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Lung Function Trajectories: a New Framework to Understand Adult Chronic Respiratory Diseases

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ABSTRACT

Lungs grow and mature *in utero* and after birth until early adulthood. Normally, lung function reaches a peak between 20-25 years of age, earlier in females, and after a relatively brief *plateau*, it declines slowly due to physiological lung ageing. There are several genetic and environmental factors with the potential to alter this normal lung function trajectory, so it is now recognized that in the general population there is indeed a range of them. Further, it is also known now that some of these trajectories have important health consequences, both for the lungs but also for other organ systems, including premature death. Here we provide a brief overview of these new concepts and discuss the potential implications of this new framework to understand adult respiratory diseases. **(BRN Rev. 2020;6(2):118-27)**

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INTRODUCTION

Lung development and growth is extremely complex[1]. It starts *in utero* and continues after birth, during infancy and adolescence until early adulthood (Fig. 1), where lung function reaches a peak value (earlier in females)[2]. After a relatively brief *plateau,* lung function declines moderately due to physiological lung ageing[3]. This *normal lung function trajectory* can be altered by several genetic and environmental factors. Indeed, it is now well recognized that there is a range of them in the general population[3,4] (Fig. 1). Further, it is also now known that some of these trajectories can have important health consequences, both for the lungs and for other organ systems such as the cardiovascular and metabolic ones, including premature death[5,6] (Fig. 2). Below we briefly review the evidence supporting this new paradigm and discuss its potential implications for the understanding of adult chronic respiratory diseases.

LUNG FUNCTION TRAJECTORIES

Altered lung growth

Between 4-12% of individuals in the general population fail to reach a forced expiratory volume in one second (FEV_1) peak in early adultwood within the predicted "normal range" for their age and sex[5]. This can be due to one or more genetic risk factors[7-9] and/or environmental conditions *in utero* and after birth[4,10], including maternal tobacco smoking and under-nourishment, premature birth, intrauterine growth restriction and broncho-pulmonary dysplasia, air pollution exposure, lower respiratory tract infections and active smoking during adolescence. Childhood "asthma" is also often considered a risk factor for low lung function in early adulthood[11] but the diagnosis of "asthma" in young children is difficult to establish objectively and, although the presence of "asthma" can conceivably impair lung growth, it is also possible that any other process impairing lung growth can cause similar, nonspecific, symptoms than those traditionally associated to asthma (dyspnoea, cough, wheezing). These environmental risk factors interact in a complex manner and change with time[12] (Fig. 3). Importantly, many of them are preventable[12]. Finally, it is also important to note that individuals who fail to attain a normal peak lung function in early adulthood suffer a higher prevalence and about a decade earlier incidence of cardiac and metabolic comorbidities, as well as premature death[5]. These observations have been later reproduced in other cohorts[13].

Accelerated lung function decline

Chronic obstructive pulmonary disease (COPD) has been traditionally considered the paradigm of an adult respiratory disease characterized by an enhanced rate of lung function decline[14] due to the inflammatory response to tobacco smoking[6]. Recent research, however, has shown that this paradigm is incomplete[6] since about 30% of COPD patients worldwide are never smokers[15], exposure to other inhaled particles and gases than those of smoking (e.g. biomass, air pollution) can also lead to COPD in adulthood[16], and not all patients with COPD exhibit enhanced lung function decline[17,18]. The latter was clearly shown in a recent study by Lange, Celli, Agustí et al. in three large independent cohorts[18]. Results showed that the rate of lung function decline was accelerated in only about half of adult COPD patients whereas the other half had

