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Spirometry: A practical lifespan predictor of global health and chronic respiratory and non-respiratory diseases

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ABSTRACT

Objectives. 1. To review and discuss available evidence supporting that spirometry is an overlooked global health marker, that could be used regularly through the lifespan to monitor human health and predict risk of chronic respiratory and other chronic non-communicable diseases (NCDs). **2.** To discuss the challenges and opportunities that this proposal faces.**Summary of key data.** First, spirometry is essential to assess and monitor respiratory health. Second, spirometry adds prognostic value to other well-accepted health markers used in clinical practice, such as blood pressure, body mass index, glucose and blood lipids, by identifying individuals at risk, not only of respiratory diseases, but also of other NCDs, particularly cardiovascular and metabolic disorders. **Conclusion.** Although we acknowledge that research gaps still exist, we propose that spirometry assessed during childhood, adolescence and early and late adulthood can be a reproducible, non-invasive, safe and affordable global health marker to identify individuals in the general population at risk of respiratory and non-respiratory NCDs. In this context, spirometry may act as the caged canaries that miners used to carry into mines to alert them of dangerous accumulations of gases, thus providing an early warning and save lives.

1. The proposal

We propose that spirometry, a practical and validated marker of respiratory function, is also an overlooked marker of global human health throughout a person's life span, from infancy to old age, because it not only relates to respiratory diseases, but it also identifies individuals at risk of suffering other prevalent chronic non-communicable diseases (NCDs), particularly cardiovascular and metabolic disorders. Accordingly, we propose that spirometry be performed in infancy, adolescence, early and late adulthood. Importantly, we are not advocating the use of spirometry as a screening tool of chronic respiratory diseases like chronic obstructive pulmonary disease (COPD), which we recognize is controversial [1]. What we propose is that repeated spirometric measurements over the lifetime may promptly identify individuals at risk of suffering several NCDs, both of respiratory and non-respiratory origin, and unhealthy ageing. The narrative review below presents the evidence that supports this proposal and discusses the challenges that it may face as well as the opportunities that it may open.

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2. Spirometry: A brief historical perspective

John Hutchinson invented the spirometer in 1846 "*with a view of establishing a precise and easy method of detecting disease*" [2]. Although he probably meant "*respiratory*" disease, in the context of the discussion that follows, it is interesting to realize that he referred only to "*disease*". The original Hutchinson's instrument only measured what he named *vital capacity* (VC). It took another 100 years for Tiffeneau and Pinelli to add the concept of "timed" VC as a measure of airflow limitation in what became widely known as the "*Tiffeneau index*", which originally referred to the ratio between the volume of gas expired in the 1st second of a forced expiratory maneuver (FEV_1) to VC [3], not to forced vital capacity (FVC), as most often used nowadays.

The term "*vital capacity*" originally coined by Hutchinson was indeed foresighted [4] since there is abundant literature describing a significant relationship between lung function and all-cause mortality [5-13]. Further, spirometry not only has prognostic value by itself, but it also *adds* prognostic value to other health markers frequently used in practice, such as arterial blood pressure, body mass index and/or glucose or lipid blood levels [13]. Yet, spirometry is not considered a global health marker and, therefore, it is not routinely measured, at variance with these other well-established health markers. Of note, spirometry is a reproducible, non-invasive and affordable test [14] that can be determined in adults and children, including preschool children [15].

3. Lung function trajectories: A paradigm change

In healthy babies born at term, lungs are not completely developed. They continue to grow and mature until they reach a peak of lung function in early adulthood (around 20-25 years of age, earlier in females) [16] which is followed by a relatively brief *plateau* phase of a few years and a mild decline afterwards due to physiological lung ageing (Fig. 1, Normal trajectory). Over the past few years, several studies have shown that normal lung function trajectory can be altered due to a set of dynamic and cumulative gene ("G) -environment ("E) interactions through time ("T"; GxExT) (Fig. 2) [17, 18]. Indeed, spirometrically determined lower than normal lung function trajectories are associated with significant cardiovascular and metabolic health consequences, as well as with premature death (Fig. 3) [19]. By contrast, supranormal trajectories (Fig. 1) are associated with healthier ageing [20]. This new longitudinal understanding of respiratory health and disease opens novel opportunities for prevention and early diagnosis-interventions [21] but, at the same time, it faces several important challenges and hurdles that need to be overcome.

