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Lifetime spirometry patterns of obstruction and restriction, their risk factors and outcomes: a prospective cohort study

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Panel: Research in context

Evidence before this study

There is evidence that both obstructive and restrictive lung function deficits in adulthood are associated with increased morbidity and mortality. Investigation of lung function trajectories over time is an emerging research area in recent years. Charactering longitudinal patterns of obstruction, restriction and their overlap from early life to later adulthood could advance the understanding of the aetiology and treatable traits, and inform prevention and management of chronic lung disease. We searched for articles in PubMed up to August 18, 2022 using search terms: "lung function", "FEV", "FVC", "FEV_1/FVC", "obstruction", "restriction" and "trajector*". Among papers investigating lung function trajectories, most only focused on FEV_1 and had data only up to early adulthood. Only a few studies investigated trajectories of FEV_1/FVC or FVC also up to early adulthood. However, no studies have investigated the clustering of trajectories of FEV_1/FVC and FVC overtime to define lifetime patterns of obstruction and restriction.

Added value of this study

Using unique population-based longitudinal data to investigate distinct trajectories of FEV_1/FVC and FVC and their clustering from the first to the sixth decade of life, our study is the first to identify and characterise lifetime patterns of obstruction and restriction, their risk factors and their consequences. We showed that those with the mixed obstructive and restrictive pattern (low FEV_1/FVC plus low FVC trajectories) had the highest risk of COPD followed by the obstructive-only pattern (low FEV_1 trajectory only). The mixed pattern was also found to have the strongest associations with childhood risk factors and adult mental health disorders. Those with the restrictive-only pattern (low FVC trajectory only) had evidence of true lung restriction and were at risk of multi-morbidities by the 6^{th} decade of life.

Implications of all the available evidence

The "mixed" and obstructive-only patterns identify those who may benefit the most from early COPD interventions. The restrictive-only pattern identifies those at higher risk of multi-morbidity. Poor lung development as indicated by restrictive-only pattern seems to be associated with poor development of other organ systems and later multi-morbidities. If confirmed by other studies, our findings can inform development of clinical algorithms for

detection of those at risk of developing COPD – and those with established yet undiagnosed COPD to enable precision preventive and tailored management strategies. Such an approach should also be used to target the high prevalence of comorbidities in the longitudinal restrictive lung function pattern. Overall, these findings highlight the untapped opportunities for tackling disease burden associated with lung function deficits.

Summary

BACKGROUND:

There is increasing interest in life-course lung function trajectories with a focus on obstructive patterns. No prospective study has investigated both obstructive and restrictive lifetime patterns concurrently while accounting for potential overlaps between them.

METHODS:

Using z-scores from spirometry measured at ages 7, 13, 18, 45, 50 and 53 years in the Tasmanian Longitudinal Health Study (n=2,422), six FEV_1/FVC trajectories and five FVC trajectories were identified via group-based trajectory modelling. Based on whether trajectories of FEV_1/FVC and FVC were 'low' (i.e. persistently low from childhood or adulthood) or normal, four patterns of lifetime spirometry obstruction and/or restriction were identified and compared against static lung volumes and gas transfer. Childhood and adulthood characteristics and morbidities of these patterns were investigated.

RESULTS:

Prevalence of the four lifetime spirometry patterns was: *low FEV_1/FVC-only,* labelled as *obstructive-only* 25.8%; *low FVC-only,* labelled as *restrictive-only* 10.4%; both *low FEV_1/FVC* and *low FVC*, labelled as *mixed* 3.5%; and neither low, labelled as *reference* 60.2%. The prevalence of COPD at age 53 years was highest in the *mixed* pattern (36.9%) followed by the *obstructive-only* pattern (21.6%). Participants with the *mixed* pattern also had the highest prevalence of parental asthma, childhood respiratory illnesses, adult asthma, and depression. Those with the *restrictive-only* pattern had lower total lung capacity and residual volume, and had the highest prevalence of childhood underweight, adult obesity, diabetes, cardiovascular conditions, hypertension and obstructive sleep apnoea.

INTERPRETATION:

This is the first to characterise lifetime phenotypes of obstruction AND restriction simultaneously using objective data-driven techniques and unique life-course spirometry measures of FEV_1/FVC and FVC from childhood to middle-age. Mixed and obstructive-only patterns identified those who may benefit from early COPD interventions. Those with the *restrictive-only* pattern had evidence of true lung restriction and identified those at higher risk of multi-morbidity by middle-age.

Funding:

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INTRODUCTION

Interest in lifetime lung function trajectories has increased in the context of emerging evidence that chronic obstructive pulmonary disease (COPD) arises from multiple 'disadvantaged' lung function pathways, including ones that start with poor lung function in childhood (1). The emerging evidence base that supports the early origins of COPD from childhood (2-4) has now led to the new paradigm of pre-COPD (5, 6), which highlights the opportunity to identify those who are on course to developing COPD (7). On the other hand, the earliest identification of those who may develop obstructive vs restrictive lung function deficits is critical to intercept lung disease processes, given that clinical management, including potential therapies for these physiologically divergent conditions, are equally disparate. Furthermore, there are very few disease-modifying therapies for obstructive and restrictive respiratory conditions in part because they are often diagnosed at advanced stages. Hence, identifying life course spirometry patterns most closely associated with the early phase development of these conditions before they are well established will provide the potential for intervening with specific preventive environmental and medical interventions.

The most compelling evidence on multiple 'disadvantaged' lung function pathways was first generated by Lange et al (8). Since then, studies on three population-based cohorts and one asthmatic cohort (4,5) have delineated a number of different FEV_1 pathways, including disadvantaged ones (e.g. reduced development and/or rapid decline), from childhood to early adulthood (9, 10). Notably, we have demonstrated six distinct FEV_1 trajectories from childhood up to the sixth decade existing at a population level, with 75% of the COPD cases arising from three of them (11). While the focus to date has been on modelling FEV_1 trajectories, trajectories of FEV_1/FVC could provide clearer lifetime patterns of airflow obstruction over the life course. More importantly, it has been suggested that the focus on obstructive patterns without taking concurrent changes of FVC into account may mask comprehensive information on respiratory health risks (12). This is important as low FVC may be due to either true restriction from reduced lung volumes or from airflow obstruction associated with air-trapping with resulting high residual volumes (RV). Finally, although given the global importance of COPD it is understandable that previous studies focused only

on airflow limitation, and this may have hidden the impact of lung restriction on overall respiratory morbidity and mortality in the general community.