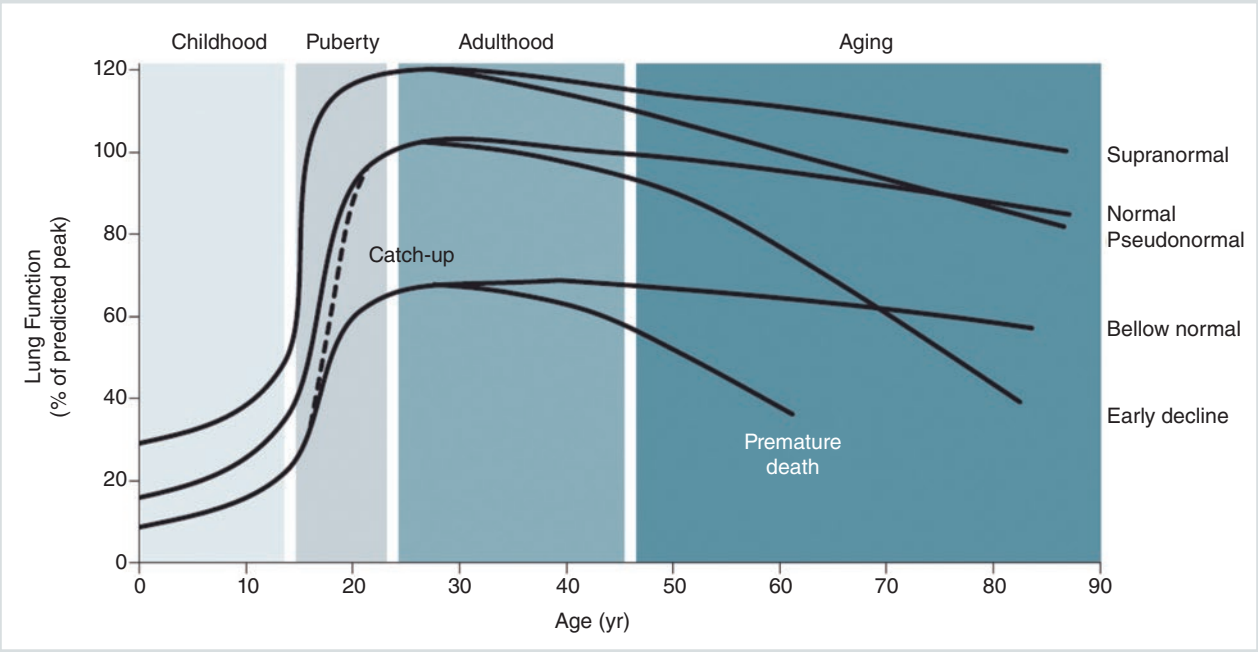

FIGURE 1. Schematic representation of several potential lung function trajectories through life *(reproduced from Agustí A, et al.[6] with permission).* For further explanations, see text.

evidence of low peak lung function in their thirties and developed COPD with a normal lung function decline rate[18]. These observations have been confirmed by other subsequent studies[19-22]. Further, a recent analysis in the Framingham Offspring Cohort and their direct descendants (Gen III cohort) has provided evidence of trans-generational reproducibility of lung function[5] (Fig. 4), albeit it should be noted that this transgenerational reproducibility may be due to genetic and/or shared environmental factors.

IMPLICATIONS FOR A NEW UNDERSTANDING OF ADULT CHRONIC RESPIRATORY DISEASES

The realization that several genetic and environmental risk factors interact dynamically over time in very complex ways (Fig. 3) and that, as a result, there is a range of lung function trajectories in the general population (Fig. 1), some of them with important health consequences, including premature death (Fig. 2), raises questions and challenges and, at the same time, opens new opportunities for prevention and early intervention of chronic respiratory disease in children and adults[23].

First, the biological mechanisms underlying these different lung function trajectories are not always well understood. In terms of defective *lung growth*, the two main, non-mutually exclusive, mechanisms proposed[3] include abnormal lung development *in utero* (since about 40% of lung function deficits at 6-7 years of age are already present at birth[24]) and failure to *"catch-up"* lung function during infancy