4. From early COPD to early multimorbidity

COPD is a major global health problem due to its high prevalence (about 10% of the adult population), rising incidence (likely in relation to increased longevity of the population) and associated costs (circa Euro 38 billion annually in the EU alone) [22]. COPD has traditionally been understood to be a self-inflicted disease caused by tobacco smoking that affects older adults (particularly males) [23]. This assumption has been challenged by recent research that demonstrated that many other risk factors beyond smoking can also lead to fixed airflow limitation (i.e. "COPD") in adulthood, including prematurity, asthma, allergies, nutrition, pollution, infections, and others (Fig. 2), showing that fixed airflow limitation in adults has roots much earlier in life [24-28]. As a result, the concept of "*early*" COPD has recently emerged [29-31].

COPD often coexists with other concomitant chronic medical conditions (multi-morbidity), including cardiovascular disease, osteoporosis, depression, and diabetes, among others [32], that worsen their health status and prognosis [33, 34]. The presence of multimorbidity in these patients has been traditionally explained by accelerated ageing [35, 36]. The same risk factors identified for COPD (smoking, environmental/ occupational indoor pollution, inactivity, prematurity, allergy, early events in life) have also been identified as risk factors for other chronic diseases, particularly cardiovascular diseases (hypertension, ischemic heart disease, chronic heart failure, cerebrovascular diseases), metabolic diseases (diabetes, obesity), bone diseases (osteoporosis), neurological diseases (cognitive dysfunction, Alzheimer's, Parkinson's), and other chronic respiratory diseases (asthma, pulmonary fibrosis, bronchiectasis).

Recent research has also shown that young adults with impaired lung function associate a higher prevalence, and about a decade earlier incidence, of cardiovascular and endocrine (diabetes) abnormalities, as well as premature death (Fig. 3), suggesting that poor lung development may be a marker of poor development of other organ systems [19]. Thus, rather than referring to a single clinical disease with associated comorbidities, we propose that it would be more appropriate to consider the complex multimorbid condition of these patients, and search for all of them simultaneously earlier in life, considering interventions targeted not to individual diseases but to a multimorbid chronic condition [37, 38]. This may have also practical consequences as 1) the early origins of

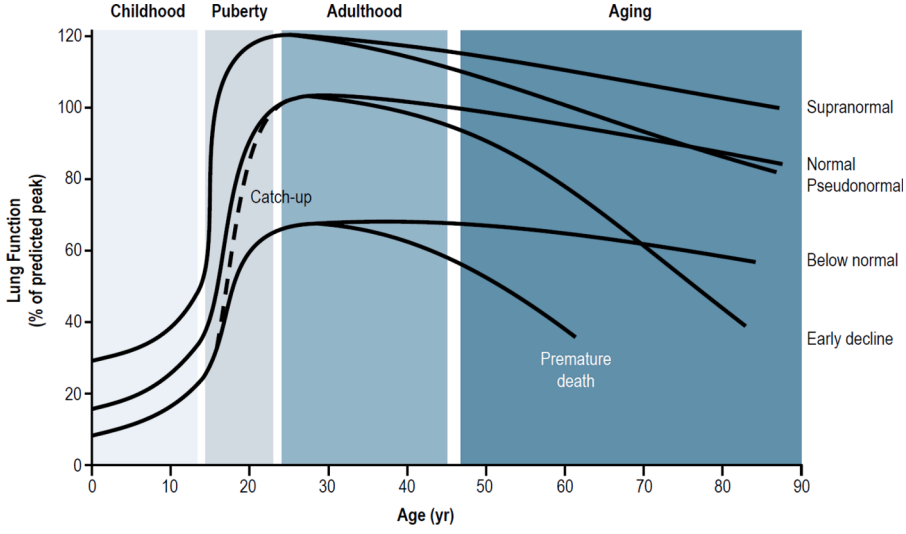

Fig. 1. Potential spirometry trajectories through life according to, on the one hand, differences in lung development during infancy, adolescence and early adulthood and, on the other, rate of lung function decline during adulthood and elderly. From Agusti et al. N Engl J Med 2019;381:1248–56 [18]. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

