09 December 2024

Lancet Review

LUNG FUNCTION TRAJECTORIES:

RELEVANCE AND IMPLEMENTATION IN CLINICAL PRACTICE

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Key words: Asthma; Chronic Bronchitis; COPD; Lung health; Spirometry; Smoking

Supported by: CADSET (Chronic Airway DiSeases Early sTratification), a European Respiratory Society (ERS) Clinical Research Collaboration (CRC). No industry support was provided for this review.

Word count: 4,171 words (excluding references, boxes, tables, and figure legend).
References: 86. Tables; 1; Figures: 3; Boxes: 1

ABSTRACT

Lung development starts *in utero* and continues during childhood and adolescence reaching its peak in early adulthood, followed by gradual decline due to physiological lung ageing. Lung function development can be altered by several host and environmental factors during the life-course. As a result, a range of lung function trajectories exist in the population. Sub-normal trajectories are associated with respiratory, cardiovascular, metabolic, and mental health comorbidities as well as with premature death.

This review presents the state of the art on lung function trajectories and sets the stage for the implementation of this knowledge in clinical practice as an innovative approach to detect ill health early and monitor its progression of individuals, as well as to promote lung health generally. Specifically, we propose that, similar to paediatric height and weight charts used globally to monitor children's growth, lung function charts could be used both for children and adults to monitor lung health status across the life-course. To this end, we introduce our freely available online "Lung Function Tracker" tool. Finally, we discuss the challenges and opportunities for effective implementation of the trajectory concept at the population level and outline an agenda of the critical research needed to support such implementation.

Abstract word count: 200 words

INTRODUCTION

While normal lung development starts in the first trimester of pregnancy, the lungs and airways are not fully developed in newborns. They continue to grow and mature during the first 20-25 years of life and, as a result, lung function assessed by spirometry peaks in early adulthood (Figure 1), from where it declines due to physiological lung ageing.[1,2] This lung function trajectory potentially can be affected at any age, positively or negatively, by host factors including diseases and external exposures. Indeed, research over the last few years has demonstrated that, at the population level, a range of different lung function trajectories can be observed with differences in the growth and/or the decline phase.[3] Importantly, sub-normal trajectories are associated with poorer long-term health-outcomes, not only respiratory (e.g. chronic obstructive pulmonary disease, COPD, the third leading cause of death globally[4]) but also cardio-vascular, metabolic and mental health, as well as premature death[5], whereas above normal trajectories are associated with healthier ageing.[6] These different trajectories are the result of multiple, dynamic and often cumulative gene (G) – environment (E) interactions throughout the life-course (T). The term GETomics has been recently proposed to highlight the importance of considering these interactions across the life-course, which ultimately determine health and disease[3] (Box 1).

There are still many unanswered questions related to the trajectory concept, including how to prevent or reverse sub-normal trajectories, how to promote normal (or above-normal) trajectories and, importantly, how to translate this recently emerged scientific knowledge about lung function trajectories into clinical practice. Spirometry is not only essential for the diagnosis of most respiratory diseases, but also estimates lung function as a global health marker that can be used to identify apparently healthy children and adults at risk of unhealthy ageing.[7] Yet, contrary to many other potential disease markers (e.g., blood pressure, cholesterol, and blood sugar levels), spirometry is rarely used in the health-care community at large, outside specialized clinics, even in patients with respiratory symptoms. In fact, despite calls to "*elevate lung health up the list of organ-related priorities*", chronic respiratory disease remains the "*poor cousin*" in terms of recognition, reporting and research funding.[8]

We propose here that there is sufficient scientific evidence on lung function trajectories to develop a roadmap for its implementation at both clinical and population levels (Table 1). Importantly, spirometry is affordable globally including in low resource settings[9], well-standardized and non-invasive. Like the paediatric anthropometry charts ("centile charts") for height and weight that have been used by paediatricians world-wide to monitor somatic growth development of children (and if growth is deviating, to initiate appropriate clinical investigations) for the last fifty years, we believe that *lung function charts* capturing longitudinal spirometry measures of both growth and decline also could be used in clinical practice globally. As a first attempt to do so, we introduce here our freely available online "Lung Function Tracker" tool (https://gli-calculator.ersnet.org/lung_tracker/). To support this proposal, below we discuss: *(1)* the scientific state-of-the-art of the lung function trajectory concept and its potential to foster interventions aimed at improving lung health through the life time, thus healthier development and ageing; *(2)* the implications of this proposal for clinical practice; *(3)* the need to develop and evaluate interventions that incorporate the trajectory perspective at the population level to improve lung health, including lung function check-up programs; and, finally, *(4)* implementation strategies that overcome the practical challenges of adopting this approach into diverse healthcare systems globally. This proposal fully aligns with the Strategic Development Goals to reduce the proportion of young adults who will die from non-communicable diseases (NCDs) before their 70th birthday[10] by addressing the risk factors for cardiovascular disease, cancer, diabetes, and chronic respiratory disease.[11]

THE SCIENCE BEHIND THE TRAJECTORY CONCEPT

The landmark study by Lange, Celli, Agusti *et al* in 2015[12] showed the extent to which COPD can develop following rapid decline of lung function in adults, the dominant paradigm across the last fifty years[13], and also when lung function does not reach its maximum peak in early adulthood, even if subsequent decline is normal. This finding, together with observed associations between childhood disadvantage and COPD [14], has highlighted the importance of understanding trajectories in health and disease.