Therefore, the novel approach of concurrently investigating both measures of FVC and FEV_1/FVC ratio longitudinally while investigating potential overlap could provide more comprehensive information necessary to allow teasing out of the physiological processes underlying spirometric obstruction with or without spirometric restriction (low FVC). In this setting, however, it is critical that true restriction is confirmed by static lung volume assessment to exclude a low FVC due to air-trapping from small airways obstruction. Such knowledge would not only improve insights into development of both early and more severe airflow limitation, but also address the current gaps in knowledge around the importance of reduced functional lung volumes at a community level. Thus, using the unique data from the Tasmanian Longitudinal Health Study (TAHS), we aimed to: 1) investigate lifetime trajectories of FEV_1/FVC ratio, FVC, and their combinations, 2) relate these combined trajectory groups to static lung volume and gas transfer measurements, and 3) investigate both risk factors for and consequences of these combined trajectory groups.

METHODS

Study design and population

Data from six phases of TAHS (13), from childhood to middle age were used (Figure S1). TAHS began in 1968 when 8,583 children born in 1961 and attending school in Tasmania were enrolled (99% of the population). At age 7 years (baseline), the children underwent pre-bronchodilator (BD) spirometry and parents completed a detailed questionnaire. Follow-up assessments were conducted at age 13, 18, 45, 50 and 53 years with surveys completed and pre-BD spirometry measured. In addition, at age 45 years both pre- and post-BD spirometry, single-breath carbon monoxide diffusing capacity of the lung ($D_L$co), and static lung volumes were measured. In the most recent follow-up (2012-2016), when the participants were 53 years old, all those from the 1968 original cohort who were alive and had up-to-date contact details were invited to complete a survey and clinical investigations. In this follow-up, pre- and post-BD spirometry and $D_L$co were performed in 2,689 participants. The current study sample were those who had lung function data at least at ages 7 and 53 years (n=2,422).

Data collection

Spirometry was conducted according to the American Thoracic Society and European Respiratory Society joint guidelines (14), with z-scores derived using the Global Lung Initiative (GLI) reference values for Caucasian ethnicity (15) which have been validated in an Australian population (16). Inflammatory-related biomarkers including C-reactive protein (CRP) and Club cell secretory protein (CC16) were assayed from blood samples collected at both 45 and 53 years to investigate their potential role as trajectory-associated biomarkers.

Definitions

Childhood factors (asthma, chronic cough, eczema, hay fever, food allergy, pneumonia, breast feeding, weight status, parental asthma and parental smoking) were defined using information provided by parental questionnaires in 1968. COPD at 53 years was defined as post-BD FEV_1/FVC<0.7 plus symptoms (shortness of breath at rest or after exercise, chronic cough or chronic sputum production) and/or exposures (a history of smoking ≥10 packyears and/or occupational exposure to vapour/gas/dust/fumes) and/or a family history of COPD (17). We additionally used lower limit of normal (LLN) derived from GLI reference equations (15) as an alternative cut-off for post-BD FEV_1/FVC to define COPD. Doctor-diagnosed co-morbidities (cardiovascular, mental-health, metabolic) were self-reported by participants at age 53 years. Further definitions are outlined in the supplement.

Data analysis

Identification of trajectories of FEV_1/FVC and FVC from ages 7 to 53 years

Group-based trajectory modelling (GBTM) was used to identify distinct groups of individuals whose measurements followed a similar pattern over time separately for both pre-BD FEV_1/FVC and FVC z-scores, at six time points (7, 13, 18, 45, 50 and 53 years) (18). Parameter values determining models with an increasing number of trajectories were derived using maximum likelihood estimation to determine the best fitting model (19, 20). This method allows handling of missing data for each individual. Goodness of fit of the models were compared using Bayesian Information Criterion (BIC). We fitted models starting with two trajectories in an iterative manner, and sequentially added classes until we obtained the optimum model based on BIC value. For models with n trajectories, we fitted different models with different polynomial functions of repeated lung function measures against age

at measurement to select the most appropriate model. We then compared the most appropriate model of n trajectories with that of n+1 trajectories to select the model with the better fit. The final model was selected when the model showed optimal Bayesian Information Criterion (BIC) values that had good class separation (entropy values>0.8). Predictors were not included in trajectory modelling. GBTM estimated the population prevalence of each lung function trajectory group, and the posterior probability of each individual belonging to each group. Assignment of each individual to a single trajectory group was based on the highest posterior probability for that individual.

Lifetime spirometry patterns based on trajectories of FEV_1/FVC and FVC

We combined the FEV_1/FVC and FVC trajectories to assess overlapping lifetime spirometry patterns. Based on whether the FEV_1/FVC and FVC trajectories were low (i.e. less than average from childhood or from adulthood) or normal, individuals were classified into four lifetime spirometry patterns: low FEV_1/FVC-only (labelled as "obstructive-only"), low FVC-only (labelled as "restrictive-only"), both low FEV_1/FVC and low FVC (labelled as "mixed"), and neither low (labelled as "reference").

Statistical analysis

Childhood and adult characteristics, other lung function measures than spirometry (i.e. total lung capacity (TLC), residual volume (RV) and its ratio RV/TLC,, functional residual capacity (FRC) and carbon monoxide diffusing capacity of the lungs ($D_L$co) and its co-efficient (Kco)), circulating biomarkers (CRP, CC16) and comorbidities were compared across the low FEV_1/FVC-only, low FVC-only, mixed, and reference patterns using chi-squared tests, t tests or Mann-Whitney tests for categorical and continuous variables, respectively, as appropriate. All analyses were performed using Stata 16 (Stata Corp, College Station, TX, USA) with a GBTM plug-in (20).

Ethics

The study was approved by the Human Ethics Review Committees of all relevant institutions. Written informed consent was obtained from all participants.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Baseline characteristics of participants

Of 8,583 individuals from the original TAHS cohort, 2,422 had lung function data at least at both ages 7 years and 53 years and comprised the study sample. Participants included in this analysis had similar baseline characteristics to those not included except that the former were more likely to be female, to have eczema, and less likely to have parents who smoked (Table S1) (11). Those deceased by 53 years also had similar baseline characteristics (Table S2).