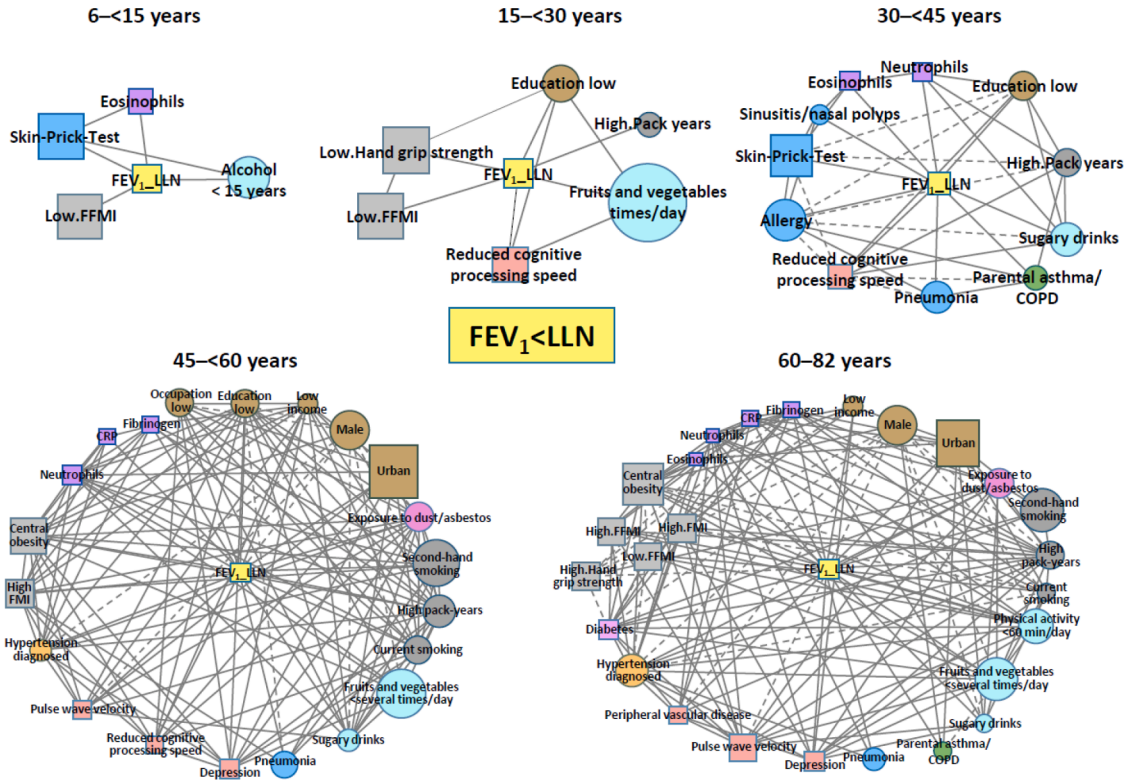

Fig. 2. Cross-sectional, first-neighbor networks of different environmental risk factors significantly related to forced expiratory volume in 1 sec (FEV_1)<lower limit of normal (LLN) at different age bins in the LEAD cohort in Vienna, Austria. Note the variety of factors, their inter-relationship and that the complexity of the network increases with age. Reprinted from Breyer-Kohansal et al. Am J Respir Crit Care Med 2020;202 292–6 [17]. Copyright © 2020, with permission from the American Thoracic Society.

chronic diseases are often overlooked, and 2) the importance predictive role of impaired lung function is overlooked, thus missing an important opportunity of early diagnosis. These and other questions [21] are now being actively investigated in a multicenter clinical research collaboration (CADSET) supported by the European Respiratory Society [39].