Lung function trajectories in population-based and clinical studies

Several methods have been used in the published literature to investigate trajectories in a population with repeated measures of lung function over time, including *a priori* investigator-defined assignment of the individuals to longitudinal changes of mutually exclusive lung phenotypes[5,15], statistical modelling of lung growth and/or lung decline (e.g., mixed models with random effects)[16], and data-driven modelling approaches (e.g., group-based modelling, latent profile analysis or latent class analysis).[17,18] Although each individual follows their own trajectory, data driven approaches identify groups of individuals following similar patterns of longitudinal development of lung function in a given population.[3] Most studies in the *general population* have identified between two and six lung function trajectories.[19] The trajectories identified (in both males and females) most often include "normal", "persistently low", "persistently high", and "accelerated decline". Importantly, to date most studies focused on the forced expiratory volume in one second (FEV_1) value, although both the forced vital capacity (FVC) and FEV_1/FVC ratio values would need to be considered to untangle the prevalence, risk factors and clinical impact of different patterns of lung function development.[20]

On the other hand, in *clinical cohorts of adult patients with COPD*, FEV_1 decline with age is highly variable. Only between 40 and 50 % of COPD patients show accelerated FEV_1 decline, with associated factors being smoking, mild-moderate airflow limitation (in contrast to much more attenuated decline in patients with severe COPD), frequency of exacerbations, positive bronchodilator response, presence of emphysema[21,22] and importantly, childhood deprivation and disadvantage factors.[14,23] Interestingly, COPD developed through different trajectories is associated with different health outcomes, i.e. normal maximally attained FEV_1 trajectory followed by rapid decline of lung function has been associated with an increased risk of respiratory and all-cause mortality compared with COPD developed through low maximally attained FEV_1 trajectory and mild or no decline later in life.[24] Other chronic lung diseases, such as interstitial lung disease and primary ciliary dyskinesia, are also associated with different lung function trajectories.[25,26]

Plasticity of individual lung function trajectories: potential for intervention

In contrast to the mean *population*-derived "fixed" trajectories, the *individual* lung function trajectory may change over time, either improving or declining, although the relative lung function level tracks with age in most individuals (e.g., a low lung function throughout the life-course).[27-29] For example, there is a trajectory that starts low in early childhood but has an accelerated growth in later childhood/adolescence, with lung function becoming normal in adulthood (labelled as "*catch-up*"; Figure 1)). Why catch-up happens only in some children is unclear and calls for research[27], but it clearly indicates early interventions can promote lung health in infancy and adolescence. Interestingly, similar catch-up trajectories have been identified for all three spirometry indices (i.e., FEV_1, FEV_1/FVC and FVC).[17,20] Whether "catch-up" may occur also in adults, either through regenerative/healing processes (e.g., in well-controlled asthma or after a COPD exacerbation), or as more resilience toward decline (i.e., 'relative catch-up'), remains to be evaluated both from an epidemiological and mechanistic point of view. However, results from longitudinal studies suggest that higher physical activity may attenuate smoking-related lung function decline in the adult general population[30] as well as in patients with COPD[31] and that weight loss may attenuate age-related decline in obese individuals.[32] On the other hand, normal, sub-normal and even above normal lung function trajectories in children and adolescents can show "*growth failure*" (Figure 1).[27] Again, the mechanisms underlying growth failure are largely unknown although risk factors have been identified (see below), but it highlights the importance of early and repeated monitoring of lung function in children and adolescents.

Interaction between early and late life risk factors: the importance of age

Both the genetic susceptibility of individuals and exposure to disadvantage factors during childhood (such as prematurity, low birth weight, low socio-economic status and childhood deprivation, lack of breast feeding, early life tobacco and/or air pollution exposure) and childhood diseases (asthma, respiratory infections and allergies) can increase the risk of sub-normal trajectories from early life.[19] However, it is not clear whether factors such as asthma or early respiratory infections are causes or consequences of a low lung function trajectory, albeit the relationship may be bi-directional.[1] Interestingly, childhood and adulthood factors (e.g., smoking and adult asthma) can interact in an additive manner ("*multiple hits*") and influence life-long lung function trajectories exponentially.[3]