Lifetime FEV_1/FVC and FVC trajectories when modelled separately

The best-fitting models identified five FVC trajectories and six FEV_1/FVC trajectories (Figure 1a and 1b). The average membership probability of individuals in each trajectory exceeded 0.7, suggesting good model adequacy (21). They were labelled by observing their shape, including baseline lung function at age 7 years (low, normal or high) and rate of adult decline (rapid or normal). The "average" trajectories had, by definition, lung function consistently around the population mean i.e. z score of 0 over time.

Figure 1A (top panel) illustrates the six FEV_1/FVC trajectories identified by GBTM. The labels and their respective prevalences are: "early low-rapid decline" 6%; "early low-normal decline" 19.5%; "early normal-rapid decline" 6.5%; "early low-catch up-normal decline" 4.5%; "early high-normal decline" 19.3%; and "normal/average" 44.2%. The overall prevalence of low FEV_1/FVC trajectories (including subgroups "early low-rapid decline", "early low-normal decline" or "early normal-rapid decline") was 32%. Interestingly, there was no major overlap between these FEV_1/FVC trajectories and our previously published FEV_1 trajectories (Table S3).

Figure 1B (bottom panel) illustrates the five FVC trajectories. The labels and their respective prevalences are: "early low-normal decline" 16%, "early low-catch up-normal decline" 4.3%, "early high-normal decline" 25.6%, "early very high-normal decline (supranormal)" 2.5% and

"normal/average" 51.6%. The overall prevalence of low FVC trajectories (including only the "early low-normal decline" trajectory") was 16%.

Lifetime spirometry patterns based on combinations of FEV_1/FVC and FVC trajectories

As illustrated in Figure 2 and S2, considering whether only one, both or none of the two measures of trajectories were 'low' or normal, we identified four patterns of lifetime spirometry: *(1)* Low FEV_1/FVC only (labelled as obstructive-only) with a prevalence of 25.8%, which included those in one of the three low FEV_1/FVC trajectory groups without a co-existent low FVC trajectory; *(2)* Low FVC only (labelled as restrictive-only) with a prevalence of 10.4%, which included those in the low FVC trajectory group without a co-existent low FEV_1/FVC trajectory; *(3)* Both low FEV_1/FVC and low FVC (labelled as mixed) with a prevalence of 3.5%, which included those in one of the three low FEV_1/FVC and the low FVC trajectory groups; and *(4)* Reference with a prevalence of 60.2%, which included those with neither low i.e. those who belonged to neither a low FEV_1/FVC trajectory nor a low FVC trajectory group.

Other lung function characteristics of the four lifetime spirometry patterns

At age 45 years, TLC, FRC, RV were significantly lower for participants with the restrictive-only pattern compared to the reference pattern, consistent with true lung restriction (Tables 1, S4, S5). By contrast, participants with the mixed pattern had a slightly but significantly lower TLC, and significantly higher levels of RV and RV/TLC compared to the reference pattern. Those with the obstructive-only pattern had significantly higher TLC, FRC, RV and RV/TLC, consistent with hyperinflation of the lungs.

At ages 45 and 53, D_{LCO}, a marker of parenchymal damage, was significantly lower for those with the mixed and restrictive-only patterns, but not the obstructive-only pattern (Table 1), while Kco was significantly lower for those with the obstructive-only pattern, significantly higher for those with the restrictive-only patterns compared with the reference pattern, but was similar for those with the mixed pattern (Table 1).

At age 45 years, the prevalence of bronchodilator reversibility was 8.5% in the obstructive-only, 5.4% in the restrictive-only, 22.2% in the mixed and 1.9% in the reference pattern. At age 53 years, the prevalence of bronchodilator reversibility in these patterns was reasonably

similar at 9.2%, 4.9%, 18.0% and 0.6%, respectively. We also compared these lifetime spirometry patterns with our previously published FEV_1 trajectories (11). Notably, 90% of participants with the mixed pattern belonged to either "persistently low" or "early below average, accelerated decline" FEV_1 trajectories while a majority of those with restrictive-only (45%) or obstructive-only patterns (64%) belonged to a "below average" FEV_1 trajectory (Table S6). Preserved ratio impaired spirometry (PRISm) overlaps mainly with restriction only and mixed patterns with a major overlap with the restriction pattern (Table S7).

Childhood characteristics of the lifetime spirometry patterns

Table 2 compares childhood sociodemographic factors, birth details and clinical characteristics of the three sub-normal spirometry patterns (i.e. obstructive-only, restrictive-only and mixed) with the reference pattern. While the prevalence of childhood asthma, bronchitis and pneumonia were significantly higher for those in all three sub-normal patterns, those with the mixed pattern had the highest prevalence of these conditions, particularly allergic asthma (Table 2). Those with the mixed pattern also were significantly less likely to have been breast fed and had a higher prevalence of parental asthma. Those with the restrictive-only pattern were more likely to be male and had a higher prevalence of being underweight in childhood suggesting that the restrictive-only pattern may characterise those with poor lung development in childhood (Table 2).

Adult characteristics of the lifetime spirometry patterns

Tables 3 compares the adult socio-demographic factors, clinical characteristics, biomarkers and comorbidities of the three sub-normal spirometry patterns with the reference pattern. Compared to the reference pattern, those with the mixed and obstructive-only patterns, but not the restrictive-only pattern had a significantly higher prevalence of adult smoking. At age 53 years, the prevalence of COPD was significantly higher in those with mixed and obstructive-only patterns and was highest in those with the mixed pattern. While the prevalence of asthma, other respiratory symptoms, and respiratory medication use were significantly higher for those belonging to all three sub-normal patterns, those with the

mixed pattern had the highest prevalence of all these surrogate markers of respiratory problems (Table 3).

Using lower limit of normal as the cut off, the prevalence of airflow obstruction (i.e. post-BD FEV_1/FVC<LLN and FVC≥LLN), airflow restriction (i.e. FVC<LLN and post-BD FEV_1/FVC≥LLN) and both (i.e. FVC<LLN and FEV_1/FVC<LLN) across the four spirometry patterns are shown in Table S8. These findings showed the severe end of lung function deficits and were in line with spirometry patterns.

