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**OPINION PAPER**

# Beyond the Horse-Racing effect: can lung disease begin before the race starts?

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## ABSTRACT

For decades, the conceptual model of the natural history of COPD has been dominated by the notion of the “horse-racing effect” and centered around the idea that an accelerated decline of lung function in adulthood is the main driver of COPD onset. However, a growing body of evidence indicates that individuals who have persistently low lung function from childhood into adulthood account for a substantial proportion of COPD cases and can develop the disease by attaining suboptimal peak lung function by young adulthood, without experiencing a faster decline thereafter. This group carries a remarkable respiratory burden but, perhaps most interestingly, is also at increased risk for cardiovascular and metabolic comorbidity and mortality. While the reasons for these associations remain unclear, it is proposed here that this comorbidity pattern is not confined to individuals predisposed to COPD (those with airflow limitations) but is instead largely driven by those with early spirometric restrictions (*i.e.*, small lungs). In this context, it is plausible to hypothesize that disrupted

nutrition, growth, and developmental processes, beginning as early as *in utero*, may affect not only subsequent lung function trajectories but also other organ systems and predispose to the development of multiple chronic conditions in adult life.

**KEY WORDS**

*Lung function; spirometric restriction; COPD; airflow limitation.*

## THE HORSE-RACING EFFECT AND THE LOW FLYER TRAJECTORY

Imagine entering a racetrack while a horse race is underway. Whichever horse is in the lead, you could safely conclude that it had been the fastest up to that point. It would also be reasonable to expect that, if the dynamics of the race remained unchanged, the same horse would continue to lead and perhaps even widen its advantage, provided that it maintained a faster pace than the other horses. For decades, this notion of the "horse-racing effect" (1, 2) – *i.e.*, the idea that there is a strong correlation between the levels of lung function at a single point in adult life and the rate by which the same lung function levels are declining – has been the cornerstone of the conceptual model of the natural history of chronic obstructive pulmonary disease (COPD), typified by smokers who develop the disease through an accelerated decline of lung function in adult life, *i.e.*, through a faster pace in the ill-fated race toward lung disease (**Figure 1**, red line).

Based on this model, we may be tempted to assume that all individuals reach the full extent of their lung function peak by their mid-20s and the rate at which their lung function declines thereafter is the main driver of COPD onset. To continue the horse-racing analogy, we would assume that all horses enter the race from the very same starting line and their fate in the race is determined solely by the pace of their gallop from then on. This may be true for horse races, but the same assumption does not hold for human lung function trajectories. Indeed, there is remarkable variability in the extent to which human beings enter young adulthood by attaining (or not) their expected peak lung function, and this variability has profound implications for their risk of developing lung disease decades later in life. Put differently: if the race to COPD truly begins once we have reached our peak lung function, we simply

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do not all start from the same starting line. Some individuals (let us call them Low Flyers) track at lower levels of lung function since early childhood: they enter the race in adult life with considerably lower lung function levels than others, keep “flying” low throughout adulthood and may cross the finish line to COPD without ever declining faster (**Figure 2**, red line).

In the real world, both models hold part of the truth and both red trajectories from **Figures 1** and **2** contribute to some extent to the development of COPD, with varying degrees in different patients. Over the past decades, though, the conceptual model of the natural history of COPD and, in turn, its epidemiological research have been largely built around the central role of an accelerated decline of lung function in adulthood, while the possible contributions of suboptimal lung function growth in childhood have received less attention. Yet, the idea that attaining a suboptimal peak lung function from childhood into young adult life may play a significant role in predisposing individuals to COPD later in life is far from new. In the 1970s, Burrows and colleagues observed that, in the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD), adults with COPD were more likely to report having had “respiratory trouble before age 16” than their peers with no COPD (3). By then, the Dutch hypothesis had already been articulated and was gaining momentum, by proposing direct links between respiratory disease in childhood and adult life and by supporting the notion that (paraphrasing William Wordsworth) (4) “the asthmatic child becomes the father of the COPD man” (5). However, it was not until this century that longitudinal studies have provided conclusive evidence that some of the roots of COPD do originate in early life and in suboptimal lung function growth in childhood. Among these studies, seminal work (6) combining data from multiple prospectives, population-based epidemiological cohorts suggested that up to 50% of COPD cases in the general population develop the disease through a lung function course that more closely resembles the trajectory of the Low Flyers than the trajectory linked to the traditional horse-racing effect. In other words, in about half of COPD cases the predominant pathway to disease is impaired lung function growth in childhood rather than accelerated decline in adult life.