To allow for early and appropriate interventions, it is important to consider the age window of transition towards an abnormal lung function trajectory. Childhood and adolescence are periods characterized by natural lung growth, partly driven by hormonal factors, thus creating a scenario that may allow individuals to "catch-up" earlier life lung function impairments.[17,29,33] Thus, it will be important to remove barriers for lung growth, such as smoking and vaping, recurrent airway infections and uncontrolled or severe asthma.[1] Tobacco smoking and exposure to environmental tobacco smoke in youth depresses peak lung function, due to impaired lung growth and airway obstruction[1,14], and leads to a subsequently lower trajectory across the rest of their life[5] (as well as increased risk of COPD[4] and cancer[34]). Conversely, higher physical activity levels and fat-free mass physical training and healthy diet in childhood and youth have been shown to enables optimal lung development and growth and which is linked to greater peak lung function values. Finally, it is important to highlight that intervening in young adults, when there is more lung function left to preserve than in older adults, may deliver greater long-term benefits.

Trajectories, multimorbidity and the theory of syndemics

There is evidence that a single low FEV_1 (or FVC) measurement in young adults is associated with higher and earlier incidence of respiratory, cardiovascular and metabolic diseases (i.e., multimorbidity)[5] as well as with worse quality of life[38] and increased mortality.[39] Multimorbidity in relation to respiratory disease is also a key finding in large-scale disease trajectory analyses.[40] More granularity is obtained when longitudinal FEV_1 and FVC trajectories are analysed in combination. Individuals with a mixed pattern trajectory (both restrictive and obstructive) had the highest prevalence of childhood respiratory illnesses, adult asthma, and depression, whereas individuals with a restrictive-only pattern had lower total lung capacity and the highest prevalence of childhood underweight, adult obesity, diabetes and cardiovascular conditions.[20] Interestingly, individuals with Preserved Ratio Impaired Spirometry (PRISm, Box 1, Appendix) suffer a similar proportion of cardiovascular and metabolic comorbidities as those with airflow limitation[41], but individuals who recover from PRISm during their adult life are no longer at increased risk.[15]

Syndemics proposes that diseases that cluster together in a given population act synergistically.[42] Understanding why they emerge together in certain social, temporal

(including age) and/or geographical contexts, and how they interact with each other can enable identification of new ways to prevent and treat these conditions. Three overarching characteristics define a syndemic of two or more diseases: *(1)* they co-occur within certain contexts; *(2)* they interact in meaningful ways, often through biological processes but also through social or psychological processes; and *(3)* they share one or more upstream factors driving their co-occurrence and interactions. The relationship of multimorbidity with lung function trajectories fulfil all these criteria[43], and there are at least three, overlapping mechanisms that may explain the link between reduced lung function and multimorbidity.[44] First, they share well-established risk factors (e.g. childhood deprivation, tobacco smoking, ageing, physical inactivity; potentially also genetics) and/or pathogenic mechanisms (e.g., chronic systemic inflammation, tissue hypoxia). Indeed, multimorbidity in COPD patients is not random.[45,46] For instance, obesity, insulin resistance, and atherosclerosis are associated with mild-moderate COPD[47], whereas heavy smoking history, low body weight, muscle wasting, osteoporosis, and arterial stiffness are linked to severe COPD, particularly with the emphysematous phenotype.[48,49] These observations may provide insights into underlying mechanisms linking lung function and multimorbidity. Second, low lung function may lead to lower physical activity that in turn is a risk factor for multimorbidity. Finally, growing evidence indicates that multimorbidity may be the result of abnormal organ systems development *in utero*[50] and early life.[51] For instance, prematurity increases the risk of COPD in adulthood[52] and being born small for gestational age (an indicator of foetal growth restriction) is not only associated with reduced lung volumes in young adults[53] but also with other chronic conditions including cardiac dysfunction.[54] Collectively, this evidence suggests that, in the presence of abnormal lung function, the possible co-occurrence of other potential morbidities (and risk factors for poor health) should be evaluated systematically, and *vice-versa,* the presence of multimorbidity should prompt lung function evaluation in clinical practice.[43] Contributing to this syndemic approach is the fact that not only parental smoking adds to impaired lung growth in children, but also that these children become more frequent smokers themselves[55], further creating (synergistic) conditions for lung disease.[56] In addition, to a high degree, lung function is heritable[57], meaning that low lung function in parents may be passed on to their offspring (via genetic and epigenetic mechanisms).[3] Thus, identifying young individuals with low lung function could provide valuable information about future lung (and global) health in their offspring.