Compared to the reference pattern, those with the mixed pattern had significantly lower CC16 and significantly higher CRP levels; those with the low obstructive-only pattern had significantly lower CC16 but similar CRP levels, while those with the restrictive-only pattern had similar CC16 but significantly higher CRP levels (Table 3).

In terms of comorbidities, compared to the reference pattern, those with the mixed pattern had a significantly higher prevalence of doctor-diagnosed depression; those with the restrictive-only pattern had a significantly higher prevalence of multiple comorbidities, including doctor-diagnosed angina/heart attack, hypertension, diabetes and obstructive sleep apnoea (OSA) as well as self-reported high risk of OSA using STOPBANG and Berlin questionnaires (Table 4). The restrictive and mixed patterns also had a significantly higher number of comorbidities compared to the reference pattern.

Adult obesity was significantly more prevalent in those with the restrictive-only pattern and less prevalent in the obstructive-only pattern, but was not associated with the mixed pattern. Given that all the investigated metabolic diseases as well as obesity were more prevalent for those with the restrictive-only pattern**,** we stratified the restrictive-only pattern into obese and non-obese sub-groups (sub-patterns) (Table S9). Interestingly, childhood asthma, bronchitis and underweight were significantly higher only for the non-obese subgroup. In contrast, at age 53, asthma, diabetes, hypertension, high cholesterol and obstructive sleep apnoea were higher for the obese subgroup.

Summary of main results

The summary of main findings is shown Table S10. The mixed pattern had the highest prevalence of COPD and other respiratory symptoms at age 53 years, parental asthma and childhood illnesses as well as biomarker levels that indicate increased inflammation

(increased CRP) and lung injury (decreased CC16 levels). The obstructive-only pattern also had increased prevalence of COPD and other respiratory symptoms at age 53 years, parental asthma and childhood illnesses and decreased CC16 levels but at a much lesser extent than the mixed pattern. In contrast to the mixed pattern, the obstructive-only pattern had normal CRP levels. The restrictive-only pattern had reduced dynamic lung volumes, increased childhood illnesses and increased comorbidities as well as increased CRP levels.

DISCUSSION

This is the first study to characterize and integrate life-course FEV_1/FVC and FVC trajectories from ages 7 to 53 years, investigating how they cluster over time. Adding FVC trajectories to FEV_1/FVC trajectories has allowed us to differentiate patterns of both potential obstruction and restriction, which were then confirmed and nuanced using static lung volumes and gas transfer data. We found six distinct FEV_1/FVC and five distinct FVC trajectories that gave rise to four spirometry patterns over the life course based on combinations of the developed trajectories. These four patterns were: obstructive-only (low FEV_1/FVC-only), restrictive-only (low FVC-only), mixed (low FEV_1/FVC plus low FVC) and normal (called "reference"). A restrictive-only pattern was found to have true lung restriction by middle-age. These patterns were differentially associated with distinct early life events and several disease states in late adulthood.

Using lung function data from age 6 to 22 years, the Raine Study reported only four FEV_1/FVC and four FVC trajectories (22). Using lung function data from ages 11 to 32 years, the Tucson study reported only two trajectories of FEV_1/FVC, but it did not develop trajectories of FVC independently (23). In contrast, we identified six FEV_1/FVC trajectories and 5 FVC trajectories from age 7 to age 53 (i.e. over 5 decades) in a much larger sample with more repeated spirometry measures. The lower number of trajectories may be due to both the Raine and Tucson studies having lung function measures that only cover late childhood period to early adulthood, less repeated measures and smaller sample sizes. Nevertheless, there are some similarities in trajectories across the Raine study and our study.

To date, no studies have investigated the clustering between FEV_1/FVC and FVC trajectories over time. Our novel approach of uncovering lifetime trajectories that differentiated

between low FEV_1/FVC and low FVC and then considering them concurrently has enabled us to better understand the natural history of lung function. This allows consideration of different physiological processes, i.e. low FVC as part of airway obstruction (mixed pattern) and/or as potential true restriction. Further, this is the first and as yet the only study to compare and contrast lung volume measures generated by body plethysmography plus data on the gas diffusion capacity of lungs (D_LCO, Kco) against phenotypes of spirometric lung function trajectories. Having both sets of data helped us to understand whether restriction is likely to be pulmonary or extra-pulmonary, which lends insight into the broad aetiology of restriction, and this is quite unique.

The highest prevalence of COPD, active asthma and other respiratory symptoms at age 53 years was observed in the mixed pattern which could be in part explained by the high prevalence of associated childhood respiratory illnesses, compounded by the high prevalence of associated personal smoking in later life. It also suggests that the low FVC component of this mixed pattern reflects worse airway obstruction especially in the small airways as supported by evidence of gas-trapping with high RV measured in middle-age (24). However, in this mixed pattern, TLC is actually slightly but statistically significantly lower than the reference pattern, which suggest some degree of co-existent restriction although this also might be due to severity of the obstruction, and this needs further exploration. This contrasts with the restrictive-only pattern which likely reflects “true” lung restriction, as suggested by lower static lung volumes in middle age but without substantial parenchymal/pulmonary vascular impairment as indicated by elevated Kco, even for the non-obese subgroup. Moreover, the higher prevalence of bronchodilator response in the mixed pattern compared to the obstruction only pattern reflects the more severe obstructive nature of the mixed group as shown by higher prevalence of asthma and wheeze.

Low levels of CC16, a protein produced by small airway Club Cells that is airway-protective (25), is a marker of lung injury, while high CRP levels is a marker of inflammation. In our study, CC16 levels were lower in the two patterns characterised by low FEV_1/FVC (mixed and obstructive-only) and CRP levels were higher in the two patterns characterised by low FVC (mixed and restrictive-only). Similar findings have been reported with COPD (25, 26) and restrictive spirometry pattern (27). For the first time, our findings highlight that a mixed

pattern where both FEV_1/FVC ratio and FVC are low throughout life is associated not only with the highest risk of COPD in middle age, but also increased serum CRP and reduced serum CC16 levels. Our biomarker findings in the mixed pattern are consistent with airway injury and remodelling as well as ongoing secondary systemic inflammation. These biomarker findings are potentially useful for diagnosing these patterns and following activity of inflammatory processes. There is a need to extend this work to other potential diagnostic biomarkers of these different patterns, which could be used in clinical practice to identify individuals who will belong to specific patterns at an early stage. Investigation into biomarkers will also lead to establishing endotypes and drug discovery through further mechanistic research.

