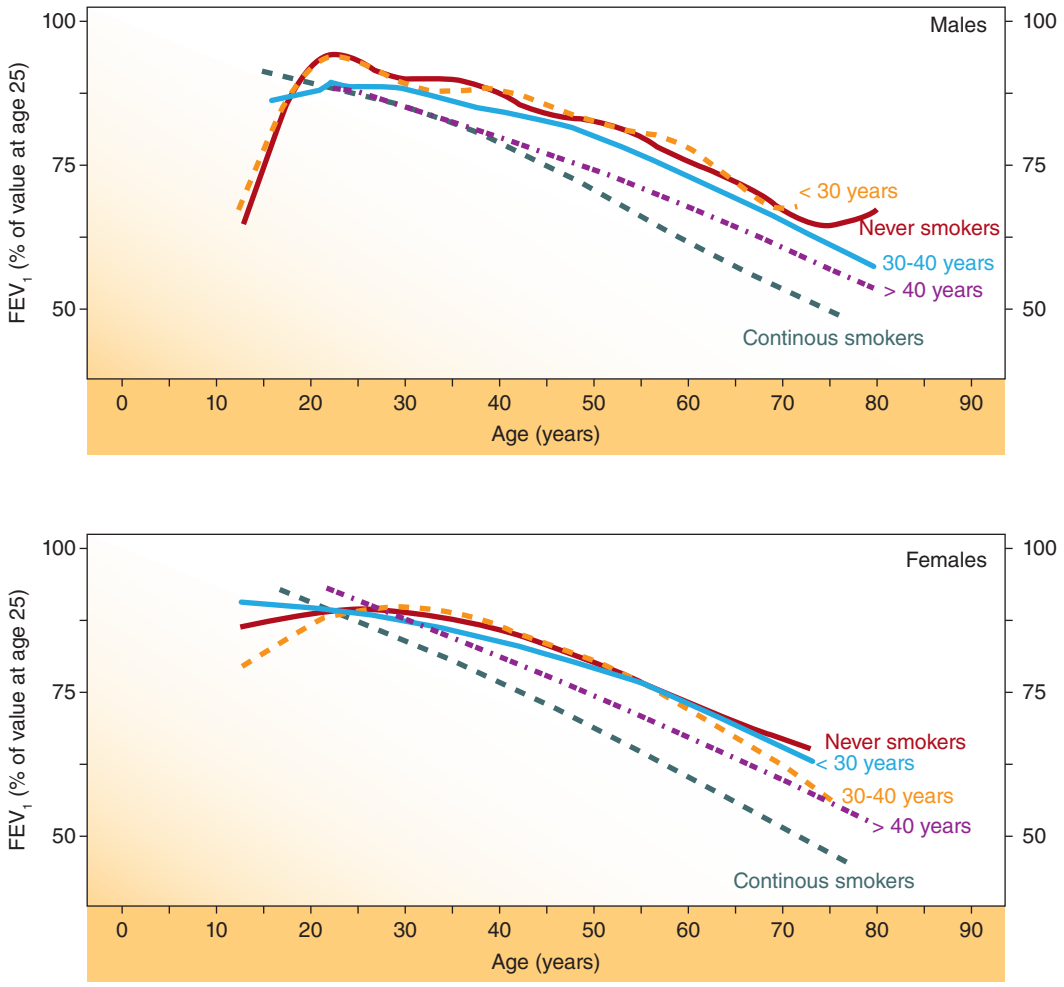

Figure 3. Forced expiratory volume in one second (expressed as % of its value at 25 years of age) changes through life in males (top) and females (bottom). Curves for never-smokers, continuous smokers, and smokers who quit before the age of 30 years, between 30-40 years, and after 40 years of age are depicted. For more information see text *(reproduced with permission from Kohansal et al.[38]).*
FEV_1: forced expiratory volume in one second.

Natural history of chronic obstructive pulmonary disease after clinical diagnosis is established and treatment started

There are no data on the natural history of untreated COPD, as treatments with meaningful benefits are available and it would be unethical to withhold them. Further, many patients with COPD have comorbidities, the treatments for which may also affect the natural history of COPD. While no COPD treatment is regarded as meaningfully affecting lung function decline, in TORCH, both salmeterol and fluticasone propionate each resulted in a statistically significant reduction in lung function decline over