5. Opportunities

NCDs, including chronic cardiovascular, respiratory, metabolic and neurologic diseases, are a major global health problem [40], most often believed to be associated with ageing. However, it is well established (albeit often overlooked) that NCDs can have a much earlier origin in life [19, 41-43], and that they often share genetic [44-46], epigenetic [47-49], and environmental risk factors that may change, interact and accumulate over a lifetime (GxExT). For instance, during pregnancy maternal smoking, intrauterine growth restriction, prematurity and bronchopulmonary dysplasia [28, 50] limit lung growth, so a proportion of affected babies will follow a low lung function trajectory (Fig. 1) with a higher risk of developing a COPD-like phenotype later in life [48, 51, 52]. Importantly, prematurity also interrupts the normal development of other organ systems [50, 53], so it can also lead to somatic growth failure and cardiovascular [54] and metabolic diseases [55] in adulthood. Likewise, during infancy, environmental risk factors of poor lung development include indoor and outdoor air pollution, poor nutrition, early respiratory infections (e.g., RSV), allergies and/or a diagnosis of "asthma", and childhood obesity [17, 28, 56-61] (Fig. 2). In adulthood, shared environmental risk factors for several NCDs include smoking, unhealthy diet, harmful use of alcohol, physical inactivity, occupational exposures and air pollution, which rarely exist in isolation [62]. Finally, in the elderly, disruption of several hallmarks of healthy ageing [63, 64] and low-level, persistent systemic inflammation (*inflammaging*) [65-67] may represent the *trait-d'union* for the concomitant development of several NCDs. Yet, despite this extensive evidence of *shared* NCD risk factors through the lifetime, NCDs research has traditionally focused on the prevention and early diagnosis of *individual* NCDs. We propose here that NCDs should no longer be viewed as individual nosological entities, but rather as the result of pathobiologically linked processes that can occur simultaneously and have their roots early in life [68]. Hence, prevention, detection and intervention, as well as clinical and basic research, should have a broader approach aimed at identifying all potential NCDs in a given individual at once and as early as possible, and make interventions targeted not to individual diseases but to a multimorbid system [38, 69]. For instance, Jensen *et al* showed that the analysis of temporal disease trajectories in an electronic health registry that covered the entire population of Denmark (6.2 million individuals) for a period of 14.9 years can be useful to predict and prevent future diseases (including COPD and other NCDs) [70] (Fig. 4). Since over two thirds of antecedents and risks to NCDs emerge during childhood and adolescence [62], children and youngsters represent a new window of opportunity for promoting healthy ageing and to prevent and treat NCDs more efficiently [38]. Further, because the incidence of NCDs increases with age, early identification of high-risk individuals is key to prevent, diagnose and treat them [40, 71]. In this context, the assessment of respiratory health by spirometry can open new opportunities for prevention and early treatment. For instance, vitamin C or D supplementation during pregnancy increase lung function after birth [72, 73]. Likewise, spirometry may identify young individuals at risk of suffering NCDs (Fig. 3) [19] in whom current therapeutic interventions may achieve better outcomes [21, 38].

On the other hand, rates of preterm birth (gestational age <37 weeks) have increased globally in the last decades, now accounting for 11% of live births [74]; fortunately, more than 95% of those born preterm currently survive to adulthood [75]. However, because prematurity is often associated with a significant number of multiple chronic