Indeed, our findings on the obstructive-only and mixed patterns, taken together, suggest a major opportunity for secondary prevention through lifetime spirometric surveillance of those with vulnerable lungs from childhood and the potential for interventions to prevent progression to COPD. Early detection of the mixed and an obstructive-only pattern can identify individuals who may benefit from early interventions to reduce the risk of full-blown COPD and/or initiate appropriate treatment to reduce the subsequent co-morbid disease burden. While the literature has now begun to develop the concept of “pre-COPD” (6, 28), early identification of COPD through screening general populations is not yet advocated (29). Thus, future research will need to ascertain potential benefits from performing spirometry or biomarkers to identify children, adolescents and/or young adults at risk of later lung disease as well as, and in particular, detecting pre-COPD.

Our findings on the associations between childhood underweight, pneumonia and adult obesity with the lifetime restrictive-only pattern suggest that both direct insults as well as poor nutrition could lead to small and under-developed lungs in childhood which can persist in physiological impairment throughout life (30). Our findings on the association between the life-time restrictive-only pattern and multimorbidity are consistent with the previous studies that have investigated adult lung restrictive impairment (31, 32). Additionally, although the obesity per se still plays a large part in these effects, we show that these associations remained after obesity was taken into account, suggesting that the high multimorbidity observed in the restrictive pattern is multifactorial. Furthermore, our findings also suggested that the restrictive-only pattern had little evidence of

parenchymal/pulmonary vascular damage given a lower mean DLco combined with an elevated Kco for both the obese and non-obese sub-groups, although the lungs were smaller in the two subgroups for different reasons.

The main strength of our study stems from the uniqueness of repeated lung function measures from the first to the sixth decade for TAHS participants, including static lung volumes during middle-age to further investigate the low-FVC-related patterns. Spirometry, lung volumes and gas transfer measures have allowed us to identify and verify restrictive deficits, but CT data would have helped to assess detailed morphology, and that will be our next step. An additional strength is the use of an objective data-driven technique which enabled us to explore potential unknown lung function trajectories which were not based on any *a priori* hypotheses. Compared to previous studies, we have lung function at multiple time points as inputs into the GBTM models, which provides greater accuracy in the identification of trajectories and probability of class membership. We used the GLI equation to facilitate generalisability and replication of our findings. Although an internal equation might better fit the data than the GLI reference equation, this would not make any difference to the overall interpretation of comparisons between the spirometry patterns.

We acknowledge the following limitations. As previously discussed (11), the lack of sufficient lung function data around age 18 years may have inhibited us from fully characterizing trajectory transitions around peak lung function. However, a sensitivity analysis excluding the limited data points at 18 years showed similar trajectories suggesting that the sparseness of data around age 18 years was unlikely to have significantly influenced the observed trajectories. While there were differences in equipment and technical standards for performing spirometry measurements in the first three follow-ups of the study, this is unlikely to have substantially influenced the relative positions between trajectories which were based on z-scores. Healthy survivor bias is possible given that the analysis was limited to those who were alive and continuing to participate in the study. However, the differences in childhood characteristics including lung function between participants and those deceased or lost to follow up, were minimal. If attrition was differential across trajectories, it would influence the lung function trajectory prevalence estimates and generalisability of these estimates, but this issue is unlikely to affect the derived trajectory groups, predictors and outcomes analysed. As TAHS participants were almost exclusively Caucasian,

generalising findings to other ethnic populations should be done with some caution. We did not have data on impacts on daily life, which may have helped to further confirm the relevance of our spirometry patterns. We observed increased levels of CRP in the restrictive and mixed patterns, but data on blood cell counts were not available in TAHS, which prevented us from teasing out the inflammatory types underlying the lung function patterns. Finally, as we performed comparisons of multiple characteristics across lung patterns, we could not rule out the possibility that a particular significant difference might potentially be due to chance. However, all comparisons were based on a priori hypotheses which conventionally does not require this statistical adjustment (33). Even so, our findings should be confirmed by replication in future longitudinal studies when similar data become available.

Conclusions

We found that the obstructive-only pattern and the mixed pattern which turns out to be even more severe obstruction, identify those who may benefit the most from early COPD interventions. The restrictive-only pattern has evidence of true lung restriction and identifies those at higher risk of multi-morbidity by middle-age. These findings on the longitudinal lung function patterns associated with the highest risk of COPD could be incorporated into clinical algorithms that are designed to identify those at high risk of developing COPD (pre-COPD) – and those with established but as yet undiagnosed COPD. If confirmed by other studies, the development of such clinical algorithms may expedite precision preventive and tailored management strategies. Such approaches can also be used to aggressively target the high prevalence of comorbidities in the longitudinal restrictive lung function pattern. Overall, these findings highlight the untapped opportunities for tackling disease burden that result from tracking early lung function deficits.

Contributors

SCD, EHW, MJA, CJL, DSB, JLP, and JH were responsible for study concept and design. SCD, EHW, GSH, PT, PF, MJA, DPJ, RRW-B and BT were responsible for acquisition of data. DSB, SCD, CJL, JLP, NSI, GSH, GB, AA, RF, AJL, BT, DJ, GRW and CVS were responsible for analysis

and interpretation of data. DSB, SCD, BE, LG and JG-A were responsible for statistical analysis. SCD, DSB, CJL, JLP and EHW were responsible for drafting of the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content and approved the submitted manuscript. SCD, EHW, GSH, PT, and MJA obtained funding. SCD, DSB and JLP had access to raw data and DSB and GB verified the data.

Data sharing

Individual participant data may be provided on request by anyone with a proposal. The proposal will be considered by the TAHS steering committee. Request can be directed to SCD (who is PI of TAHS and corresponding author of this paper). Data for all TAHS participants may be provided.