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In this context, it should be acknowledged that, while the conceptualization of major trajectories leading to COPD serves the critical purpose of understanding the natural history of the disease, in reality every individual and every case of COPD follows a lung function trajectory across the lifespan that is essentially unique and likely different from that of anyone else. Yet, the existence of a group of individuals whose lung function trajectories, even in their uniqueness, are characterized by the common trait of being persistently low across large part of the lifespan has been confirmed unequivocally by multiple recent studies that used unbiased, data-driven approaches in the general population (7). In fact, amid the substantial variability in the number and shape of the lung function trajectories identified across these studies, the most consistent finding was the existence of a group of individuals with levels of lung function that remained low from childhood to adulthood.

**DETERMINANTS AND CONSEQUENCES OF PERSISTENTLY LOW LUNG FUNCTION**

As scientific attention to this group has grown, so has the number of studies that have attempted to identify the factors that increase the risk of following this trajectory of persistently low lung function. This list is rapidly expanding and includes, among others, genetic predisposition, multiple social determinants of health, pregnancy-related factors, pre- and perinatal factors such as preterm birth, early respiratory insults such as lower respiratory tract infections and pneumonia, early environmental exposures such as air pollution and environmental tobacco smoke, poor nutrition, and, perhaps most importantly, persistent childhood asthma. Whatever the determinants of this persistently low lung function trajectory, it is now well established that individuals who belong to this group have a remarkably high respiratory morbidity burden. Compared with their peers, they have higher rates of asthma, respiratory symptoms, dyspnea, and they are substantially more likely to develop early-onset COPD (8).

Further, the consequences of persistently low lung function may also include an increased risk for premature mortality. In the adult TESAOD cohort, we found that participants who attained low levels of forced expiratory volume in one second ($FEV_1$) by young adult life had a significantly increased risk



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of dying prematurely compared with their peers who attained higher peak $FEV_1$ levels (9). A surprising observation of that study was that this excess mortality was only marginally attributable to COPD deaths and was instead predominantly due to an increased risk of death from heart disease, a finding in line with reports from other epidemiological cohorts showing that low peak lung function in early adulthood is associated with a broad range of cardiovascular and metabolic comorbidities (10).

Therefore, it appears that the Low Flyer trajectory carries a morbidity and mortality burden that extends beyond the respiratory system to include multiple comorbidities. One possible explanation for these observations can be found in the well-known coexistence of cardiovascular disease among many COPD patients. However, a different hypothesis is proposed here: that the increased cardiovascular risk among Low Flyers is not confined to individuals predisposed to COPD (*i.e.*, those with airflow limitation), but is instead largely driven by those with low lung volumes (*i.e.*, with spirometric restriction).

**SPIROMETRIC RESTRICTION AND THE "SMALL LUNGS" HYPOTHESIS**

In this context, it is noteworthy that, in most studies, the Low Flyer trajectory has been modelled using $FEV_1$ alone, without simultaneous consideration of forced vital capacity (FVC). This distinction is critical because a low $FEV_1$ in young adulthood characterizes at least two fundamentally different groups: individuals with airflow limitation (*i.e.*, low $FEV_1$ with relatively preserved FVC) and individuals with spirometric restrictions (*i.e.*, both low $FEV_1$ and FVC), which may indicate smaller lungs. Large-scale, multicohort studies (11) have demonstrated that, in adulthood, the latter group has a substantially higher risk for coronary heart disease-related hospitalizations and mortality, not only compared with individuals with normal lung function but also compared with individuals with airflow limitation. Of note, this excess risk is particularly pronounced when spirometric restriction is already present at younger ages (11).