IMPLICATIONS FOR CLINICAL PRACTICE

Spirometry: a reality check

Spirometry is a pivotal test in any patient with respiratory symptoms and/or risk factors to contribute to the establishing of a diagnosis of a respiratory disease, determine its severity and guide appropriate treatment. It is a well standardised, easy to perform and an inexpensive test. Yet, *(1)* in a real-world setting, spirometry is grossly underused[58]; *(2)* thresholds currently used to diagnose lung disease in adults (e.g., FEV_1/FVC <70%; FEV_1/FVC<LLN; lower limit of normal) may not be sensitive or specific enough to identify children, adolescents or young adults at risk;[59,60] and, *(3)* it is unclear if established treatment for adult respiratory diseases[4,61] is necessary for asymptomatic subjects with impaired spirometry or will improve respiratory and other long-term outcomes if started earlier.[58] This reality check identifies important knowledge gaps that, as discussed below, require and deserve research.

Clinical practice vs. General population lung health

In specialized paediatric and adult pulmonary/allergology clinics, spirometry is well-established in routine care. Yet, a single spirometry measure does not provide the ability to monitor and visualize lung function changes over time. The freely available online tool *"Lung Function Tracker"* (https://gli-calculator.ersnet.org/lung_tracker/) only requires age, height, sex and spirometry measures (FEV_1 and FVC in litres) to return plots of lung function level and potential change over time (if repeated data are entered), along with individual-level reference curves (see also Appendix 2 for details). Lung function trajectories can either be mapped across the entire life-course (4-90 years) or focussed on developmental (i.e., 4-25 years; Figure 2A) or lung ageing periods (i.e., 26-90 years; Figure 2B). We believe that this tool can be easily implemented into commercial software and electronic health records to augment interpretation and dissemination of results.

By contrast, the identification of individuals at risk of poor future health outcomes using spirometry as a population screening test is less straightforward. The implementation of any

population-based screening program needs to consider potential benefits and harms as well as cost-benefit and health economy aspects.[62] Jungner and Wilson proposed several criteria to support a population screening test.[63] Importantly, most of them are clearly met here (Box 2, Appendix): lung health is important, the natural history of normal and abnormal lung function trajectories is now relatively well understood, and there is a sufficiently long latent period where mild lung disease (or pre-disease state) is present, offering opportunities for early intervention.[58] Further, potential benefits including closer health monitoring and early implementation of preventive or therapeutic measures are large, whereas costs are relatively low and risks are marginal, since spirometry is well standardized, non-invasive, relatively easy to perform and interpret and a relatively affordable and widely available test. Thus, as discussed below, the population-wide implementation of spirometry as a lung health check deserves careful consideration[7] (see Table 1 and Box 2, Appendix). Although the added value of population wide screening of lung function is not yet clear, implementation of lung health checks at population level may be an important first step to empower individuals with knowledge about their overall health status (including *lung health*).

Clinical response to abnormal spirometry

The detection of abnormal spirometry values should trigger a clinical response at any age, including additional diagnostic work-up as needed (i.e., body plethysmography, imaging, biomarkers), using a *personalized (precision) medicine approach*[64] that consider the specific *treatable traits* present in that specific individual according to current guidelines.[4,61] This response should consider:

(1) A thorough clinical review seeking risk factors germane to that specific individual. These may relate to long-past events, such as premature birth decades earlier, but also more recent exposures, such as smoking, nutritional status, living and working environment. Both undernutrition and obesity, both during childhood and adulthood, have been linked to reduced life-time lung function.[53,65] Further, a maternal pregnancy intervention trial (vitamin A) conducted in a chronically undernourished population showed improved lung function in offspring.[66]

(2) Individuals travelling in a low lung function trajectory without a currently diagnosable respiratory disease are at greater risk of developing these conditions subsequently.[12] Therefore, their *active monitoring* with periodic lung function measurement, review of symptoms and risk factor management can prevent disease development or its early detection. Identification of individuals at risk of chronic disease offers the potential for targeted, early interventions e.g., modifying smoking behaviour[59], encouraging physical activity[30], minimize occupational exposure[67] and/or vaccination recommendations[68] though, we acknowledge the paucity of RCTs and evidence-based recommendations for many of the potential interventions.

(3) We currently lack the implementation of a simple tool to *effectively monitor lung function trajectories over time*. We anticipate that the introduction of the "Lung Function Tracker" tool proposed here might be a starting point for further development and optimization of other lung function trajectory visualization/modelling tools and software.