Declaration of interests

CJL, EHW, AJL, DSB, MJA, JLP and SCD hold an investigator-initiated grant from GlaxoSmithKline for unrelated research. SCD holds an investigator-initiated grant from AstraZeneca for unrelated research. MJA holds investigator-initiated grants from Pfizer, Boehringer Ingelheim, and Sanofi for unrelated research; has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi; and received a speaker's fee from GlaxoSmithKline. AJL has received non-financial support from Primus Pharmaceuticals for unrelated research. All other authors declare no competing interests.

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Figures and tables

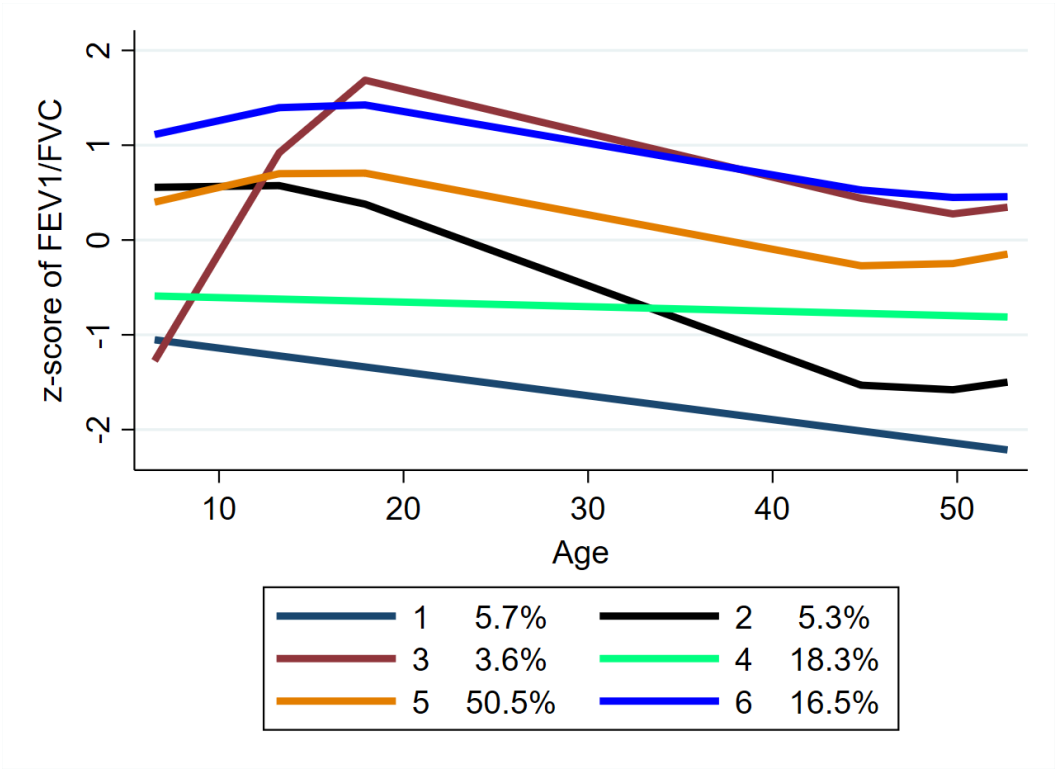

Figure 1a: Lifetime FEV_1/FVC trajectories and prevalence

Line 1 represents "early low- rapid decline", line 2 represents "early normal- rapid decline", line 3 represents "early low-catch up-normal decline", line 4 represents "early low- normal decline", line 5 represents "average (normal)" and line 6 represents "early high-normal decline" trajectories, respectively. Numbers in the box refer to prevalence.

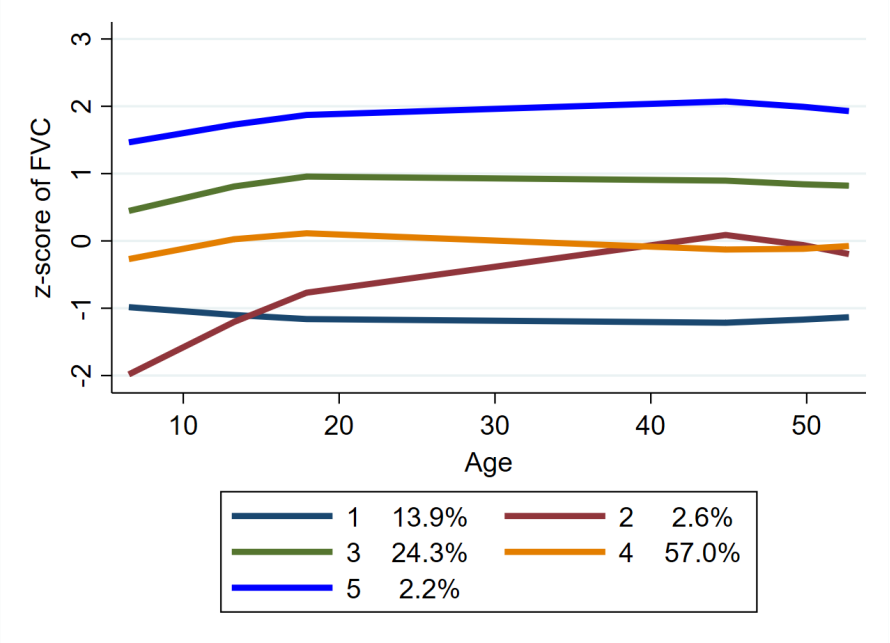

Figure 2b: Lifetime FVC trajectories and prevalence

Line 1 represents “early low-normal decline”, line 2 represents “early low-catch up-normal decline”, line 3 represents “early high-normal decline”, line 4 represents “average (normal)”, line 5 represents “early very high-normal decline (supranormal)”. Numbers in the box refer to prevalence.