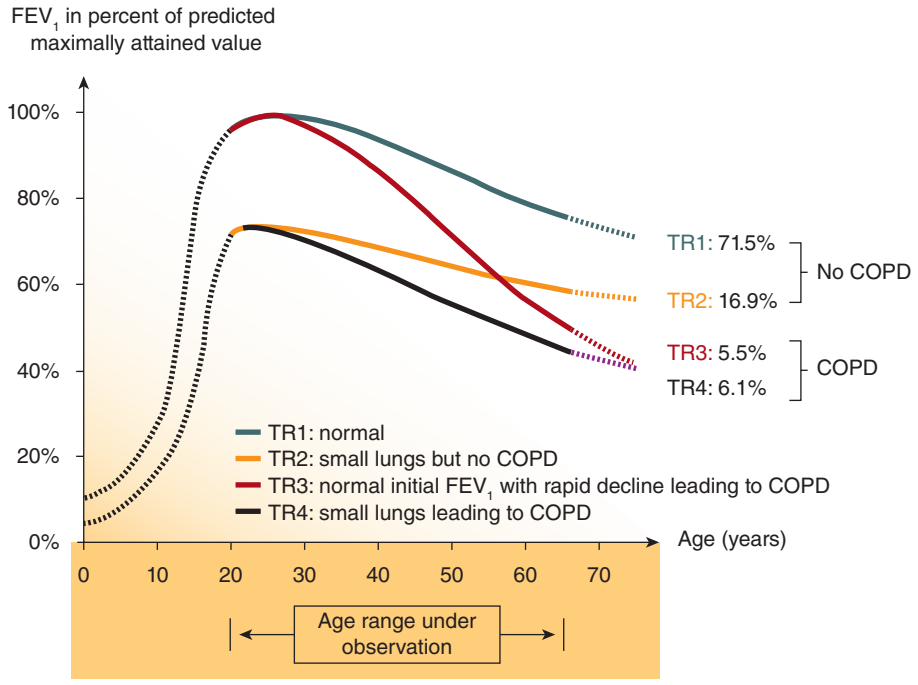

FIGURE 4. Four different lung function trajectories through life and the proportion of individuals in each trajectory according to a combined analysis of the Framingham Offspring Cohort, the Copenhagen City Heart Study and the Lovelace Smoker cohort. For further information see text *(reproduced with permission from Lange et al.[43]).*
FEV_1: forced expiratory volume in one second; TR: trajectory.

three years of 13 ml/year[45]. The combination was even more effective, although the difference from placebo of 16 ml/year did not achieve the 20 ml/year reduction generally regarded as important – albeit somewhat arbitrarily chosen[46]. UPLIFT assessed whether tiotropium could slow lung function loss. While there was no effect in the total population, among those with milder disease a 6 ml/year reduction in lung function decline was observed[47,48]. Concurrent treatment of subjects in UPLIFT with other medications including inhaled corticosteroids and long acting ß-agonists makes it difficult to conclude that there is no effect of treatment. Similarly, as treatments for comorbidities associated with COPD may also affect COPD natural history, understanding the natural history of COPD will be problematic.

The classic Fletcher-Peto curve shows lung function loss accelerating with increasing age. However, several studies have documented that the rate of FEV_1 decline in patients with COPD is steeper in patients with mild-to-moderate than in those with severe-to-very severe airflow limitation[48-50] (Fig. 5). Further, patients with moderate to very severe airflow limitation included in different randomized clinical trials