TRAJECTORY-BASED INTERVENTIONS TO IMPROVE LUNG HEALTH

Knowledge gaps and research needs

Potential trajectory-based interventions and lung health check-up programs aimed at improving lung health of the population will need to be rigorously developed and evaluated.[69,70] Special attention needs to be paid to those factors that can affect the validity and reliability of the evaluation of different trajectories, e.g., the type of spirometry device, secular trends in lung function patterns (i.e., cohort effect[71]), and population specific lung function trends. For example, whether trajectories need to be defined by geographic region following the WHO approach, a multi-ethnic approach following the GLI approach[72], or as suggested in a recent ATS statement, to use race-neutral reference equations[73] will need to be addressed. Research needs to explore also how often spirometry needs to be measured (e.g., more frequent visits for those identified at low level of lung function early), in respiratory patients the potential influence of recent/ongoing exacerbation (vs. spirometry during stable periods) and the need for additional measures and screening for other non-pulmonary diseases. Adaptation to low-and-middle income (LMIC) countries, given the high prevalence of risk factors including malnutrition, smoking, indoor pollution and infections,

will also be needed.[59] With a broad introduction of spirometry measures also in LMICs, there is much to gain when it comes to diagnostics and treatment optimization.[74]

A theoretically-based programme of support for promoting lifestyle change will need to be developed and tested to support implementation of lung function screening (i.e., lung health checks). The commonly used COM-B framework recognises that Capability, Opportunity and Motivation interact to produce Behaviour change.[75] Participation in a screening programme is an opportunity when feedback of lung function, supported by motivational interviewing[76] could trigger a decision to quit smoking, increase exercise or lose weight. Capability could be enhanced by lifestyle 'apps'[77], and supported by 'very brief advice' from healthcare professionals.[78]

Finally, research on the efficacy and effectiveness of drug and non-drug interventions that can help modify the trajectories is also needed. To date, only two preventive trials (on bronchodilators)[79,80] have investigated how best to arrest the progression of those who have low lung function and/or symptoms prior to manifestation of COPD, which have found small but promising benefits. Some methodological limitations such as lack of study power[80] and not considering the baseline lung function level[79] may have affected their ability to detect a clinical relevant effect. Nevertheless, both provided proof of concept that interventions given before the current COPD diagnostic threshold is reached could slow progression to COPD.[58] Investigating the efficacy of potential therapies stratified by trajectories may help develop precision preventive approaches.

The need for general trajectory-based interventions

With all these caveats in mind, the following lung trajectory scenarios with their corresponding actions/interventions can be conceived (Table 1): *(1)* detection of suboptimal lung function levels/trajectories in early life could trigger education about risk avoidance and risk modification, as well as monitoring for subsequent adverse health outcomes. We would therefore propose that spirometry could be measured at schools in children between 6 and 10 years of age. If this first spirometry is abnormal, specific, personalized medical care actions should be started including lung function tracking and clinical follow-up (Figure 3); *(2)* abnormal spirometry in young adults (25-45 years) can identify people at risk of

unhealthy ageing (including COPD) at a point in time when preventive (e.g., quit smoking, adjust working environment, engage in physical activity) and/or therapeutic measures can be implemented earlier and are likely to be more effective than if considered in the elderly.[4,58]; finally, *(3)* any clustering of suboptimal trajectories within a geographical area (see Syndemics above) could be a marker of, for example, pollution '*hot spots*', thus leading to more targeted public health interventions (e.g., urban planning or transportation policies tacking high air pollution levels).

IMPLEMENTATION STRATEGIES TO FACILITATE DEPLOYMENT OF A TRAJECTORY PERSPECTIVE IN ROUTINE HEALTHCARE

Implementation of any new intervention in routine healthcare is strongly influenced by context, which determines the adaptations necessary for effective adoption of health interventions in diverse healthcare systems.[81] Thus, strategies to promote implementation of the trajectory concept will need to address whole systems, including supporting the needs of patients and the public, recognising the skills needed by healthcare personnel and (crucially) the organisation change and essential infrastructure required to enable adoption. Although interventions, dissemination and implementation are often described sequentially, it may be more efficient to consider these phases in parallel, exploring implementation in the process evaluation of pragmatic effectiveness trials, and using hybrid designs to establish effectiveness.[82]

Shaping the context for optimal lung health

National strategies aimed at promoting the development and preservation of lung health are the context within which a lung-health screening programme is implemented. Societal awareness of the importance of protecting children's lung health[83], complete avoidance of tobacco smoking, improving outdoor and indoor air quality, [84-86] and promoting beneficial healthcare interventions (e.g., childhood vaccination programs and adequate nutrition, exercise) will influence attitudes to lung health checks and the uptake of associated behaviour change interventions programmes. Conversely, media campaigns, such as those led by the European Lung Foundation and the European Respiratory Society ("Healthy Lungs

for Life"[88]) may be reinforced by the population-level findings of a lung-health screening programme. Aligned with the Strategic Development Goals[10] and WHO initiatives for preventing NCDs[11] the universal implementation of these measures will require engagement both by individuals and those responsible for shaping public health and governmental policy.[87]

Patient and public resources

Resources that provide information for patients and the general public to promote understanding of lung function trajectories in relation to health and disease, and support decisions about behaviour change (exemplified by the European Lung Foundation[88]) will be needed. These need to be accessible, regardless of language, age group, cultural background, literacy levels or accessibility to on-line platforms.