FEV_1/FVC trajectories		FVC trajectories				
		LOW	NORMAL OR HIGH			
		Early Low-normal decline	Early low-catch up-normal decline	Early high-normal decline	Early very high-normal decline	Normal
LOW	**Early low-rapid decline**	21 (0·8%)	0	36 (1·5%)	7 (0·3%)	74 (3·0%)
	Early normal- rapid decline	18 (0·7%)	4 (0·2%)	20 (0·8%)	6 (0·3%)	79 (3·3%)
	Early low-normal decline	45 (1·9%)	8 (0·3%)	140 (5·8%)	14 (0·6%)	238 (9·8%)
NORMAL OR HIGH	Early low-catch-up-normal decline	11 (0·4%)	5 (0·2%)	13 (0·5%)	1 (0·1%)	57 (2·3%)
	Normal	169 (6·9%)	27 (1·1%)	306 (12·6%)	23 (1·0%)	698 (28·8%)
	Early high-normal decline	73 (3.1%)	20 (0·8%)	73 (3·0%)	1 (0·1%)	235 (9·7%)

1	Low **FEV_1/FVC -only pattern (Obstructive-only pattern)** Individuals on one of three low **FEV_1/FVC trajectories but NOT on the low FVC trajectory**	626 (25·8%)
2	Low **FVC -only pattern (Restrictive-only pattern)** **Individuals on the low FVC trajectory but NOT on any of the low FEV_1/FVC trajectories**	253 (10·4%)
3	Both low (referred to as **Mixed pattern**) Individuals on BOTH a low **FEV_1/FVC trajectory and the low FVC trajectory**	84 (3·5%)
4	Neither (referred to as the reference pattern) Individuals NEITHER on a low **FEV_1/FVC trajectory NOR on the low FVC trajectory**	1459 (60·2%)

Fig 2. Trajectories of FEV_1/FVC and FVC and their overlap patterns

Table 1. Static lung volumes and gas transfer across lifetime spirometry patterns

	Lifetime spirometry patterns			
	Obstructive-only (n=626)	**Restrictive-only (n=253)**	**Mixed (both) n=(84)**	**Reference (n=1459)**
45 years data				
TLC, z-score, mean (SD)	**0·75 (0·98)*** **	**-0·49(0·58)*** **	**0·04(0·80)*** **	0·43(0·63)
Difference vs Ref, mean (95%CI)	**0·32(0·20,0·44)**	**-0·92(-1·1,-0·73)**	**-0·39(-0·63,-0·15)**	Ref
RV, z-score, mean (SD)	**0·28(0·93)*** **	**-0·37(0·62)** **	**0·35(0·90)*** **	-0·11(0·76)
Difference vs Ref, mean (95%CI)	**0·39(0·26,0·51)**	**-0·25(-0·44,-0·07)**	**0·46(0·20,0·71)**	Ref
FRC, z-score, mean (SD)	**0·36(0·89)*** **	**-0·58(0·67)*** **	0(0·63)	-0·05(0·75)
Difference vs Ref, mean (95%CI)	**0·41(0·29,0·53)**	**-0·53(-0·71,-0·35)**	0·05(-0·19,0·30)	Ref
IC, mL, mean (SD)	3467(895)	**3144(694)***	3164(799)	3380(792)
Difference vs Ref, mean (95%CI)	86(-42,215)	**-236(-417,-55)**	-216(-462,28)	Ref
RV/TLC , z-score	**-0·32(0·58)*** **	**-0·34(0·53)** **	**0·10(0·64)*** **	-0·52(0·57)
Difference vs Ref, mean (95%CI)	**0·20(0·11,0·28)**	**0·18(0·04,0·31)**	**0·61(0·43,0·79)**	Ref
D_LCO, z-score, mean (SD)	0·27(1·1)	**-0·13(0·95)*** **	**-0·12(1·1)** **	0·36(0·99)
Difference vs Ref, mean (95%CI)	-0·09(-0·25,0.07)	**-0·50(-0·75,-0·25)**	**-0·49(-0·82,-0·16)**	Ref
KCO, z-score, mean (SD)	**-0·04(1·1)*** **	**0·70(0·97)*** **	0·34(1·3)	0·30(0·97)
Difference vs Ref, mean (95%CI)	**-0·34(-0·50,-0·18)**	**0·40(0·15,0·64)**	0·04(-0·28,0·37)	Ref
VA, z-score, mean (SD)	**0·50(0·92)*** **	**-0·97(0·74)*** **	**-0·63(0·86)*** **	0·15(0·86)
Difference vs Ref, mean (95%CI)	**0·34(0·21,0·47)**	**-1·1(-1·3,-0·92)**	**-0·79(-1·0,-0·52)**	Ref
53 years data				
D_LCO, z-score, mean (SD)	0·22(1·0)	**-0·31(0·84)*** **	**-0·28(1·2)*** **	0·28(0·84)
Difference vs Ref, mean (95%CI)	-0·06(-0·15,0·02)	**-0·60(-0·73,-0·47)**	**-0·56(-0·78,-0·35)**	Ref
KCO, z-score, mean (SD)	**-0·11(1·1)*** **	**0·71(1·1)*** **	0·33(1·2)	0·31(1·0)
Difference vs Ref, mean (95%CI)	**-0·43(-0·53,-0·32)**	**0·40(0·25,0·55)**	0·02(-0·22,0·26)	Ref
VA, z-score, mean (SD)	**0·37(0·93)*** **	**-1·2(0·78)*** **	**-0·73(0·73)***	-0·06(0·79)
Difference vs Ref, mean (95%CI)	**0·43(0·35,0·51)**	**-1·2(-1·3,-1·1)**	**-0·67(-0·86,-0·48)**	Ref

* p<0·05: **p<0·01; ***p<0·001 compared to the reference group.

a z-score represents the number of standard deviations (SD) from the mean of the external reference population (GLI) used to develop the reference. A negative z-score means that it is lower compared to the mean of the GLI population used to develop the reference. The difference in z-scores between each pattern and the reference pattern shows the difference in lung function between patterns. For example, the difference in RV/TLC between the obstructive only pattern and the reference pattern of 0·2 SD indicates that the obstructive only pattern had more air trapping than the reference pattern.