The public health implications of the comorbidity pattern observed in individuals with spirometric restriction are not trivial, as this group may account for a significant proportion of Low Flyers in young



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adulthood. In both the Lifelines and BAMSE cohorts, the majority of young adults with $FEV_1$ levels below the lower limit of normal did not have a reduced $FEV_1$/FVC ratio compatible with airflow limitation, suggesting that reduced lung volumes, rather than airflow limitation, may represent the predominant pulmonary issue in a substantial proportion of Low Flyers (12). To investigate the early-life origins of this group of adults with low $FEV_1$ and FVC, but preserved $FEV_1$/FVC ratio, we conducted a multicohort study (13) and observed that the majority of these young individuals with spirometric restriction also had low total lung capacity ascertained by plethysmography, an observation compatible with having indeed “small lungs”. Most importantly, we identified being born small for gestational age and having a mother who experienced nutritional problems during pregnancy (particularly anemia and excessive vomiting) as two of the strongest risk factors for having small lungs by young adulthood. These associations were not confounded by obesity. In the TESAOD cohort, we had previously shown that participants with spirometric restriction were at increased risk for mortality by heart disease, stroke, and diabetes, independent of body mass index (14).

**DEVELOPMENTAL ORIGINS OF THE LOW FLYER TRAJECTORY**

Putting all this evidence together, it is plausible to hypothesize that disrupted nutrition, growth, and developmental processes, beginning as early as *in utero*, may affect not only subsequent lung function trajectories (whether related to airflow limitation or small lungs), but multiple organ systems, ultimately setting the stage for the adult multimorbidity patterns shown by individuals with persistently low lung function. Consistent with this scenario, it is well established that individuals who experience fetal growth restriction are at increased risk for a wide range of chronic conditions later in life (15), including, but not limited to, lung disorders.

In this context, the profound connection between *in utero* developmental processes and childhood lung function raises the possibility that the pathogenetic bases of the Low Flyer trajectory (and its comorbidities) may already be established at birth. Indeed, in the Tucson Children’s Respiratory Study, pulmonary function assessed as early as 2 months after birth was strongly associated with

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lung function trajectories between the ages of 11 and 32 years, with the Low Flyers having remarkably lower levels of maximal expiratory flow at FRC shortly after birth as compared with their peers (16).

## NOT WRITTEN IN STONE: PLASTICITY AND OPPORTUNITIES FOR PREVENTION

It's our fate to develop lung disease, then, already written in stone by the time we are born? No, it is not. Multiple lines of evidence show that lung function at birth may shape, but does not determine conclusively, the risk for adult lung disease. First, despite being very strongly correlated with each other, pulmonary function at birth explained less than 15% of the variability in adult lung function in the population-based TCRS birth cohort (17), underscoring the importance of developmental processes, exposures, and events occurring after birth; both during childhood for lung growth and during adulthood for decline. Second, in the COPSAC study, while children with asthma already showed significant airflow deficits as neonates, those deficits progressed with age and neonatal lung function accounted for only a minority of the accumulated airflow deficit associated with asthma by early school-age (18). Third, trajectory-modelling studies have demonstrated that, although the majority of children belonging to the Low Flyer trajectory remain on that trajectory as they transition into adult life, some experience improvements in lung function and move to more favorable trajectories by adulthood (19, 20).

Thus, there is reason for hope that early interventions targeting not necessarily only pregnancy, but also infancy and childhood may modify the course and fate of children destined to the Low Flyer trajectory and prevent them from developing chronic lung disease decades down the road. Integrated risk prediction models combining early pulmonary, cardiovascular, and metabolic parameters and molecular markers could also be developed for early identification of individuals on the Low Flyer trajectory, with the ultimate aim of preventing multimorbidity later in adulthood.

## CONCLUSIONS

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The paradigm shifts discussed above are reshaping the conceptual model of COPD and chronic lung conditions in adult life bringing renewed focus on the early roots of these diseases, but this should not lead us to overlook the importance of pathogenetic processes that also operate in adult life. Decades of epidemiological research, together with countless encounters with patients with COPD in adult pulmonology clinics, have taught us that noxious exposures in adulthood (*e.g.*, cigarette smoking, air pollution, occupational exposures) can lead to COPD and lung function deficits even among individuals who attained a perfectly normal peak lung function by early adulthood.