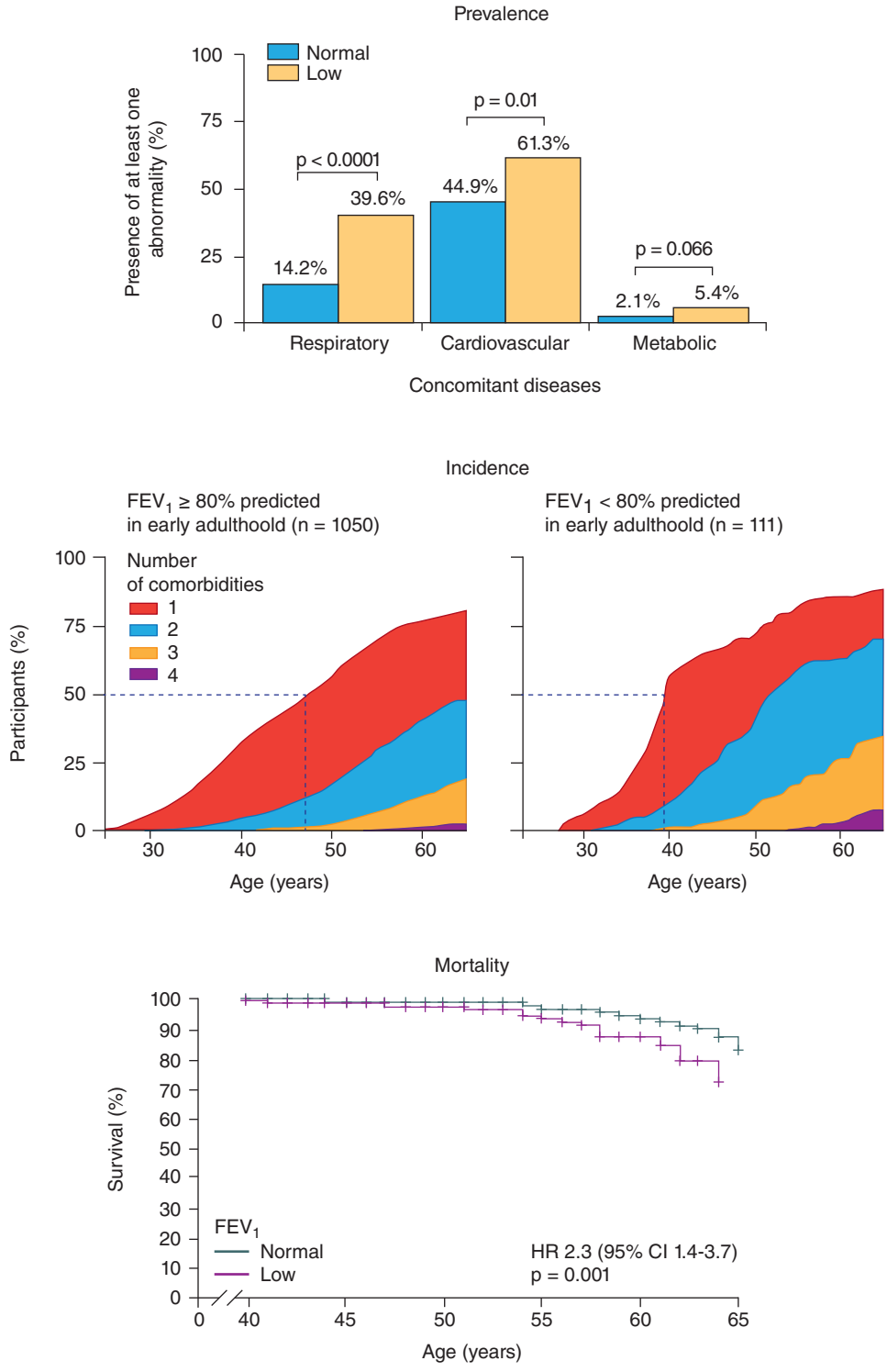

Figure 2. Increased prevalence, incidence and mortality in individuals with low lung function in early adulthood *(reproduced from Agustí A, et al.[5] with permission).* For further explanations, see text.
CI: confidence interval; FEV_1: forced expiratory volume in one second; HR: hazard ratio.