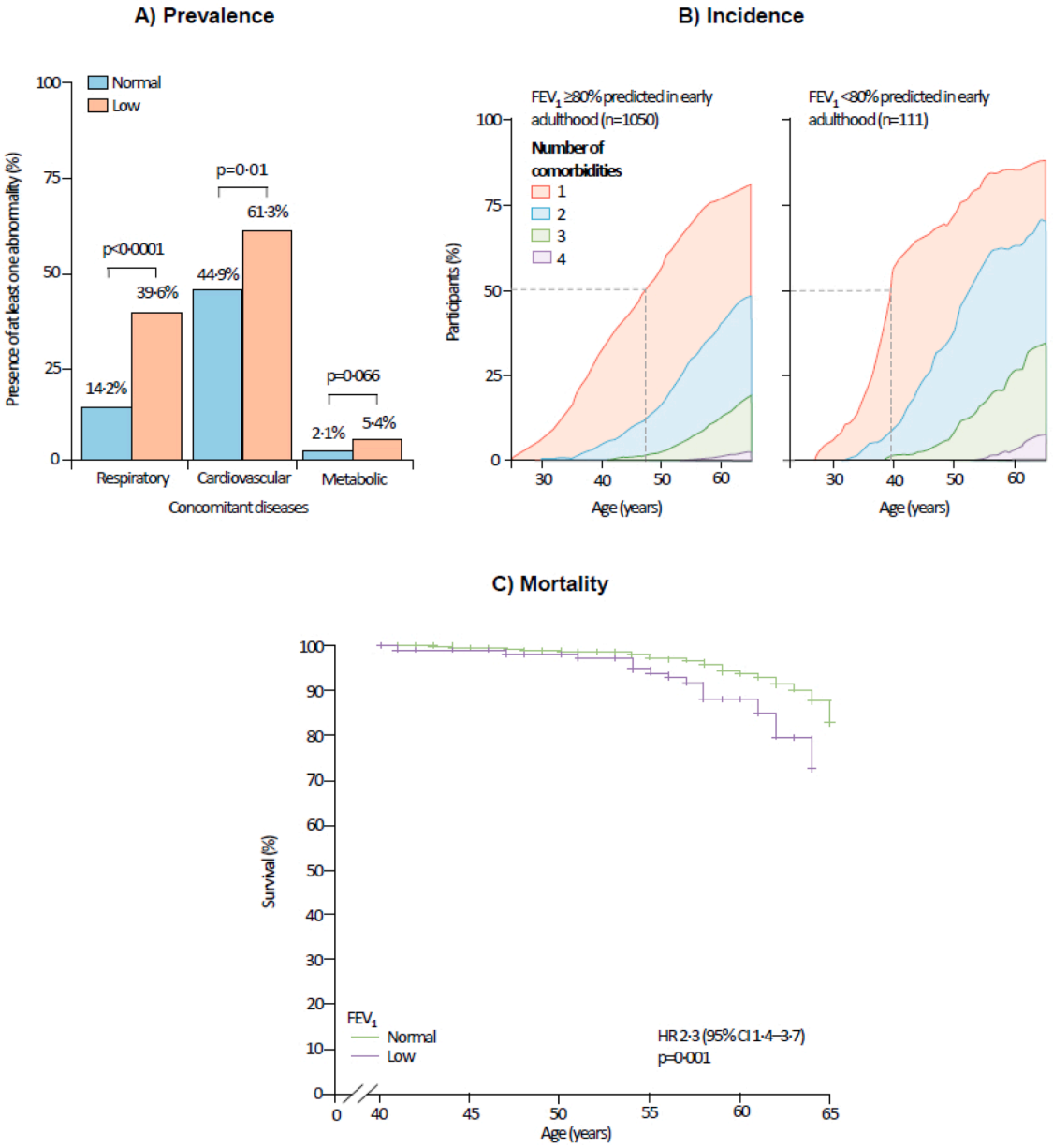

Fig. 3. Participants in the Framingham Offspring Cohort with forced expiratory volume in 1 sec (FEV_1)<80% reference had a higher prevalence at 25 years of age of respiratory, cardiovascular and metabolic abnormalities than those with normal spirometry. They also showed a decade earlier incidence of cardiovascular and metabolic conditions and premature death. A) Prevalence: Proportion of participants with at least one respiratory, cardiovascular, or metabolic abnormality by lung function level in early adulthood; B) Incidence: Cumulative incidence of respiratory, cardiovascular, and metabolic abnormalities during follow-up; C) Mortality: Kaplan-Meier survival curves and Cox model HRs by lung function in early adulthood. Reprinted from Agustí et al. Lancet Respir Med 2017;5:935–45 [19]. Copyright © 2017, with permission from Elsevier.

diseases in adulthood [50, 52], a marked increase in the health-care demand of adult survivors of preterm birth is expected, similarly to what has already happened with children with cystic fibrosis whose life expectancy has increased extraordinarily in the last decades mainly by treating comprehensively the patient rather than focusing only on the pulmonary component [76-77]. In fact, it has been suggested that persons born prematurely require early evaluation, long-term follow-up and preventive actions to reduce the risk of multiple NCDs later in life [78]. In this setting, spirometry offers a simple, non-invasive, reproducible method to identify young individuals at risk of suffering NCDs later. Of note, this paradigm may apply even to acute diseases, as very recently illustrated by the observation that being born with low birth weight is an independent risk factor (adjusted OR 3.61 [1.55–8.43], p= 0.003) of severe COVID-19 requiring ICU admission in middle aged adults (46–53 years) [79].

In summary, we propose that spirometry could be a useful tool to ascertain human health (not only respiratory) if measured along the lifetime, during childhood and/or adolescence and adults, particularly if exposed to high-risk occupational settings [19, 61]. Needless to say, that we fully endorse avoiding smoking initiation and reinforcing early quitting as well as the benefits of healthy lifestyles starting early in life [80]. In this context children are central for health promotion [81] because they have a unique brain plasticity [82] that offers a window of opportunity to instil life-long lasting healthy habits and preventing the development of NCDs [83]. School is crucial in this mission since improved health literacy has been associated with reductions in risk behaviours for chronic diseases and decreased rates of hospitalisation [84].