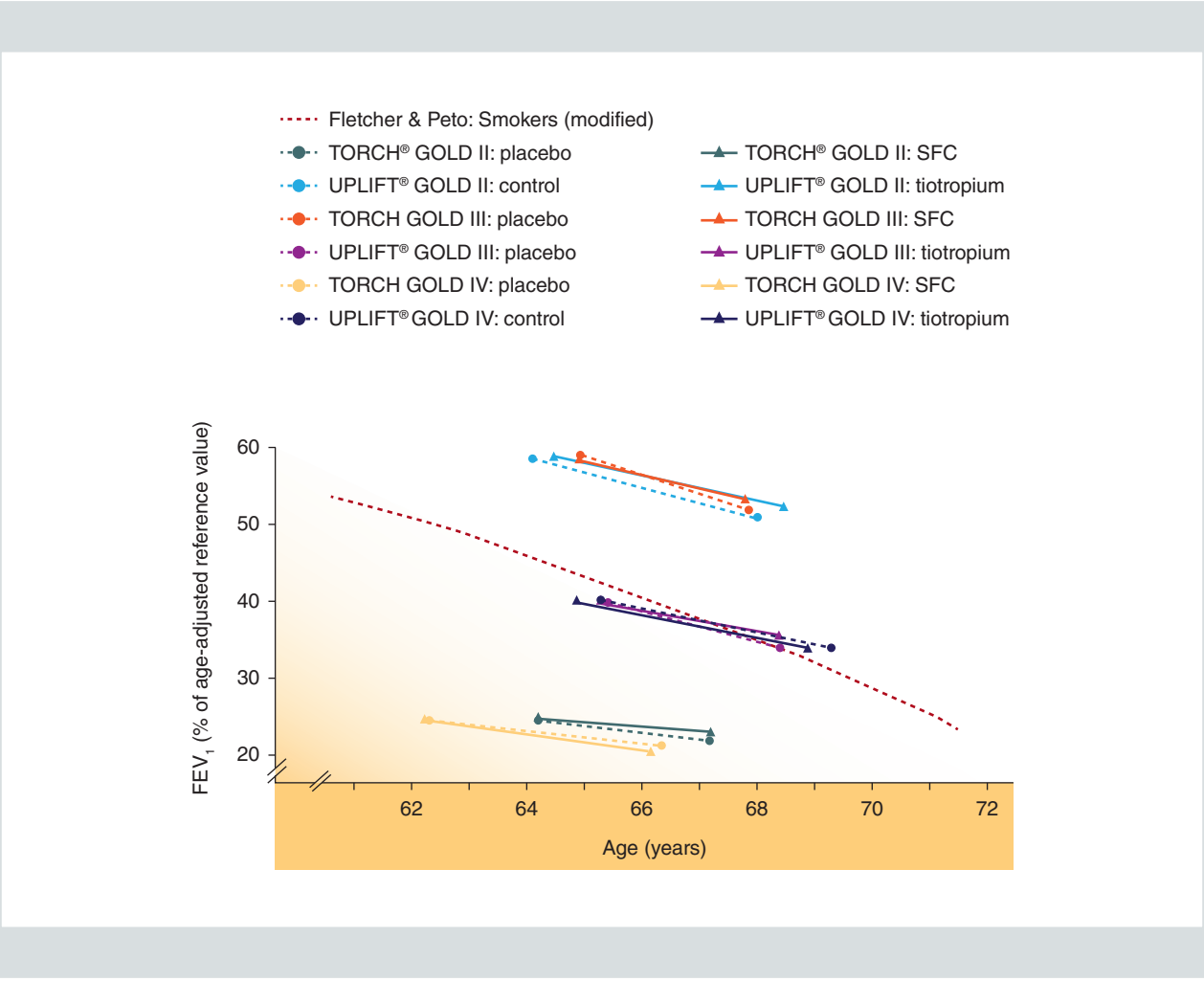

Figure 5. Forced expiratory volume in one second changes in the different arms of the TORCH[73] and UPLIFT[47] studies superimposed on top of the predicted Fletcher and Peto model (dashed line). For further explanations see text *(reproduced with permission from Decramer et al.[74]).* FEV_1: forced expiratory volume in one second.

have a similar age (Fig. 5). This suggests that studies designed to modify the rate of decline of FEV_1 need to focus on younger individuals with milder disease. Importantly, some of these individuals may have normal rates of decline, while others may have accelerated rates of decline, as suggested by Fletcher et al. and as recently demonstrated by Lange et al.[43], and suggested by others[51]. Thus, biomarkers that can determine individual disease trajectories will be important for the design of COPD prevention and treatment trials.

The ECLIPSE study also demonstrated that FEV_1 does not uniformly decline with age in patients with treated COPD[50]. Not only was decline variable, 8% of COPD patients included in ECLIPSE had an increase of more than 20 ml/year over the three years of follow-up. Interestingly, Fletcher et al. noted in the appendix of their monograph that lung function may improve over time in some COPD patients[1], and other studies have confirmed that in a minority of COPD patients, lung function improves over time[52,53].

Clinically important chronic obstructive pulmonary disease

The concept of "clinically important COPD" has also evolved since the publication of the work by Fletcher et al. They commented that about 13% of smokers would eventually be diagnosed with COPD, generally because of the presence of symptoms of dyspnoea, cough, and/or sputum[1]. This has been rounded off and incorrectly quoted as: "15% of smokers will get COPD." In fact, while susceptibility is variable, more than 50% of smokers will develop the airflow limitation criteria for COPD[54,55], though the majority remain undiagnosed[56]. The majority of the undiagnosed COPD patients generally have milder airflow limitation, which has raised the question of what is clinically important COPD.