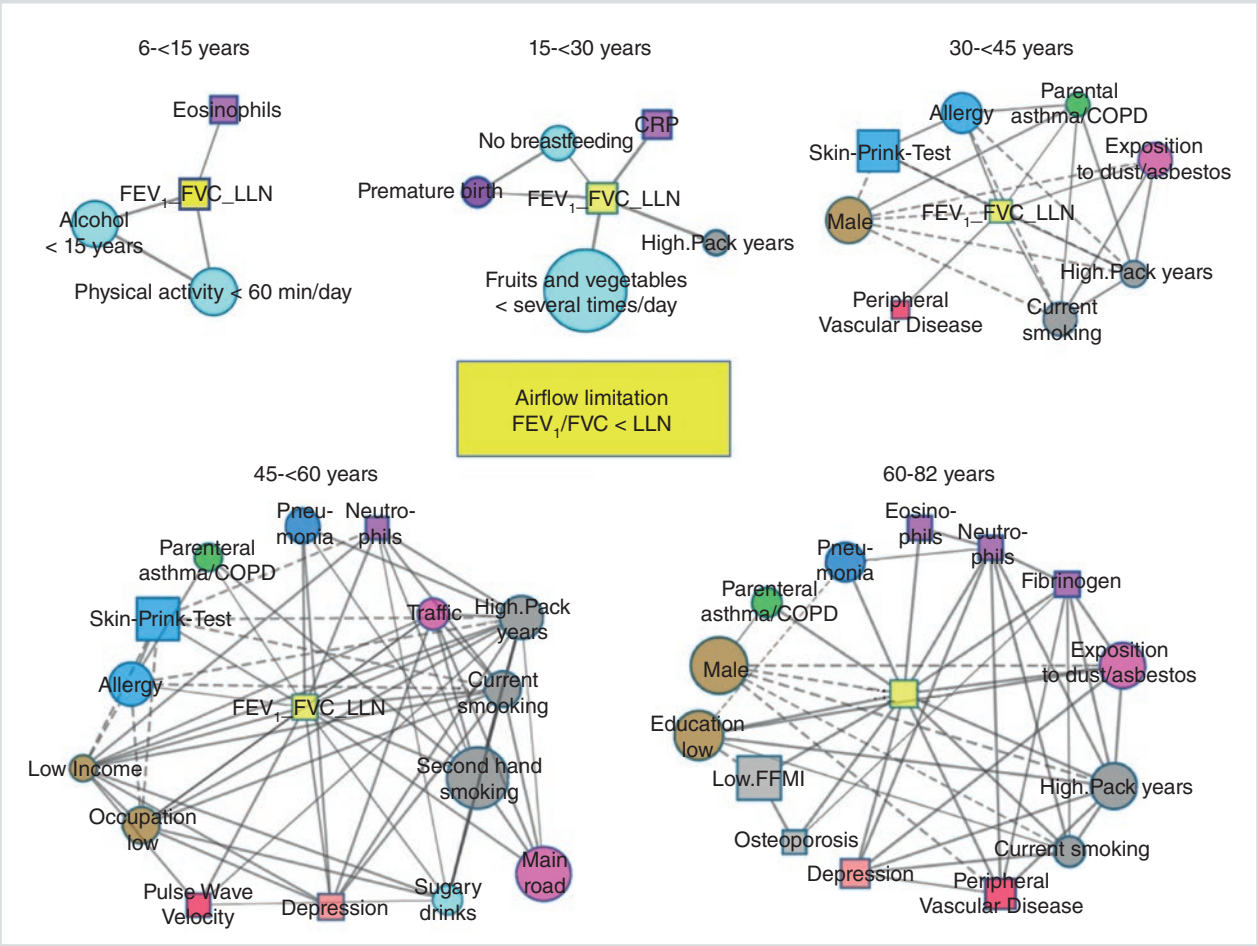

Figure 3. Networks of associations with airflow limitation (yellow node at the center of the network) with different environmental factors in different age bins *(reproduced from Breyer-Kohansal R, et al.[12] with permission).* For further explanations, see text.
COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; LLN: lower limit of normal.

and adolescence[25] (the term *catch-up* here refers to the observation that many environmental conditions cause growth impairment but, when they resolve, some (not all) children regain a normal growth trajectory[26,27]). On the other hand, in terms of *enhanced lung function decline* in adulthood, albeit oxidative stress, protease-antiprotease imbalance and an abnormal inflammatory response have been traditionally considered their main underlying biological mechanisms[28], now we know that many other ones also participate, including cellular senescence and apoptosis, airway fibrosis and remodelling, stem cell exhaustion, extracellular matrix alterations, autophagy, autoimmunity to neo-epitopes and reductions of endogenous anti-ageing molecules[6]. In essence, it is the interplay between two major biologic mechanisms, organ development, maintenance and repair (green triangle in figure 5, which decreases with age), and cumulative tissue injury and ageing (red triangle in figure 5,