Table 2. Childhood characteristics of lifetime spirometry patterns (concurrent patterns of low FEV_1/FVC and FVC trajectories)

	Lifetime spirometry patterns			
	Obstructive-only (n=626)	**Restrictive-only (n=253)**	**Mixed (both) (n=84)**	**Reference (n=1459)**
Childhood characteristics (at 7 years)				
Male sex	50.0	**54·5***	55·9	46·3
Ever asthma	**23·9****	**20·2****	**39·3*****	13·4
Allergic asthma	13·4	8·7	27·4	6·3
Non-allergic asthma	10·5	11·5	11·9	7·2
Ever bronchitis	**53·9****	**53·6***	**67·9*****	46·4
Ever pneumonia / pleurisy	**15·6***	**17·2***	**19·3***	11·6
Weight at 7 years				
Underweight	2·4	**7·5****	1·2	3·3
Normal	86·5	84·9	87·7	85·1
Overweight	11·1	7·5	11·1	11·7
Breast feeding				
Breast fed only	41·5	43·7	39·3	43·6
Breast and bottle	33·3	28·2	27·4	32·3
Bottle only	25·2	28·2	**33·3***	24·2
Parental characteristics				
Parental asthma	**22·2****	22·2	**27·7***	17·2
Maternal smoking	36·3	32·8	40·9	31·9
Light/moderate	31·5	25·6	32·5	27·7
Heavy	4·7	6·9	8·4	4·2
Paternal smoking	58·5	61·6	57·3	56·5
Light/moderate	37·4	39·8	39·2	37·5
Heavy	19·8	21·2	17·8	18·1
Low birth weight ł	6·9	6·7	5·6	6·9
Preterm birth ł	14·9	15·3	17·4	14·6
Small for gestation ł	20·1	18·9	27·9	21·9
SES in childhood				
1 (highest)	28·4	22·6	23·1	24·0
2	6·9	8·0	5·1	7·5
3	29·1	29·7	26·9	30·4
4	24·5	22·6	37·2	28·4
5	11·3	17·2	7·7	9·7

* p<0·05: **p<0·01; ***p<0·001 compared to the reference group; Data are in %. ł data were only available for a subsample

Table 3. Adult characteristics of lifetime spirometry patterns (concurrent patterns of low FEV_1/FVC and FVC trajectories)

	Lifetime spirometry patterns			
	Obstructive-only (n=626)	**Restrictive-only (n=253)**	**Mixed (both) n=(84)**	**Reference (n=1459)**
COPD	**21·6****	0·8	**36·9****	0·1
Active asthma at 53 years	**17·6****	**16·3****	**36·9****	5·9
Chronic cough	**26·2***	23·3	**43·4****	21·7
Chronic sputum production	**14·3****	**16·6****	**27·5****	9·2
Shortness of breath at rest in last year	**11·3****	7·5	**18·3****	5·1
Shortness of breath after exercise in last year	**20·3****	**26·1****	**47·6*****	12·2
Wheezing in last year	**26·8****	**26·6****	**54·2****	14·8
Use of medicines for breathing in the prior year	**18·3****	**16·5****	**38·5****	7·7
Chest illnesses in last 3 years	26·7	27·6	**34·1***	22·9
Obesity	**24·2****	**50·2****	34·5	33·2
BMI, kg/m^2, mean (SD)	**27·4(5·1)*****	**31·0(6·6)*****	29·6(6·3)	28·5(5·2)
Smoking status at 53 years				
Never	39·2	48·6	30·1	49·0
Past	36·8	39·8	43·4	39·2
Current	**24·0****	11·6	**26·5****	11·8
Pack-years, median (IQR)	**1·8 (0-20.0)****	0 (0-15.0)	**8·9 (0-30.0)****	0 (0-8·8)
SES				
1 (highest)	33·7	38·5	25·6	36·1
2	13·5	13·8	13·4	15·3
3	33·4	27·9	40·2	33·8
4	7·8	7·3	9·8	7·3
5	11·6	12·6	11·0	7·6
Biomarkers, lung function including static lung volumes				
CC16 at 53 years (N=746), median (IQR)	**5·8 (4·2-8·9)***	6·5 (4·5-9·4)	**5·0 (4·2-6·9)****	7·4 (5·3-9·7)
CC16 at 45 years (N=744), median (IQR)	**5·8 (4·4-7·9)****	6·7 (4·7-8·9)	**4·8 (3·6-6·3)****	6·7 (4·7-8·8)
CRP at 53 years (N=2207), median (IQR)	2·3 (1·0-4·9)	**4·4 (1·8-8·2)*****	**4·2 (2·2-9·5)*****	2·5 (1·2-5·4)
CRP at 45 years (N=796), median (IQR)	2·9 (1·3-5·2)	**5·3 (1·9-8·8)****	**4·9 (1·7-8·2)***	2·6 (1·1-5·6)

Data expressed as percentages unless otherwise specified; * p<0·05: **p<0·01; ***p<0·001 compared to the reference group.

Table 4. Prevalence of comorbidity at 53 years of lifetime spirometry patterns (concurrent patterns of low FEV_1/FVC and FVC trajectories)

	Lifetime spirometry patterns			
	Obstructive-only (n=626)	**Restrictive-only (n=253)**	**Mixed (both) (n=84)**	**Reference (n=1459)**
Doctor-diagnosed Anxiety	17·4	19·4	21·4	17·0
Self-reported mild-severe anxiety (GAD7)	**30·8****	28·4	28·5	23·5
Doctor-diagnosed Depression	23·0	24·5	**33·3****	19·9
Self-reported mild-severe depression (PHQ9)	23·8	19·2	24·0	20·5
Doctor-diagnosed Angina, heart attack, %	1·8	**4·7%***	4·7	2·3
Doctor-diagnosed Coeliac disease	0·5	0	1·2	0·8
Doctor-diagnosed Hypertension	22·2	**33·6****	25·0	23·4
Doctor-diagnosed High cholesterol	22·2	24·9	29·7	21·3
Doctor-diagnosed Diabetes	4·6	**13·4****	9·5	5·6
Doctor-diagnosed Cancer	7·4	7·1	8·3	6·5
Doctor-diagnosed Arthritis	4·6	3·9	7·1	4·1
Doctor-diagnosed TIA or stroke	0·9	0·8	0	0·9
Doctor-diagnosed GERD	11·8	10·7	16·7	11·3
Doctor-diagnosed OSA	4·0	**9·5****	4·8	3·8
Questionnaire-based OSA				
- OSA-risk by Berlin (High/Low)	34·0	**51·3*****	42·8	33·9
- OSA-risk by STOPBANG - Low/High	56·7	**67·1*****	65·4	54·3

* p<0·05: **p<0·01; ***p<0·001 compared to the reference group; Data are in %. GERD: gastroesophageal reflux disease. OSA: obstructive sleep apnea.