In 1995, the American Thoracic Society Statement on Diagnosis and Management of COPD classified all individuals with $FEV_1 > 50\%$ as having mild disease[57]. Further, the lung function impairment of these individuals was regarded as being insufficiently compromised to cause symptoms. Therefore, treatment of these individuals was not recommended. Since that time, it has become recognized that COPD patients develop symptoms of dyspnoea whenever tachypnea leads to dynamic hyperinflation[58]. The most common cause of tachypnea is exertion. However, dyspnoea on exertion is easily avoided by becoming progressively more sedentary. As a result, COPD patients become remarkably restricted in their activities, but do not necessarily complain of dyspnoea. Dynamic hyperinflation, together with abnormal gas exchange, can develop even in very mild COPD and can compromise exercise performance[59,60]. Individuals with mild COPD are also at increased risk for extrapulmonary problems. The increased risk of cardiac disease associated with COPD, for example, is present with very modest decrements in lung function; there is approximately a threefold increased cardiovascular risk as the FEV_1 approaches the accepted lower normal range of 80% predicted compared to the best group with 110% predicted FEV_1[61]. The recognition that COPD patients with mild disease have physiologic limitations and an adverse prognosis has led to efforts to intervene to improve function and outcome of patients beyond the 13% Fletcher et al. suggested would come to diagnosis.

Features other than forced expiratory volume in one second

Relatively little is known about the natural history of features of COPD other than the FEV_1. Chronic mucus hypersecretion often coexists with mild COPD, where it is a risk factor for subsequent decline in lung function[39], hospital admission[62], mortality in general[63], and pneumonia[64]. Cough and sputum resolve with smoking cessation in the majority of subjects[65], but the natural history of these problems among those where there is not resolution is not well described.

Exacerbations generally increase as FEV_1 increases, but the relationship is weak[66]. Similarly, exacerbation risk generally increases with time and the inter-exacerbation interval for severe exacerbations shortens[67].

COPD is now recognized as a complex disease that has extrapulmonary manifestations[9]. Importantly, these extrapulmonary features

are often the most important problem faced by patients. The natural history of these extrapulmonary manifestations in COPD is largely unknown. It is clear, however, that the presence of multiple comorbidities is common and increases risks and costs of care[10,68].

IMPLICATIONS OF THE NEW UNDERSTANDING OF THE NATURAL HISTORY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE FOR FUTURE STUDIES

The COPD population is extremely heterogeneous, for the reasons described above. This may have important effects on both the natural history and response to therapy. For example, several studies suggest that the benefit of inhaled glucocorticoids for reducing COPD exacerbations is limited to those patients with higher eosinophils[69,70]. Whether the benefits of inhaled glucocorticoids on slowing lung function loss is similarly limited (and of a greater magnitude) in this specific subgroup of patients is unknown. Unfortunately, most information on the COPD natural history, including both observational and interventional studies, derives from studies using simple definitions based largely on airflow limitation in populations limited to smokers. As a result, little is known about the differences in COPD natural history associated with different exposures, genetic risk factors, or developmental effects.

Because COPD is a major public health problem, a major public health goal has to be to improve its natural history. Prior efforts attempting to address this question have been largely unsuccessful, in part because they were based on the simple model of the Fletcher-Peto curve. For example, the EUROSCOP trial assessed the effects of inhaled budesonide on the rate of lung function decline and found no benefit[71]. Whether a trial focusing on mild individuals with higher eosinophils, or only on those individuals clearly following an accelerated decline of lung function trajectory might have been successful remains unknown. A notable exception of interventional studies in COPD, however, was the Lung Health Study[37]. Importantly, this study of smoking cessation enrolled only smokers, who therefore had the potential to benefit from the intervention. A parallel requirement for other mechanistic interventions is likely to be required in future studies designed to alter the natural history of COPD.

SUMMARY

The study of Fletcher et al. was a landmark study that greatly advanced our understanding of COPD. Recent advances have extended our learning, and this new information need to be incorporated into our conceptual framework of the COPD natural history. Specifically, recognition that COPD is a life-long condition, and that early life events and childhood health and growth, as well as adult exposures, contribute to COPD risk is essential. In addition, COPD disease progression appears to be most rapid, at least for those individuals losing airflow at an accelerated rate, when the disease is moderate rather than later in the disease course, although dropouts and selection bias may have affected these conclusions. Finally, it is likely that the many aetiologies that contribute to COPD pathogenesis will have different natural histories. These new

understandings will be important in the development of interventions designed to alter the natural history of the many patients who suffer COPD.

CONFLICT OF INTEREST

Dr. Vestbo reports personal fees from AstraZeneca, personal fees from Boehringer-Ingelheim, personal fees from Chiesi Pharmaceuticals, personal fees from GlaxoSmithKline, personal fees from Novartis, outside the submitted work. Dr. Agusti reports grants and personal fees from AstraZeneca, grants and personal fees from GlaxoSmithKline, grants and personal fees from Menarini, personal fees from Novartis, grants from Merck Sharp & Dohme, personal fees from Boehringer-Ingelheim, personal fees from Chiesi Pharmaceuticals, personal fees from Teva, outside the submitted work. Dr. Rennard declares no relevant conflict of interest.

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