Professional skills and clinical requirements

The professionals responsible for lung health checks will vary according to geographical location such as urban vs rural and healthcare context such as primary-care vs secondary care, but most will need training to achieve required skills. Respiratory specialists already have the knowledge, competence, and infrastructure to ensure effective implementation of the trajectory concept in clinical practice (Table 1). Education of other health care professionals, including but not limited to general paediatric, general medicine and primary care physicians, nurses, allied health professionals, pharmacists and school health services staff will be needed.

Organisational change and priorities

Organisational strategies will need to be adapted to suit local routines and referral practices. The implementation of lung function charts in clinical care globally should be followed by real-world studies on feasibility and effectiveness of using lung function trajectories in

different settings, and clinical use will need to be adapted to local, regional and global practices.[90] The introduction of "Lung function tracker" is a first step in this direction.

Stakeholder engagement and advocacy

Advocacy will be crucial as the general public, patients, health care professionals and policy makers need to be bought into the concept that abnormal lung function trajectories predict disease and allow earlier preventive and/or therapeutic interventions that can improve respiratory as well as overall health. National and local community stakeholders should be consulted and co-design implementation of a trajectory perspective in clinical practice and for population respiratory health screening.

CONCLUSIONS

Despite being identified as a priority NCD, chronic lung diseases are often undetected, under-reported and untreated. It is now clearly demonstrated that trajectories associate with the health status across the lifespan. Specifically, sub-normal trajectories are associated with poor health outcomes compared to those normal or above normal. We propose here to use lung function charts to monitor trajectories of individuals to allow for prompt interventions and optimized management. To this end, we introduce the "Lung Function Tracker" as a freely available online trajectory tool.

Going forward, we propose that we are ready to start addressing the prerequisites and investments needed for potential general lung health programs measuring spirometry at least once in children, adolescents or early adults, and repeating it if sub-abnormal or respiratory symptoms occur at a later stage.[91,92] In an era of personalised healthcare, this would be an innovative way forward to protect and improve lung health at population level and promote both healthier growth and ageing globally.

Acknowledgements

Authors thank the European Respiratory Society, AstraZeneca, Chiesi, GSK, Menarini Group and Sanofi for their support to CADSET, a Clinical Research Collaboration aimed at understanding the mechanisms and impact of lung function trajectories during the lifetime in health and disease (https://www.ersnet.org/science-and-research/clinical-research-collaboration-application-programme/cadset-chronic-airway-diseases-early-stratification/). CADSET has created the necessary momentum and critical mass to discuss and agree on the content of this manuscript.

Author contributions

Conceptualisation: EM, RF, SCD, JW, AA.

Concept feedback and development: JPA, DB, AB, AC, JGA, SG, RBK, JH, LL, FDM, SKM, PP, HP, SS, LEGW, GW.

Software (Lung Function Tracker): EM, JH, SS, SKM, GW.

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Competing interest statement

Outside this manuscript, LL has given lectures sponsored by Chiesi and IPSA vzw, a non-profit organization facilitating lifelong learning for health care providers and received consulting fees from AstraZeneca, all paid to her institution. EM has received lecture fees or advisory board fees from Airsonett, ALK, AstraZeneca, Chiesi and Sanofi. AA has received lecture fees and/or advisory board fees from AstraZeneca, Chiesi, GSK, Menarini, MSD, Sanofi and Zambon, and research grants from AstraZeneca, GSK, Menarini and Sanofi. SS has received lecture fees from Vyaire medical and consulting fees from Chiasi and ndd. JGA's institution has received consulting and lecture fees from AstraZeneca (not related to this study); JGA has received lecture fees from Esteve and Chiesi (not related to this study). SCD has received investigator initiated grants from GSK and AZ. HP has received lecture fees (not related to

this paper) from Teva and Sandoz. AC reports personal fees from Novartis, Sanofi, Stallergenes Greer, AstraZeneca, GSK, and La Roche-Posay, outside the submitted work.

"Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms: "Trajectories, lung health, catch-up, multimorbidity, syndemics, getomics, copd, lung function, spirometry" until 22nd August 2023. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

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Table 1. Opportunities and challenges towards implementing lung function trajectories in clinical care, towards personalized respiratory medicine.

Opportunities

- To educate relevant stakeholders and the community (healthcare professionals; patient and civil society organizations etc) on the existence of lung function trajectories, predictors across the life-course and future adverse outcomes (party ongoing already).
- To acknowledge that spirometry measured early in life not only contribute to diagnosing respiratory diseases, but it is also a marker of global health that can identify individuals at risk of suffering cardiovascular and metabolic comorbidities, unhealthy ageing, and premature death.
- To use tools / software such as lung function growth charts (e.g., "Lung Function Tracker") to facilitate the interpretation of different lung function trajectories and in the clinic guide appropriate therapeutic actions (see examples in Figure 2A-B).
- To identify new treatments, by investigating the underlying pathophysiology of different lung function trajectories and to identify predictive biomarkers that can be used to detect trajectories: genetics, biomarkers and beyond. AI-applications to be explored.