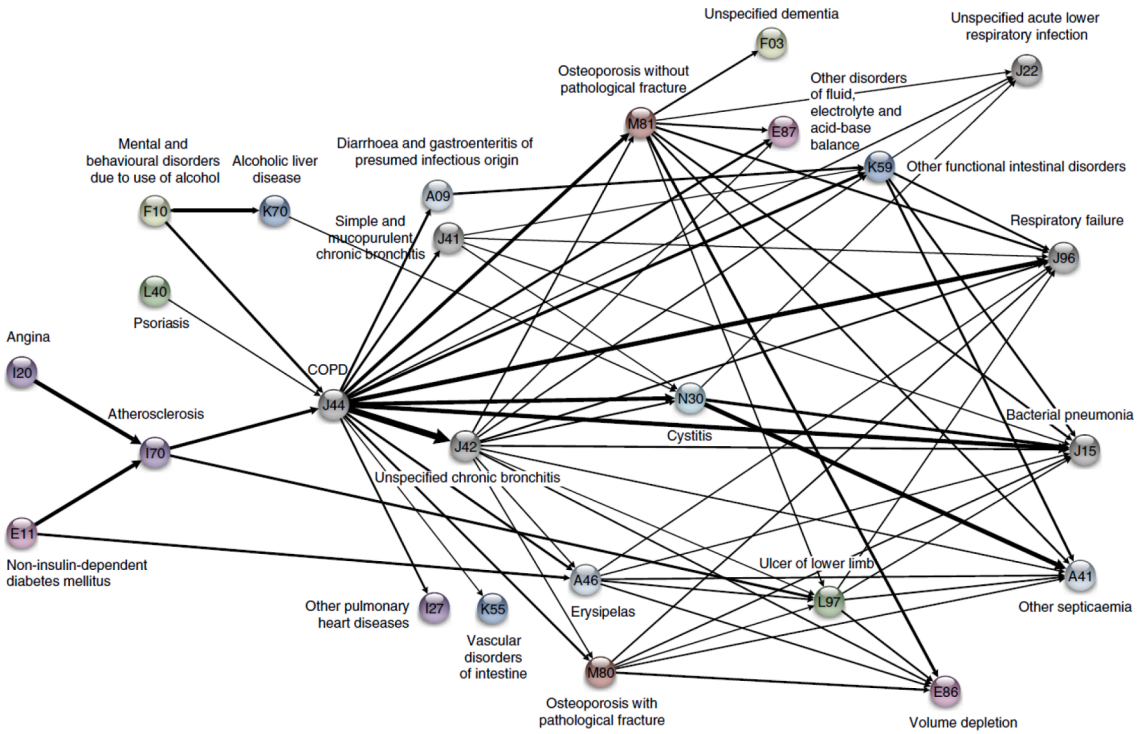

Fig. 4. COPD disease trajectory cluster showing five preceding diagnoses leading to COPD and some of the possible outcomes. Reproduced from Jensen et al. Nat Commun 2014; 5: 4022 [70].

6. Challenges

Our proposal that lung function, easily measured with spirometry, is an often-overlooked global health marker and that spirometry should be regularly monitored through the life span faces several challenges. First, it requires empirical validation. Currently available data pertain to population analyses but the specificity, sensitivity, and positive and negative predictive values of abnormal spirometric values (and severity thresholds) need to be explored and validated at the individual level at different ages. The use of modern mobile digital technologies can facilitate this [85-87].

Second, understanding the biologic basis of the different and cumulative GxExT interactions through life is a formidable scientific challenge that is required to design proper preventive and interventional strategies. For instance, a proportion of children born with reduced lung function do regain a normal trajectory (Fig. 1) [26]. Why this "catch-up" does not occur in all children is unclear at present, but the understanding of its biologic basis may facilitate interventions to help those children who don't catch up to do so or, eventually, adults to regain better lung function [26].

Finally, our proposal requires significant communication and education efforts to raise awareness in the general population and among practicing physicians about the potential early life origin of NCDs [21]. In fact, few adult clinicians seek birth and perinatal histories routinely. Further, in general adult clinicians work in a separate silo to gynaecologists, neonatologists and paediatricians [88]. As a result, a substantial knowledge gap regarding health and disease in the transition from childhood to adulthood exists [89-91]. This "black box" needs to be filled with appropriate epidemiological, clinical, translational and basic research.

7. Conclusions

Although significant research gaps still exist, we propose that spirometry can be an efficient, safe and inexpensive global health marker with the potential of identifying, at any age, a group of individuals in the general population at risk of respiratory and non-respiratory NCDs in whom to intervene promptly. A brief historical analogy is worth mentioning. Miners used to carry caged canaries down into the mine to alert of dangerous accumulation of gases, thus providing an early warning to exit the mine and save their lives [92]. We propose here that lung function assessment by spirometry is an overlooked global health marker that can also act as "a canary in the mine".

Conflicts of Interest

AA reports personal fees from Chiesi Farmaceutici during the conduct of this work. Outside the submitted work he reports grants and personal fees from GlaxoSmithKline, Menarini, Chiesi Farmaceutici and AstraZeneca, and personal fees from Zambon.

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