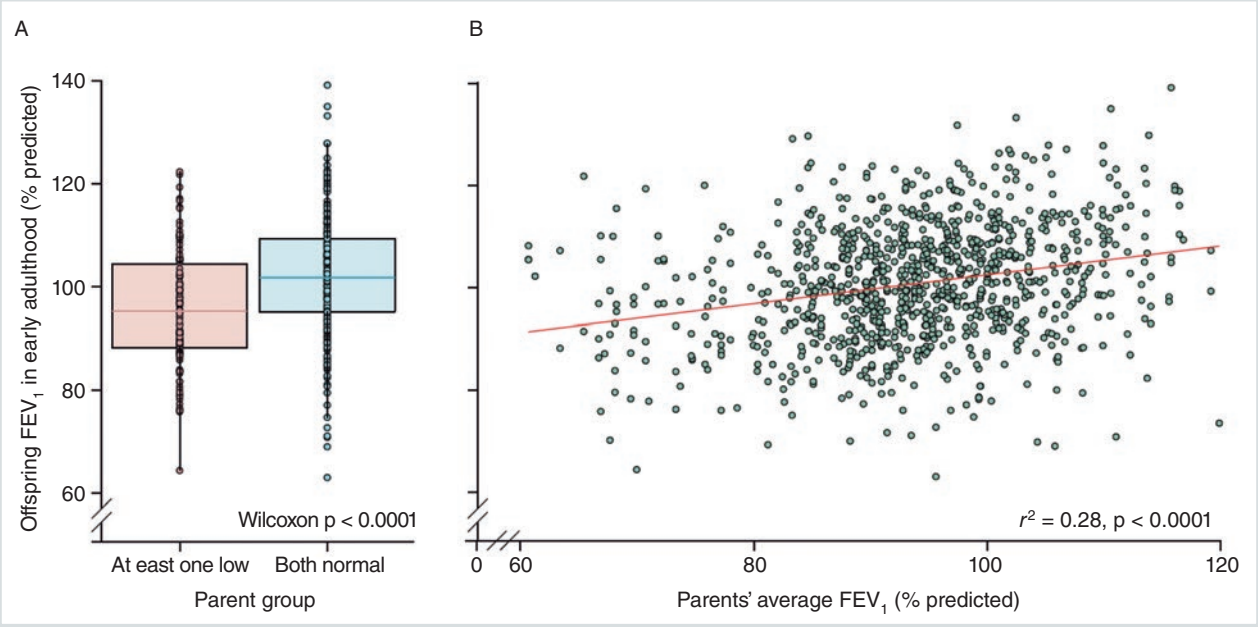

FIGURE 4. Trans-generational reproducibility of low FEV_1 in early adulthood. *Panel A:* Box plot showing median FEV_1 (% predicted) of participants in the GenIII cohort with at least one parent in the Framingham Offspring Cohort (FOC) classified as low in early adulthood and participants with both FOC parents classified as normal. *Panel B:* Scatter plot showing the relationship between early adulthood FEV_1 (% predicted) of GenIII participants and parents' average early adulthood FEV_1 (% predicted) *(reproduced from Agustí A, et al.[5] with permission).* For further explanations, see text.
FEV_1: forced expiratory volume in one second.

which increases with age) what determines health and life expectancy (top triangle in figure 5), including lung function trajectories (Fig. 1) and associated comorbidities (Fig. 2). Of note, due to gene-environment interactions (Fig. 3), the slope of these two main mechanisms (green and red triangles in figure 5) may change (for better or worse) in different individuals (as indicated by the dashed arrows, green and red, in figure 5). Understanding much better the role and interactions of all these putative mechanisms may open new therapeutic alternatives to promote lung growth and stop lung function decline[29].

Second, it is conceivable that, if for whatever genetic and/or environmental factors reviewed above the lungs do not develop properly, other organ systems may do so too. After all, genes are the same in all cells and many environmental factors (e.g., smoking, pollution, diet, exercise,…) can affect many other organs than the lungs. In fact, several genetic variants associated with lung function are also associated with birth weight and height as well as with cardio-metabolic risk[30,31]. Collectively, these observations indicate that low peak lung function in early adulthood may be a warning sign of abnormal development and dysfunction in other systemic organs. If so, spirometry may actually become a reliable, reproducible, non-invasive and cheap method to identify high-risk individuals with disordered lung development (and, potentially, other organ systems too), who

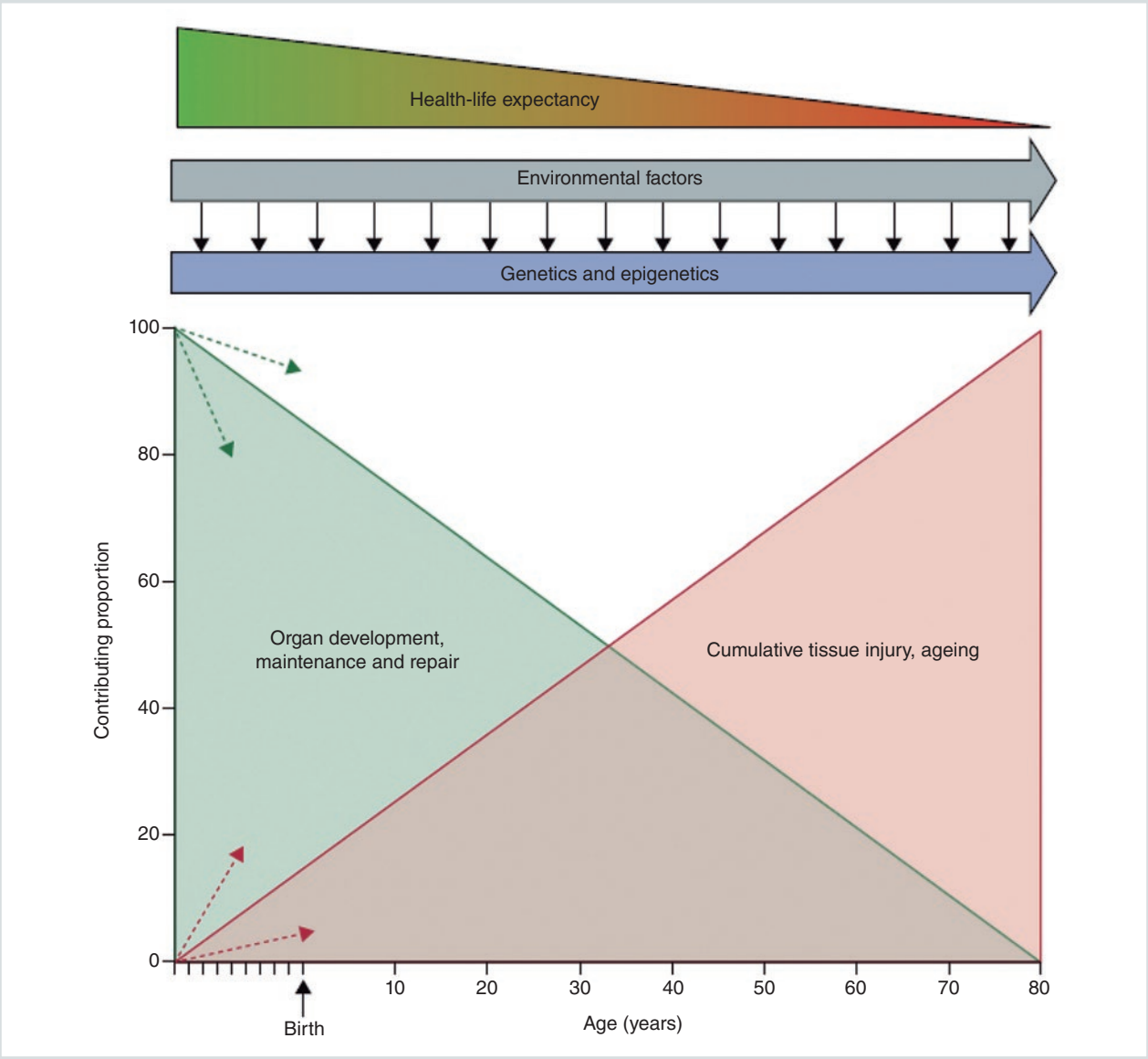

Figure 5. The interplay between two major biologic mechanisms (organ development, maintenance and repair [green triangle] and cumulative tissue injury and ageing [red triangle]) determines over a lifetime health and life expectancy (top triangle). Dashed arrows (green and red) indicate that the slope of these lines can vary (for better or worse) in different individuals. 'Contributing proportion' refers to the proportion of the processes, represented by the green and red triangles, contributing to health status and life expectancy *(reproduced from Agustí A, et al.[29] with permission).* For further explanations, see text.

can be monitored over time and treated earlier if necessary[29].

Third, to date, three studies have investigated the risk of mortality in different lung function trajectories. Our group was the first to show that all-cause mortality during follow-up in the Framingham Offspring Cohort was higher in individuals with low lung function in early adulthood (hazard ratio [HR] 2.3 [95% CI

1.4–3.7], p = 0.001)[5]. Smoking had an additive but independent effect on mortality, and we did not find statistically significant differences in cause-specific mortality between high and low lung function groups, but there was a numerically higher cardiovascular mortality in participants with low lung function[5]. We also explored this relationship in an independent cohort (Coronary Artery Risk Development in Young Adults Study [CARDIA]) and found that all-cause mortality before the age of 50 years in CARDIA participants with low lung function in early adulthood was three times higher than that of people with normal lung function (3% versus 0.7%, odd ratio [OR] 4.1 [95% CI 1.7–9.6], p = 0.001)[5]. Subsequently, Vasquez et al. reported similar findings in the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD), a population-based prospective cohort study of non-Hispanic white households initiated in Tucson, Arizona, in 1972[13]. These authors confirmed our previous observations[5] by showing that individuals who achieve low levels of FEV_1 and forced vital capacity (FVC) in early adulthood had increased risk for early cardiopulmonary mortality[13]. Associations appeared stronger for FEV_1 than FVC, possibly because the former is able to capture deficits related to both obstructive and restrictive patterns[13]. Finally, very recently, Marott et al.[32] have reported somewhat conflicting and difficult to interpret results in patients with COPD recruited from the general population. For this analysis, Marott et al. studied 1,170 young adults who were enrolled in the Copenhagen City Heart Study in 1976–1978 or in 1981–1983, when they were 21-40 years old. About twenty years late, in 2001–2003, when participants were 41-66 years old, 144 individuals (12.3%) had developed COPD: 79 of them (6.8%) through normal maximally attained FEV_1 trajectory, and 65 (5.6%) with reduced peak lung function (FEV_1 69 ± 7 % of reference) at recruitment (21-40 years of age)[32]. All participants were then followed until 2018 and mortality was compared between COPD patients who had developed COPD through low maximally attained FEV_1 trajectory (n = 65) versus those who developed the disease through normal maximally attained FEV_1 trajectory (n = 79)[32]. Results showed that all-cause mortality from 2001-2003 until 2018 (adjusted HR, 1.93 [95% CI, 1.14–3.26], p = 0.01), and in particular mortality caused by non-malignant respiratory disease (adjusted HR, 6.20 [95% CI, 2.09–18.37], p = 0.001), was higher in individuals who develop COPD through the normal maximally attained FEV_1 trajectory[32]. The authors hypothesized that these two COPD trajectories may reflect different lung pathologies and that the normal maximally attained FEV_1 trajectory represents individuals with emphysema as a predominant pathological disease process, whereas the low maximally attained FEV_1 trajectory mostly includes individuals with less emphysema[17,21,33]. As acknowledged by the authors, however, this study has some significant limitations, including: (1) a likely survival bias, since participants had to be alive in 2001-2003, when they were 41-66 years old, to enter the study (baseline data for this analysis), while the two studies previously published in the general population have both shown that individuals with low lung function in early adulthood (< 30 years of age) die prematurely[5,13]; (2) the rather small number of participants included in the two COPD trajectories (65 versus 79); (3) a potentially confounding effect of medications, which was not considered in the analysis; and, (4) the lack of imaging data or diffusing capacity for carbon monoxide (DL_{CO}) measurement, which may have helped to assess

the proposed influence of emphysema. In any case, these three studies[5,13,32] clearly indicate that there is a significant association between lung function trajectory and mortality risk.

Fourth, in relation to prevention and treatment, it is well established that quitting smoking reduces the rate of lung function decline[2,34] and that several other interventions can potentially prevent abnormal lung development, such as decreasing exposure to air pollutants (including maternal smoking) during pregnancy, childhood and puberty[4,20,35], close follow-up of survivors of very preterm birth[36], encouraging immunization and developing better vaccines against acute infant viral diseases[4,20], promoting physical activity[37-39] and healthy diet[40-42], including vitamin A[42] and vitamin C[43] supplementation. CC16 is being investigated as a potential therapeutic target in this setting[44,45].

A final comment relates to the observation that about 12% of the general population may follow a "supranormal" lung function trajectory[20] (Fig. 1). If exposed to noxious environmental conditions, these individuals may have lost lung function and still remain within the normal range[6]. Potentially, this can contribute to explaining the apparent paradox of identifying individuals with symptoms and/or evidence of lung damage (emphysema) with preserved spirometry[6].

CONCLUSIONS

Several genetic and environmental risk factors conspire to generate a range of lung function trajectories through life, and some of them are associated with significant implications for health and disease. A better understanding of the biological mechanisms underlying these trajectories may help prevent and/or treat them. However, we need to act earlier[46]. Promoting the use of spirometry in schools may be a good alternative for that[46]. In this context, spirometry can act as a *"canary in a coal mine"*[47]. After all, remember that a key spirometric variable is the "vital" capacity[48]. What a name!

DISCLOSURES

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