Challenges

- To obtain global engagement, also in low-income settings where spirometry may be challenging to perform.
- To liaise with healthcare providers and medical technology companies to continue developing and optimising tools, software for lung function trajectory assessment and interpretation (e.g., through new spirometry device or software).
- To assess the health economics impact of considering trajectories in clinical practice (cost and savings).
- To develop pragmatic approaches to determine lung function trajectories in the absence of past lung function measurements, including biomarkers and risk prediction algorithms.
- To do randomized clinical trials based on the trajectory of the patient (inclusion criteria) aimed at modifying it and associated clinical consequences (outcomes).
- To develop and refine digital tools to monitor respiratory health remotely.

761 **FIGURE LEGENDS**

762 **Figure 1.** Potential lung function trajectories in relation to age from childhood to adulthood
763 representing a high lung function trajectory (blue), normal (green) and low (orange). During
764 childhood and adolescence, catch-up (green dotted line) and growth failure (purple dotted line) may
765 occur while accelerated decline patterns can been observed in adulthood (red and black dotted
766 lines).

767 **Figure 2A-B:** Output from the "Lung Function Tracker" (https://gli-
768 calculator.ersnet.org/lung_tracker/) exemplified as a fictive pediatric patient followed from age 8 to
769 19 years (Figure 2A) and an adult patient followed from age 40 to 60 years (Figure 2B). In both
770 figures, the individual FEV1, FVC and FEV1/FVC ratio trajectories are visualized, respectively.

771 **Figure 3**: Proposed algorithm to guide actions following spirometry testing/screening in children,
772 adolescents or adults.

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BOX 1.

Spirometry – what are we measuring?

Spirometry is the standard test to measure lung function (i.e. how well the lungs work). Main lung function parameters are forced expiratory volume in the first second (FEV_1, measuring how fast the air can be expelled), the forced vital capacity (FVC, measuring how much air can be expelled from the lungs), and their ratio (FEV_1/FVC, measuring the degree of airflow limitation) A reduced FVC may indicate restrictive impairment whereas reduced FEV_1/FVC ratio diagnoses the presence of airflow limitation. A reduction in any one of these measures has been associated with poor health outcomes later in life**.** While a simplified spirometry test to register FEV_1 only may increase feasibility and practical implementation, as it does not need the full expiration to measure FVC, it would limit the overall assessment of lung health.

Beyond spirometry - what could be missed with spirometry?

Although spirometry is a robust tool to measure lung health (and general health) that can be useful to rule-in (but not necessarily to rule-out) lung disease, it is not the most sensitive test to identify early manifestations of lung disease. Nevertheless, most long-term studies are based on spirometry, and while there are other pulmonary function tests that are easier to perform and more sensitive to early lung disease (e.g., forced oscillometry[1]), these are yet to become widely available.

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786 **APPENDIX, FUNDING:**

787 CADSET is a Clinical Research Collaboration (CRC) endorsed by the European Respiratory Society
788 (ERS) with the collaboration of AstraZeneca, Chiesi, GSK, Menarini Group and Sanofi. However, no
789 industry support was provided for this review. Besides, EM and RF acknowledge being the recipients
790 of an ERC grant; EM: TRIBAL, No 757919 (and also Swedish Research Council and HLF grants) and RF:
791 PredictCOPD, No 101044387. SD is supported by NHMRC Leadership Investigator Grant. AA is
792 supported by ISC-III PMP21/00090, AA-RF by PI21/00735 and SEPAR grants. AB is a PI in the Asthma
793 UK Centre for Applied Research. HP is a PI in the NIHR Global Health Research Unit on Respiratory
794 Health (RESPIRE), the NIHR Programme Grant for Applied Research: RP-DG-1016-10008 and a
795 grantholder on the Horizon Europe: 101095461. ISGlobal acknowledges support from the grant
796 CEX2018-000806-S funded by MCIN/AEI/ 10.13039/501100011033, and from the Generalitat de
797 Catalunya through the CERCA Program. GW is supported by the Office of China Postdoctoral Council
798 (No. 56 Document of OCPC, 2022). L.E.G.W.V. is supported by grants from the Family Kamprad
799 Foundation (20190024) and the Swedish Heart and Lung Foundation (20200150).

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801 **APPENDIX BOX 1.**

802

DEFINITIONS

- **GETomics**: Term aimed to describe omics information in relation to cumulative gene (G) x Environment (E) interactions over Time (T).
- **Lung function trajectory**: a lung function path followed over the life-course by an individual or a population.
- **Preserved ratio impaired spirometry (PRISm):** a normal ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC ≥0.70) but FEV1 less than 80% of predicted.
- **Syndemics**: Term to refer to diseases that cluster together and act synergistically.
- **Trajectome**: Range of lung function trajectories that exist in the population.