Hence, to be fully comprehensive and effective, prevention and treatment strategies of adult lung disease must target all stages across the lifespan. While promoting healthy lung function aging in adult life remains vital, every effort should also be made to help children attain the highest possible peak lung function, i.e., the optimal starting point before they enter the adult race to decline. This may translate into longer and healthier lives, not just for their lungs.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflicts of interest

SG is a cofounder of a start-up, Aspiro Therapeutics, with the goal of developing novel CC16-based therapeutics. SG is also the principal investigator of a research grant funded by Grifols.


### Financial support

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### Author contributions

SG contributed entirely to the work.

### Ethical approval

*Human studies and subjects*

N/A.

### Publication ethics

*Plagiarism*

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The author declares no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

*Data falsification and fabrication*

All data reported are accurate and authentic.

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**Figure 1: A simplified COPD model centered around the Horse-Racing effect.** Individuals enter young adult life at optimal peak lung function and those who experience the steepest decline thereafter (red line) are at increased risk of COPD. Lung function levels in mid-adult life are strongly correlated with rate of decline (horse-racing effect). In this model, an accelerated rate of lung function decline is the main driver of COPD onset.

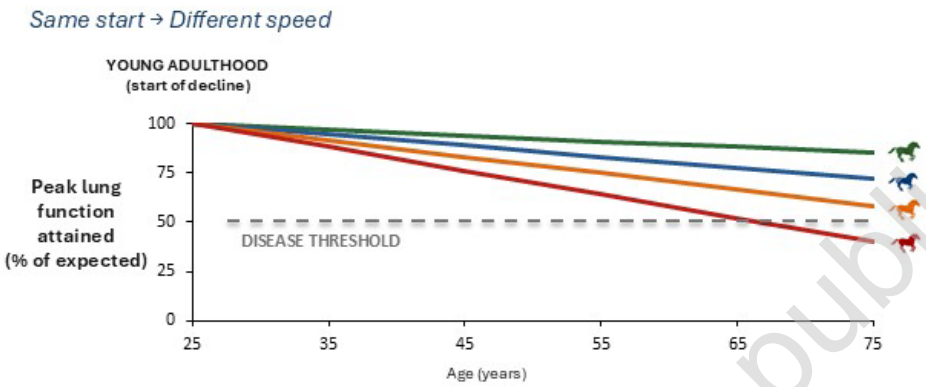
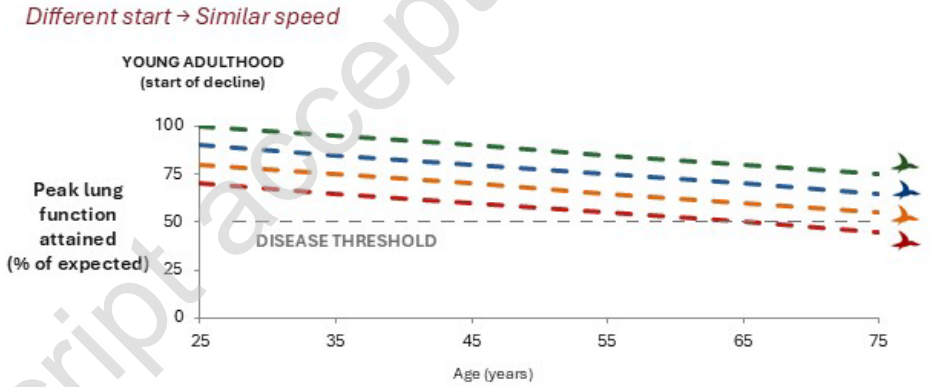



**Figure 2: A simplified COPD model centered around the Low Flyer concept.** Individuals enter adult life at different levels of peak lung function because of differences in lung development *in utero* and childhood. Once decline starts, individuals who entered adult life with the lowest levels of lung function (Low Flyers, red line) are at increased risk of COPD later in life, even without experiencing an accelerated decline. In this model, attainment of suboptimal peak lung function by young adult life is the main driver of COPD onset.




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