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804 **APPENDIX BOX 2.**

Wilson and Jungner's principles of screening	**Applied to the trajectory concept to prevent chronic respiratory disease?**
The condition sought should be an important health problem.	Yes, COPD affects 10% of the adult population; asthma affects 10% of both children and adults
The natural history of the condition, including development from latent to declared disease, should be adequately understood.	Yes, trajectory science summarized above.
There should be a recognizable latent or early symptomatic stage.	Yes, the pre-COPD phase when the ratio is preserved; mild asthma is well-known.
There should be a suitable test or examination.	Yes, spirometry
The test should be acceptable to the population.	Yes, non-invasive
There should be an agreed policy on whom to treat as patients.	Need a consensus and guidelines on how to treat pre-COPD. Guidelines exist for asthma.
There should be an accepted treatment for patients with recognized disease.	Yes, asthma and COPD treatment guidelines exist.
Facilities for diagnosis and treatment should be available.	Yes.
The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	Need cost-benefit calculations in different regions of the world and in different settings.
Case-finding should be a continuing process and not a "once and for all" project.	Need to engage with healthcare providers.
The condition sought should be an important health problem.	Yes, high disease burden and mortality.

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Appendix Table 1. Considerations for the roadmap to improve lung health		
Considerations	**Questions for intervention development**	**Questions for implementation strategies**
Context	• What support services are available? Smoking cessation services? Additional investigation? Access to pharmacotherapy?	• What are the (diverse) settings in which a lung health screening program could be introduced? • What is the public health context? Would targeting screening in high-risk populations be more cost effective? • What incentives are available to support implementation? • What aspects of the policy context need to be addressed? Tobacco legislation? Air-quality regulation?
Patients and the public	• What information will be needed for patients the public? • How can information be presented to optimize behavior change? • How do patients and the public view the prospect of lung health checks? • How to patients and the public (children, adolescents, adults, elderly) feel about the experience of lung health screening?	• What public awareness campaigns can be implemented effectively and sustained? How to engage civil society and community organizations? • What formats of information are required to ensure no-one is disadvantaged? • What are the societal implications of having abnormal lung function detected at screening? (e.g. on career options in adolescents; life insurance or travel insurance for adults?)
Healthcare professionals	• What behavior change interventions are feasible and effective to deliver at the time of the lung health check? • What is the appropriate clinical response to abnormal spirometry in children, adolescents, adults, elderly?	• Who are the appropriate personnel? Specialist care, primary care, lung physiology services, school health services, community health workers etc • What professional training is needed? • How can use of lung function charts be facilitated?
Organisations	• What are the time and resource implications of delivering a lung health check and the subsequent follow up? • What models of screening are optimal? Full quality assured spirometry, or screening FEV_1/FVC with hand-held meters?	• What organizational infrastructure will be needed to operate a screening program? • Is one reading sufficient? How will longitudinal screening programs be organized at population level? How will a lifetime of readings be collated on centile charts? • What pathways are needed for arranging further tests of specialist review?

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Appendix 2:

Methods, "Lung Function Tracker (*for review only*)

The Lung Function Tracker is a freely available tool designed for monitoring and visualization of individual lung function changes over time. The tool requires individual-level data input, including age, height, sex, ethnicity, and spirometry measurements (FEV1, and FVC in liters). In return, it provides information about the lung function levels and potential changes (if multiple data points are provided) with individual-based lung function value reference curves. The individual-level reference curves included in the output plots are calculated based on the GLI lung function equations [1] and WHO height curves [2, 3].

The Lung Function Tracker allows users to map and plot lung function across the entire life-course. Overall, two kinds of outputs can be selected by the users; lung function values (FEV1, FVC and FEV1/FVC values, respectively) or GLI z scores. For the output, the users can illustrate the individual lung function trajectory during the entire life-course (from 4 to 90 years), or during the lung developmental period (from 4 to 25 years) or the lung aging period (from 26 to 90 years).

The Lung Function Tracker assumes that changes in height z-scores follow a linear trend from the ages of 4 to 19 years and that changes in height values follow a linear trend from 19.1 to 90 years. During the ages of 4 to 19 years, Lung Function Tracker uses WHO height curve to convert height values into z-scores, linking the z-scores with lines consequently to generate a z-score curve, and then changing the z-score curves back to height values curves. For individuals aged 19.1 to 90 years, the height values were linked with lines to generate the height curves, and then the height curves were smoothed. Subsequently, the GLI equation is employed to calculate the lung function values corresponding to the height value curves, enabling the calculation of reference curves.

The Lung Function Tracker will be freely available at https://gli-calculator.ersnet.org/lung_tracker/ upon publication of the manuscript.

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Screenshot form the Lung Function Tracker website: