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Childhood predictors and adult COPD risk of lung function trajectories: a prospective cohort study from the first to the sixth decade

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Panel: Research in context

Evidence before this study

While there is evidence that accelerated lung function decline is associated with COPD development, the relationship between the full expression of lung function, encompassing an individual's lifetime trajectory capturing both growth and decline, and COPD, has never been reported. We searched for articles in PubMed up to July 28, 2017 using the search terms: "lung function", "growth", "decline", "pattern*" and "trajector*". From 266 identified papers, only two classified lung function trajectories based on more than 2 repeated lung function measurements. However, one was restricted to participants with childhood asthma and both were unable to capture the lung function decline phase due to duration of the follow-up (maximum age at last measurement being 32 years*)*. Additionally, it is critical to understand how child and adult factors interact to determine membership of healthy as well as adverse lifetime trajectories to inform lifetime preventive strategies and promote lung health. Such evidence does not currently exist.

Added value of this study

Our findings of associations between distinct lung function trajectories and risk of *COPD* provide novel insights into the role of lifetime lung function trajectories in the aetiology of COPD, and show the potential for interventions promoting healthy lung function and lessening COPD risk. Our study is the first to model lung function trajectories from childhood to the sixth decade of life in a general

population. We identified six distinct trajectories. Three trajectories exhibiting lower lung function in childhood with subsequent normal or accelerated decline had increased the risk of COPD, and collectively accounted for most COPD cases. Most importantly, moderate/severe COPD cases (GOLD stage 2 or more) arose only from these three trajectories. Early life factors including allergic diseases, lung infections, parental asthma and maternal smoking predicted three unfavourable lung function trajectories. Personal smoking amplified the effect of maternal smoking on belonging to the worst lung function trajectory.

Implications of all the available evidence

Reducing maternal smoke exposure and personal smoking, and encouraging immunization, are identified as public health targets to prevent adverse lung function trajectories and reduce future COPD burden. Clinicians and patients with asthma should be made aware of the potential long-term implications of non-optimal asthma control throughout life, and this should be investigated in future intervention trials.

SUMMARY

Background

Lifetime lung function is related to quality of life and longevity. Over the lifespan, individuals follow different lung function trajectories. It is important to identify these trajectories, their determinants and outcomes but no study has done this beyond the fourth decade.

Methods

We modelled trajectories of forced expiratory volume in 1 second (FEV_1) measured at 7, 13, 18, 45, 50 and 53 years (n=2438). The trajectories identified were then related to childhood factors and Chronic Obstructive Pulmonary Disease (COPD) risk.

Findings

Six trajectories were identified: “early below average, accelerated decline” (4%, n=97), “persistently low” (5·6%, n=136), “below average” (31·6%, n=772), “persistently high” (12·1%, n=293), “early low, accelerated growth, normal decline” (8%, n=196), and “average” (38·7%, n=944). The first three trajectories had increased risk of COPD at age 53 compared with the average group: OR 35(95%CI 19·5-64); 9·5(4·5-20·6); and 3·7(1·9-6·9) respectively. Early-life predictors of the three trajectories included childhood asthma, bronchitis, pneumonia, hayfever, eczema, parental asthma, and maternal smoking. Personal smoking and active adult asthma increased the impact of maternal smoking and childhood asthma respectively on the “early below average, accelerated decline” trajectory.

Interpretation

We identified six potential FEV_1 trajectories, two of which were novel. Three trajectories contributed 75% of COPD burden and were associated with modifiable early-life exposures whose impact was aggravated by adult factors. We postulate that reducing maternal smoking; encouraging immunization; and avoiding personal smoking, especially in those

with smoking parents and/or low childhood lung function, may minimize COPD risk. Clinicians and asthmatic patients should be made aware of the potential long-term implications of non-optimal asthma control for lung function trajectory throughout life, and this should be investigated in future intervention trials.

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INTRODUCTION

Lifetime lung function is related to quality of life and longevity. Recent studies highlight that low lung function, especially low forced expiratory volume in 1 second (FEV_1) in early adulthood is associated with incidence of respiratory, cardiovascular, and metabolic abnormalities, and all-cause mortality.[1,2] Over the lifespan, lung function progresses though different growth and decline phases[3,4] and individuals have unique lifetime lung function trajectories based on these phases. Trajectories may have different risk factors and different consequences for chronic lung disease risk, particularly chronic obstructive pulmonary disease (COPD), the expected third largest cause of death globally by 2030.[5] Insights into how lung function trajectories develop over the lifespan are important for lung disease prediction, prevention and management.

Repeated lung function measurements from childhood into late adulthood are needed to identify lifetime lung function trajectories but data are sparse. Among the few studies with longitudinal lung function measurements, only two studies[6,7] have published lung function trajectories based on more than two time points, one being restricted to subjects with childhood asthma.[7] However, both were unable to capture the decline phase, vital for lung health outcomes in later life, as they had data only to the fourth decade. While there is evidence that both maximally attained FEV_1 and its decline are associated with the COPD development [8], the relationship between the full expression of lung function, encompassing an individual's trajectory capturing both growth and decline, and COPD, has never been reported. Furthermore, it is critical to understand how childhood and adult factors interact to determine membership of healthy as well as adverse lifetime trajectories.

Despite inter-individual variation in lung function trajectories within a general population, there may be distinct subpopulations following similar FEV_1 trajectories. The Tasmanian Longitudinal Health Study (TAHS), a population-based cohort study with multiple assessments of lung function, provided an opportunity to investigate lung function trajectories into the sixth decade. We aimed to: (1) characterize population FEV_1trajectories from the first to the sixth decade; (2) investigate their

childhood predictors and interaction with adult asthma and personal smoking; (3) relate trajectories to COPD risk.

METHODS

Study design and data collection

Six waves of TAHS[9] were used. TAHS began in 1968 when 8,583 Tasmanian children born in 1961 and attending school in Tasmania were enrolled. At age 7 (baseline), the children underwent a clinical examination including pre-bronchodilator (BD) spirometry and parents completed a questionnaire. Follow-up assessments were conducted at 13, 18, 45 and 50 years with pre-BD spirometry measured. In the most recent follow-up in 2015, when the participants were 53 years old, all those from the original cohort who were alive and had up-to-date contact details were invited to attend a clinical study. Pre- and post-BD spirometry were performed in 2,689 participants. Those with at least two waves of lung function data at age 7 and 53 comprised the study population (n=2438) (see supplement).

Lung function measurements

Pre- and post-BD spirometry was conducted according to the American Thoracic Society and European Respiratory Society joint guidelines.[10] Spirometry z-scores were derived from the Global Lung Initiative (GLI) reference equations[11] which have been validated in an Australian population.[12]

Definition of variables (see supplement)

Childhood factors (asthma, bronchitis, eczema, hayfever, food allergy, pneumonia, breast feeding, weight status, parental asthma and parental smoking) were defined using the information provided by parents in 1968. COPD was defined as post-BD FEV_1/FVC<Lower Limit of Normal (LLN) at 53 years. Other adulthood factors were defined using information provided by participants at age 53 years.

Statistical analysis

Identification of lung function trajectories

Pre-BD FEV_1 z-scores at six time points (7, 13, 18, 45, 50 and 53 years) were analysed using group-based trajectory modelling (GBTM) to identify distinct subgroups of individuals whose measurements followed a similar pattern over time.[13] GBTM estimated the population prevalence of each lung function trajectory subgroup, and the posterior probability of each individual belonging to each subgroup. Parameter values determining models with an increasing number of trajectories were derived using maximum likelihood estimation to determine the best fitting model (see Supplement).[14,15] This method allows handling of missing data for each individual, and produces asymptotically unbiased parameter estimates. As well as model fit, interpretation of trajectories was also considered in the selection of the final model. Assignment of a single trajectory subgroup to each individual was based on the modal method (the highest posterior probability for that individual).

Investigating factors associated with identified lung function trajectories

We first examined the association between each childhood predictor and the six-category trajectory variable using multinomial logistic regression. Childhood predictors were retained based on a 5 degree-of-freedom likelihood ratio test. Then we employed two modelling approaches in parallel: In the first, we used logistic regression to investigate associations between each childhood predictor and lung function trajectories, where each trajectory was compared with the "average" trajectory - the "non-disease" group. For each childhood predictor, a specific minimal sufficient set of potential confounders was selected based on causal diagrams (Directed Acyclic Graphs [DAGs]).[16] Interactions between parental and personal smoking, childhood asthma and adult active asthma were tested. Using the likelihood ratio test, an interaction term with p-value < 0.1 was retained in the final model. For comparison, we used a second approach in which all childhood predictors with a p-value < 0.15, computed using likelihood ratio test, were included in a single multivariable multinomial logistic regression model adjusted simultaneously for all childhood predictors. The results of these two approaches were almost similar, thus only results for the first were presented. Associations between

lung function trajectories as a predictor and COPD at 53 years were investigated using logistic regression; in case of groups with sparse data (for COPD cases), penalized maximum likelihood logistic regression was used to reduce bias in estimates of regression coefficients.[17] Population-attributable fractions of COPD were estimated for trajectories.[18] All analyses were performed using Stata 13.0 (Stata Corp, College Station, TX, USA) with a GBTM plug-in.[15]

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 sponsor 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 8583 participants from the original cohort, 2438 with longitudinal lung function data were analysed. The participants included had similar baseline characteristics to those not included except for more females and more eczema, and fewer smoking parents (Table S1 in supplement). Those included and those deceased by 53 years also had similar baseline characteristics (Table S2).

Lung function trajectories

The best fitting model identified six lung function trajectories (Figure 1). The average membership probability of individuals in each trajectory exceeded 0·7, suggesting good model adequacy.[19] Based on lung function at age 7 years and growth and decline rates, trajectories were given the following labels: “average” (38·7%; n=944), “early below average, accelerated decline” (4%; n=97), “persistently

low" (5·6%; n=136), "early low, accelerated growth, normal decline" (8·0%; n=196), "persistently high" (12·0%; n=293), and "below average" (31·6%; n=772) (see supplement). The "average" trajectory had lung function consistently around the population mean over time. The means of the raw values of FEV_1 at six time points among trajectories are presented in Figure S1. In a sensitivity analysis, exclusion of the data point with the smallest number of observations (at 18 years) yielded six very similar lung function trajectories (Figure S2).

Childhood factors and lung function trajectories

Prevalence of childhood factors among lung function trajectories are shown in Table 1. Adjusted associations between these factors and lung function trajectories compared to the average trajectory are presented (Table 2). Individuals with the "early below average, accelerated decline" trajectory were more likely to have childhood asthma (OR 3·1: 95%CI 1·9-5·2), bronchitis (2·0: 1·2-3·2), hayfever (2·0: 1·2-3·4), pneumonia (2·0: 1·2-3·5), and a heavy smoking mother (2·5: 1·1-5·9).

The "persistently low" trajectory was associated with childhood asthma (OR 1·7: 95%CI 1·2-2·7), particularly frequent asthma symptoms (4·2: 2·2-7·8) and early asthma onset (2·0:1·1-3·4), eczema (1·8: 1·1-3·0), and parental asthma (1·8: 1·1-2·9). A modest association was seen between this trajectory and food allergy (1·8: 0·94-3·4), and childhood underweight (2·2:0·95-5·2). There were synergistic effects between childhood asthma and eczema (p=0·07) and hayfever (p=0·06). Participants with childhood asthma, eczema and hayfever had a 4·9 (1·9-12) fold risk increase for the "persistently low" trajectory.

Having the "below average" trajectory was associated with childhood pneumonia (OR 1·3: 95%CI 1·0-1·8). The effects of the childhood factors on the three trajectories listed above were independent of adult personal smoking.

Females and underweight children were more likely to have an "early low, accelerated growth, normal decline" trajectory (OR 1·7: 95%CI 1·2-2·3 and 2·6:1·3-5·2, respectively). The effect of

underweight on this trajectory became non-significant when weight gain between 7-11 years was added to the model (OR 2·0:0·9-4·5).

No significant associations were observed between childhood factors and the "persistently high" trajectory.

The interactions of adult asthma and smoking with childhood factors, and lung function trajectories

The prevalences of adult active asthma and personal smoking are presented in Table 3. Adult active asthma and personal smoking were independently associated with three trajectories: "early below average, accelerated decline", "below average" and "persistently low" (Table S3).

We observed a significant interaction between heavy maternal smoking and personal smoking defined using pack-years ($p<0·001$) for the risk of belonging to the "early below average, accelerated decline" trajectory. The adverse impact of maternal smoking increased with increasing personal smoking (Figure S3).

There was evidence of interaction between childhood asthma and adult active asthma for the risk of the "early below average, accelerated decline" trajectory ($p=0·08$) with the effect of childhood asthma mainly evident in participants with adult active asthma.

Lung function trajectories (based on pre-BD FEV1) and COPD (based on post-BD measures) at 53 years

At 53 years, those in the "early below average, accelerated decline" trajectory had the highest prevalence of COPD (46%), followed by the "persistently low" trajectory (12·5%) and the "below average" trajectory (6%) (Figure 2). Compared with the "average" trajectory, these three trajectories had 35 (95%CI 19·5-64), 9·5 (4·5-20·6), and 3·7 (1·9-6·9) fold increased risk of COPD respectively (Table S4). The distribution of COPD cases among trajectories is presented in Figure S4. The

population-attributable fractions for the three trajectories “early below average, accelerated decline”, “persistently low”, and “below average” in relation to COPD were 35·4%, 12·6% and 27·2%, respectively. For moderate/severe COPD (an addition of FEV_1<80% predicted values), all cases only arose from three trajectories, “early below average, accelerated decline”, “below average” and “persistently low”.

We replicated the analysis by defining COPD using the FEV_1/FVC <0.7 and findings were not materially different to those using LLN (table S5). We found similar results using a clinical definition of COPD (see supplement) (Table S6).

DISCUSSION

Our study is unique in that it is the first to characterize lung function trajectories in a large general population sample from early childhood to the sixth decade. This is of considerable importance because understanding lifetime lung function is crucial for population-based interventions to promote advantaged trajectories and prevent disadvantaged ones. We identified six distinct FEV_1 trajectories including two novel trajectories, namely, “early below average, accelerated decline” and “early low, accelerated growth, normal decline”. These two trajectories contradict the notion that lung function established in childhood tracks through life. Three of the six trajectories had increased risk of developing COPD by middle-age, namely, “early below average, accelerated decline”, “below average”, and “persistently low”. Seventy-five percentof COPD cases at 53 years was attributable to these three trajectories. Most importantly, moderate/severe COPD cases arose only from these three trajectories. Childhood asthma, bronchitis, pneumonia, hayfever, eczema, parental asthma and maternal smoking during childhood increased the risk of these three trajectories. We showed that aggravation of the impact of childhood risk factors by adult personal smoking and active asthma lead to our newly established “early below average, accelerated decline” trajectory.

To date only two published studies[6,7] have identified lung function trajectories. Both were unable to incorporate the adult decline phase, as they had data only into early adulthood. McGeachie and

colleagues[7] described four FEV_1 trajectories from age 7 to 26 years in 684 asthmatics. This study provided novel insights into how lung function changed over time in asthmatics, but cannot be compared with our population-based results. Furthermore, we used an unsupervised modelling method, which facilitates capture of distinct groups with similar trajectories. The population-based Tucson Children's Respiratory Study[6] modelled lung function from 11 to 32 years in 599 participants identifying only a persistently low and a normal trajectory. The reasons they identified fewer trajectories than our analysis may include smaller sample size and shorter follow-up.

Using similar statistical methodology to ours, a study from two population-based birth cohorts (MAAS and ALSPAC) published in this issue of the journal, found four FEV_1trajectories between ages 5 and 24 years (persistently high, average, below average and persistently low).[20] We also found these trajectories, and identified two further trajectories. Our study's ability to tease out more trajectories may be explained by our larger sample size and follow-up into the decline phase.

COPD risk attributed to our identified trajectories provides insight into potential origins of and pathways to COPD. The "below average" and "persistently low" trajectories representing a pathway to COPD with mostly childhood origins contributed half the COPD cases in our study. This was supported by Lange and colleagues[8] who found half of their participants with COPD had normal adult lung function decline, but lower baseline lung function in early adulthood. Yet our "early below average, accelerated decline" group carried the highest risk of COPD, and although representing only 4% of our study sample, contributed substantially to COPD cases (a population-attributable fraction of 35·4%). These findings highlight the importance of preventing both early life adverse exposures that may lead to poorer lung growth and adult risk factors contributing to accelerated decline.[21-23]

We believe we are the first to establish the early life factors determining FEV_1 trajectories into the sixth decade. Previous studies have investigated early life factors only on single phases of lung function trajectories i.e. impaired growth[24-29] or accelerated decline.[30-32] Maternal smoking, allergic diseases, and pneumonia increased the risk of the "early below average, accelerated decline"

trajectory. Interestingly, personal smoking and adult asthma modified the effect of maternal smoking and childhood asthma on being in the "early below average, accelerated decline" trajectory. A similar interaction related to smoking had been identified in other studies examining lung function deficits[33,34] and decline.[32] Together, these findings suggest that maternal smoking not only adversely affected early lung function, but predisposed children to more rapid lung function decline if they later smoked. Expressed another way, personal smoking not only accelerated FEV_1 decline but also amplified the impact of early life exposure to tobacco smoke on lung function, possibly by preventing recovery from early acquired deficits.[35] Similarly, our findings highlight the potential role of lifelong asthma control in promoting lung health and preventing COPD.

Our "persistently low" trajectory was associated with asthma, eczema, food allergy, parental asthma and childhood underweight. Additionally, asthma in combination with either eczema or hayfever had a multiplicative rather than additive effect on the risk of following this trajectory. Consistent with our findings, the MAAS and ALSPAC study (published in this issue of the journal) found that the "persistently low" trajectory was associated with asthma/wheeze and allergic sensitization.[20] Similarly, Lodrup Carlsen and colleagues reported a persistently impaired lung function pattern from birth to 16 years in asthma with eczema and hayfever.[36] These findings suggest that arresting the atopic march, believed to drive these early allergic comorbidities, may help prevent subsequent adverse lung function and COPD. In addition, the association between parental asthma and the "persistently low" trajectory in our study suggests a role for genetic factors as evident in the MAAS and ALSPAC study.[17]

We found that those with early low lung function tracked as either "persistently low" or "early low, accelerated growth, normal decline". This split of the early low lung function group is supported by the Perth Infant Asthma Follow-up study (PIAF) published in this issue of the journal.[17] While some infants with poor lung function in the PIAF continued in the low FEV_1 trajectory, the majority had improvement in their lung function through adolescence and moved to the normal or above average FEV_1 trajectories. Our "early low, accelerated growth, normal decline" trajectory may be related to

birth weight, given weight "catch-up" was reported in children with low birth weight and those with catch-up growth showed improved lung function.[37] We did not have full birth weight information to explore this effect. However, we found that childhood underweight predicted the "early low, accelerated growth, normal decline" and the "persistently low" trajectories. Interestingly, unlike the "persistently low" trajectory, the association between childhood underweight and "early low, accelerated growth, normal decline" trajectory became non-significant when controlled for weight gain between 7 and 11 years. This suggests that childhood underweight followed by accelerated weight gain may be related to accelerated lung growth in this group. Another difference between these trajectories was that the "persistently low" trajectory had more than double the prevalence of persistent childhood asthma. It is possible that while the two trajectories had similar early acquired lung function deficits, persistent asthma prevented the catch-up in the "persistently low" trajectory.

Early below average and accelerated decline" trajectory had the highest prevalence and intensity of smoking. Thus, this trajectory resembles the lung function pattern among "susceptible smokers" as originally framed by Fletcher and Peto.[3] While the "below average" group had similar lung function to the "early below average, accelerated decline" group up to age 20 years, it had much lower rates of personal smoking, which may have prevented an accelerated decline in lung function. In contrast, the prevalence and intensity of smoking were extremely low in the three best trajectories i.e. "persistently high", "early low, accelerated growth, normal decline", and "average". These are likely to reflect the lung function trajectories in non-smokers.

Evidence of a link between low lung function in early adulthood and prevalence and incidence of respiratory, cardiovascular, and metabolic abnormalities, and all-cause mortality has been recently reported.[1,2] Our findings also support some of these associations. In addition to the significantly higher prevalence of respiratory conditions (table 3), the three unfavourable lung function trajectories had higher prevalences of diabetes and obstructive sleep apnoea, compared with the average trajectory (table S7). Higher prevalences of hypertension and heart attack/myocardial infarction were also seen for the "below average" and "persistently low" trajectories. Together, our

findings and others highlight the significant burden of comorbidity associated with low lung function, and indicate the importance of early identification of this high-risk group.

Identification of lifetime lung function trajectories in a general population, their determinants and consequences, has been a fundamental but challenging question for respiratory experts for decades. An ideal longitudinal study with a large sample size, multiple waves of lung function measurement spanning from early life through old age, and with perfect follow-up would fully explore this question, but the ideal study does not exist. Most current longitudinal studies have a limited sample sizes with limited repeated lung function measurements. To date, with its population-based design, large sample size and long follow-up period, TAHS provides the best existing data with which to answer this question. Over six decades, we have lung function measurements from childhood to middle age which enable good classification of trajectories over these periods. We acknowledge that not having sufficient lung function data around age 18 years is a key weakness which may mean that we have missed trajectory transitions around peak lung function. However, the lack of sufficient data at this peak lung function period would be unlikely to significantly affect trajectories in childhood and middle age. In a sensitivity analysis, when the data point at 18 years was excluded, we still identified six similar lung function trajectories. We encourage researchers to develop long term studies of large birth cohorts with repeated lung function from infancy to old age to replicate our findings and provide a more comprehensive picture of lung function over the entire life course. However, given logistic difficulties, results from such studies would not be available for decades.

Besides the uniqueness of our data, the use of GBTM was a strength. This data driven technique enabled us to explore potential unknown lung function trajectories which were not based on any a priori hypotheses. Most of the identified trajectories were similar to those found in other cohorts (Tucson, MAAS and ALSPAC). Moreover, the identified shapes and associations between risk factors and trajectories further support their biological plausibility.

A limitation of this study is that GLI equations were not available in 1968 and equipment changed over time. This could lead to an imperfect fit of GLI equations at different times, but this would have little effect on the relative positions between trajectories. Of note, the last measurement in our study is at an age when the burden of COPD is just starting to emerge as most patients with COPD are diagnosed in their sixties. The effect of adverse lung function trajectories on COPD risk may become clearer in future follow-ups of this study when COPD prevalence will be higher.

To identify trajectories from early life to the sixth decade, the analysis was restricted to those who were alive and continuing to participate in the study at age 53; hence there is a high attrition rate. Importantly however, the death rate for TAHS participants by age 53, was small (4.7%) and consistent with Australian population statistics.[38] Most importantly, comparisons of childhood lung function and characteristics between participants and: those deceased and; non-participants showed minimal differences. If attrition was differential across trajectories, it would influence the lung function trajectory prevalence estimates and generalisability of these estimates however this issue is unlikely to affect the patterns or the associations between these trajectories and the predictors/outcomes observed.

Diagnosis of childhood asthma is difficult, and there is conceptual ambiguity concerning the exact nature of asthma, which is likely to be an umbrella term for a range of conditions. Children with abnormal lung development may present with asthma-like symptoms, while airway inflammation associated with asthma may lead to reduced lung function. The possibility of these bidirectional associations between poor lung development and childhood asthma has been raised[39], but it remains unclear which occurs first. Future cohort studies with lung function measured at birth and close follow-up for asthma diagnosis may help elucidate this issue."

Our findings have clinical and public health implications. Visual presentations of lung function trajectory scenarios may be useful in educational programs on the dangers of smoking. Routine spirometry measurements in school students to identify those with low lung function may help early

identification of high risk groups for whom early interventions such as avoidance of smoking and hazardous occupational exposures can be implemented. Although not directly tested, our findings raise the possibility that reducing maternal smoke exposure; encouraging immunization; and avoiding personal smoking, especially for those with smoking parents and those with low childhood lung function; would promote healthy lung function trajectories and lessen COPD risk. Clinicians and patients with asthma should be made aware of the potential long-term implications of non-optimal asthma control throughout life, and these should be investigated in future intervention trials.

CONCLUSION

This world-first characterization of lung function change from the first to the sixth decade revealed six distinct trajectories which may represent population patterns. In our model, most COPD, especially when more severe, was attributable to three trajectories exhibiting lower lung function in childhood with either subsequent normal or accelerated decline. Our findings suggest that early life factors including allergic diseases, lung infections, parental asthma and maternal smoking influence the three unfavourable lung function trajectories. Personal smoking may amplify the effect of maternal smoking and adult asthma may amplify the effect of childhood asthma to determine membership of the worst lung function trajectory.

Authors' contributions

Study concept and design: S.C.D., E.H.W., G.G.G; M.J.A. Acquisition of data: S.C.D., E.H.W., M.C.M; J.A.B, P.S.T, S.M, Analysis and interpretation of data: D.S.B., S.C.D., J.A.B, M.C.M. Drafting of the manuscript: D.S.B., S.C.D., J.A.B., M.C.M. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: D.S.B, S.C.D., J.A.B. Obtained funding: S.C.D., E.H.W., M.J.A, S.M.

Conflicts of interest

Authors have no conflicts of interest

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454

455 **Figure legends**

456 **Figure 1.** Trajectories of lung function (FEV_1 z-score) from 7 to 53 years of age. The six trajectories

457 represent the latent growth patterns of lung function.

458 **Figure 2.** Prevalence of COPD among six lung function trajectories at 53 years (%).

Table 1: Childhood characteristics of participants according to lung function trajectories from 1st to 6th decade (% (n))

	Lung function trajectory groups					
	Early below average, accelerated decline	**Persistently low**	**Early low, accelerated growth, normal decline**	**Persistently high**	**Below average**	**Average**
	(n=97)	**(n=136)**	**(n=196)**	**(n=293)**	**(n=772)**	**(n=944)**
Childhood characteristics (at 7 years)						
Male sex	52/97 (53%)	72/136 (53%)	73/196 (37%)*	126/293 (43%)	392/772 (51%)	465/944 (49%)
Ever asthma	36/97 (37%)*	38/135 (28%)*	32/196 (16%)	48/291 (16%)	137/766 (18%)	137/940 (14%)
Asthma phenotype						
Transient	3/96 (3·1%)	8/133 (6%)	8/193 (4·2%)	16/287 (5·6%)	36/758 (4·8%)	39/935 (4·2%)
Late onset	11/96 (11·5%)	7/133 (5·3%)	7/193 (3·6%)	12/287 (4·2%)	43/758 (5·8%)	43/935 (4·6%)
Persistent	21/96 (22%)	21/133 (15·8%)	14/193 (7·3%)	16/287 (5·6%)	50/758 (6·6%)	50/935 (5·4%)
Ever bronchitis	68/97 (70%)*	75/135 (55%)	97/196 (49%)	132/291 (45%)	386/765 (50%)	449/942 (47%)
Ever eczema	18 (18)*	27/123 (20%)*	24/195 (12%)	28/291 (10%)	75/765 (10%)	98/937 (10%)

Ever hay fever	26/94 (28%*	18/134 (13%)	28/194 (14%)	32/287 (11%)	106/763 (14%)	117/932 (13%)
Ever food allergy	11/96 (11%)	17/134 (13%)*	14/196 (7%)	21/291 (7%)	55/762 (7 %)	60/940 (6%)
Ever pneumonia/pleurisy	21/96 (22%)*	19/134 (14%)	18/196 (9%)	29/287 (10%)	120/760 (16%)*	116/931 (12%)
Weight status at 7 years						
Underweight	3/95 (3%)	7/134 (5%)	13/196 (7%)*	5/290 (2%)	30/766 (4%)	25/937 (3%)
Normal	77/95 (81%)	116/134 (87%)	165/196 (84%)	241/290 (83%)	665/766 (87%)	803/937 (85%)
Overweight	15/95 (16%)	11/134 (8%)	18/196 (9%)	44/290 (15%)	71/766 (9%)	109/937 (12%)
Breast feeding						
Breast fed only	36/97 (37%)	56/134 (42%)	73/195 (37%)	136/290 (47%)	309/763 (41%)	427/941 (45%)
Breast and bottle	32/97 (33%)	36/136 (27%)	66/195 (34%)	95/290 (33%)	248/763 (33%)	293/941 (31%)
Socio-economic status						
1st (highest)	18/94 (19·2%)	28/123 (22·8%)	45/182 (24·7%)	74/278 (26·6%)	185/732 (25·3%)	226/908 (24·9%)
2nd	7/94 (7·5%)	14/123 (11·4%)	11/182 (6%)	17/278 (6·1%)	47/732 (6·4%)	73/908 (8%)
3rd	32/94 (34%)	34/123 (27·6%)	53/182 (29·1%)	80/278 (28·8%)	210/732 (29·9%)	276/908 (30·4%)

4th	29/94 (30·8%)	30/123 (24·4%)	53/182 (29·1%)	78/278 (28%)	190/732 (26%)	248/908 (27·3%)
5th	8/94 (8·5%)	17/123 (13·8%)	20/282 (11%)	29/278 (10·4%)	91/732 (12·4%)	85/908 (9·4%)
Parental characteristics						
Parental asthma	19/94 (20%)	37/131 (28%)*	30/189 (16%)	58/283 (21%)	155/740 (21%)	156/915 (17%)
Maternal smoking						
Light/moderate smoking	34/94 (36%)*	38/131 (29%)	51/189 (27%)	67/282 (24%)	226/740 (30%)	255/913 (28%)
Heavy smoking	9/94 (10%)*	7/131 (5%)	7/189 (4%)	15/282 (5%)	37/740 (5%)	36/913 (4%)
Paternal smoking						
Light/moderate smoking	37/90 (41%)	58/127 (46%)	62/174 (36%)	110/270 (41%)	269/697 (39%)	304/867 (35%)
Heavy smoking	20/90 (22%)	19/127 (15%)	35/174 (20%)	48/270 (18%)	135/697 (19%)	162/867 (19%)
FEV_1 at 7 years, mean (±SD)						
z-score	-0·23 (±0·64)*	-1·66 (±0·6)*	-1·57(±0·57)*	1·15 (±0·7)*	-0·33 (±0·62)*	0·31 (±0·6)
% predicted	97 (±8)*	79 (±8)*	80·2 (±7)*	114 (±9·3)*	96 (±8)*	104 (±8)

FEV_1/FVC at 7 years, mean (±SD) (%)	88·4 (±0·1)	87·7 (±0·1)	87·3 (±0·1)	92·6 (±0·1)	90·7 (±0·1)	92 (±0·1)

** significant difference from the "average" trajectory (p<0.05)*

Table 2: Associations between childhood clinical factors and each of lung function trajectories compared to the "average" trajectory

	Lung function trajectory groups - OR (95%CI)				
	Early below average, accelerated decline	**Persistently low**	**Early low, accelerated growth, normal decline**	**Persistently high**	**Below average**
Asthma†	3·1 (1·9;5·2)**	1·7 (1·1;2·7)*	1·1 (0·7;1·8)	1·2 (0·8;1·8)	1·1 (0·8;1·5)
Frequent asthma at 7 years †					
Never asthma	1	1	1	1	1
Infrequent	2·7 (1·5;4·9)**	0·9 (0·5;1·8)	0·9 (0·5;1·6)	1·1 (0·7;1·8)	0·9 (0·6;1·3)
Frequent	4·4 (2·1;9·1)***	4·1 (2·2;7·8)***	1·7 (0·8;3·5)	1·3 (0·7;2·5)	1·4 (0·9;2·2)
Asthma onset †					
Never asthma	1	1	1	1	1
<3 years	3·1 (1·7;5·5)***	2·0 (1·1;3·4)*	1·1 (0·6;2·0)	1·3 (0·8;2·0)	1·1 (0·8;1·5)

≥3 years	3·2 (1·4;7·0)**	1·2 (0·5;2·9)	1·0 (0·4,2·3)	0·8 (0·4;1·8)	1·0 (0·6;1·7)
Bronchitis‡	2·0 (1·2;3·2)**	1·1 (0·7;1·6)	1·1 (0·7;1·4)	0·9 (0·7;1·2)	1·1 (0·9;1·3)
Frequent bronchitis at 7 years †					
Never bronchitis	1	1	1	1	1
Infrequent	1·9 (1·1;3·1)*	1·1 (0·7;1·6)	1·0 (0·7;1·3)	0·9 (0·7;1·2)	1·0 (0·8;1·3)
Frequent	2·5 (1·3;4·8)**	1·2 (0·6;2·2)	1·2 (0·7;2·1)	0·9 (0·6;1·5)	1·3 (0·9;1·8)
Pneumonia/pleurisy ł	2·0 (1·2;3·5)**	1·1 (0·6;1·9)	0·6 (0·4;1·1)	0·8 (0·5;1·3)	1·3 (1·0;1·8)*
Eczema ‖	1·3 (0·7;2·3)	1·8 (1·1;3·0)*	1·3 (0·8;2·3)	1·1 (0·6;1·6)	0·9 (0·6;1·3)
Hay fever ‖	2·0 (1·2;3·4)**	0·9 (0·5;1·6)	1·4 (0·8;2·2)	0·7 (0·5;1·1)	1·0 (0·8;1·4)
Food allergy ‖	1·5 (0·7;3·1)	1·8 (0·94;3·4)	1·2 (0·6;2·3)	1·3 (0·8;2·2)	1·2 (0·8;1·8)
Parental asthma ¶	1·2 (0·7;2·1)	1·8 (1·1;2·9)*	0·9 (0·5;1·4)	1·4 (0·9;2·0)	1·2 (0·9;1·6)
Maternal smoking §					
Light/moderate smoking	1·3 (0·8;2·2)	1·0 (0·7;1·6)	0·8 (0·5;1·2)	0·7 (0·5;1·0)	1·0 (0·8;1·2)
Heavy smoking	2·5 (1·1;5·9)*	1·7 (0·7;4·0)	1·0 (0·4;2·4)	1·5 (0·8;2·9)	1·3 (0·8;2·2)
Paternal smoking §					

Light/moderate smoking	1·3 (0·7;2·1)	1·6 (0·9;2·5)	1·0 (0·7;1·5)	1.4 (0·9;1·9)	1·2 (0·9;1·5)
Heavy smoking	1·2 (0·6;2·1)	1·0 (0·6;1·8)	1·0 (0·6;1·6)	1·1 (0·7;1·6)	1·1 (0·8;1·5)
Breast feeding Δ					
Bottle only	1	1	1	1	1
Breast only	0·7 (0·4;1·2)	0·7 (0·5;1·1)	0·7 (0·5;1·1)	1·1 (0·7;1·5)	0·8 (0·6;1·0)
Bottle & breast	0·9 (0·5;1·6)	0·7 (0·4;1·1)	0·9 (0·6;1·4)	1·1 (0·8;1·7)	0·9 (0·7;1·2)
Weight status at 7 years √					
Underweight	1·3 (0·4;4·2)	2·2 (0·95;5·2)	2·6 (1·3;5·2)**	0·7 (0·3;1·8)	1·5 (0·8;2·5)
Overweight	1·6 (0·9;2·8)	0·6 (0·3;1·2)	0·8 (0·5;1·4)	1·3 (0·9;2·0)	0·8 (0·6;1·1)
Sex					
Female	0·8 (0·5;1·2)	0·8 (0·6;1·2)	1·7 (1·2;2·3)*	1·2 (0·9;1·5)	0·9 (0·8;1·1)

*P<0·05; ** p<0·001; *** p<0·001

†For asthma, model adjusted for parental asthma, childhood pneumonia/pleurisy, infantile eczema, parental smoking, sex, breast feeding and childhood SES.

‡For bronchitis, model adjusted for childhood asthma, childhood pneumonia/pleurisy, infantile eczema, parental smoking and childhood SES.

ŧ For pneumonia/pleurisy, model adjusted for breast feeding and childhood SES.

‖For eczema, hay fever and food allergy, models adjusted for childhood asthma, parental asthma, parental smoking, sex and childhood SES.

¶ For parental asthma, models adjusted for sex, parental smoking and childhood SES.

§ For parental smoking, models adjusted for parental asthma, childhood asthma and childhood SES.

Δ For breast feeding, model adjusted for parental asthma, parental smoking and childhood SES.

√ For childhood weight status, model adjusted for childhood pneumonia/pleurisy, sex, breast feeding and childhood SES.

Table 3: Clinical characteristics at 53 years according to lung function trajectories from 1st to 6th decade

Characteristics	Lung function trajectory groups					
	Early below average, accelerated decline	Persistently low	Early low, accelerated growth, normal decline	Persistently high	Below average	Average
	(n=97)	(n=136)	(n=196)	(n=293)	(n=772)	(n=944)
COPD	44/95 (46%)*	17/136 (12·5%)*	1/194 (0·5%)	1/289 (0·4%)	44/765 (6%)*	12/936 (1·3%)
Active asthma at 53 years	56/97 (58%)*	53/135 (39%)*	35/196 (18%)	41/291 (14%)	179/771 (23%)*	153/944 (16%)
Atopic asthma	28/97 (29%)	21/135 (15·6%)	18/196 (9·2%)	12/291 (4%)	77/771 (10%)	69/944 (7·3%)
Non-atopic asthma	28/97 (29%)	32/135 (23·4%)	17/196 (8·8%)	29/291 (10%)	103/771 (13%)	84/944 (8·7%)
Asthma-COPD phenotypes						
Neither	21/95 (22%)	79/135 (58%)	159/194 (82%)	246/287 (86%)	557/764 (73%)	774/936 (83%)
Asthma alone	30/95 (32%)*	39/135 (29%)*	34/194 (18%)	40/287 (14%)	163/764 (21%)	150/936 (16%)
COPD alone	19/95 (20%)*	3/135 (2·2%)	0/194 (0%)	1/287 (0·4%)	30/764 (4%)	9/936 (1%)

Overlap	25/95 (26%)*	14/135 (10·4%)*	1/194 (0·5%)	0/287 (0%)	14/764 (1·8%)	3/936 (0·3%)
Chronic cough	41/96 (42·7%)*	40/135 (29·6%)	35/196 (17·8%)	46/291 (15·8%)*	198/770 (26%)	219/941 (23·2%)
Chronic sputum production	32/95 (33·7%)*	32/133 (24%)*	16/196 (8·2%)	20/291 (6·8%)	95/769 (12·3%)	96/942 (10·2%)
Shortness of breath at rest in last year	17/96 (17·7%)*	16/133 (12%)*	13/195 (6·7%)	11/292 (3·8%)	61/768 (8%)	59/938 (6·3%)
Shortness of breath after exercise in last year	50/97 (51·6%)*	53/134 (40%)*	20/195 (10·3%)	34/292 (11·6%)	136/769 (17·7%)*	117/940 (12·5%)
Wheezing in last year	57/97 (58·8%)*	54/135 (40%)*	28/196 (14·3%)	33/293 (11·3%)	184/768 (24%)*	140/942 (14·9%)
Pre BD lung function at 53 years ǂ						
$FEV_{1,}$ z-score	-2·35 (±0·59)*	-1·61 (±0·52)*	0·30 (±0·51)	1·35 (±0·58)*	-0·81 (±0·46)*	0·29 (±0·52)
$FEV_{1,}$ % predicted	67·1 (±8·7)*	77·7 (±7·4)*	104 (±6·8)	112 (±7·5)*	88·9 (±6·4)*	104 (±6·8)
FEV_1/FVC, %	66·5 (±0·1)*	73 (±0·1)*	79·8 (±0·1)	79·5 (±0·1)	75·6 (±0·1)*	78·5 (±0·1)
Post BD lung function at 53 years ǂ						
FEV_1, z-score	-1·94 (±0·65)*	-1·28 (±0·57)*	0·45 (±0·54)	1·54 (±0·57)*	-0·5 (±0·62)*	0·5 (±0·55)
FEV_1, % predicted	73 (*±9·3*)*	82·4 (±8·0)*	106 (*±7·3*)	120 (±7·5)*	93 (*±8·2*)*	107 (±7·3)

FEV_1/FVC, %	68·9 (±0·1)*	75·6 (*±0·1*)*	81·8 (*±0·1*)	81·6 (*±0·1*)	78·1 (±0·1)*	80·7 (±0·1)
Use of medicines (inhaler, oral or injection) for breathing problems in the prior year	41/88 (47%)*	38/132 (29%)*	15/191 (8%)	21/290 (7%)	103/755 (%)*	79/933 (8·5%)
Smoking status at 53 years						
Never	22/96 (23%)*	63/134 (47%)	91/195 (47%)	142/291 (49%)	319/765 (42%)*	470/936 (50%)
Past	43/96 (45%)	43/134 (32%)	87/195 (44%)	123/291 (42%)	294/765 (38%)	346/936 (37%)
Current	31/96 (32%)*	28/134 (21%)*	17/195 (9%)	26/291 (9%)	152/765 (20%)*	120/936 (13%)
Pack-years, median (IQR)	13·5 (0-29)*	0·43 (0-19·5)*	0 (0-10)	0 (0-6)	0·6 (0-18·3)*	0 (0-9)

ł mean (± SD)

** significant difference from the "average" trajectory (p<0.05)*

References

1. Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017; **5**: 935–45.

2. Vasquez MM, Zhou M, Hu C, Martinez FD, Guerra S. Low Lung Function in Young Adult Life Is Associated with Early Mortality. *Am J Respir Crit Care Med* 2017; **195**: 1399–401.

3. Fletcher C, Peto R. The natural history of chronic airflow obstruction. BMJ 1977;**1**:1645–8.

4. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet* 2015;**385**:899–909.

5. World Health Organization. World health statistics 2008. (Accessed December 9, 2016, at http://www.who.int/whosis/whostat/2008/en/)

6. Berry CE, Billheimer D, Jenkins IC, et al. A Distinct Low Lung Function Trajectory from Childhood to the Fourth Decade of Life. *Am J Respir Crit Care Med* 2016;**194**:607–12.

7. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med 2016*;**374**:1842–52.

8. Lange P, Celli B, Agustí A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med 2015*;**373**:111–22.

9. Matheson MC, Abramson MJ, Allen K, et al. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). *Int J Epidemiol* 2016. DOI: 10.1093/ije/dyw028

10. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J 2005*;**26**:319–38.

11. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;**40**:1324–43.

12. Hall GL, Thompson BR, Stanojevic S, et al. The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology* 2012;**17**:1150–1.

13. Nagin DS. Analyzing developmental trajectories: A semiparametric, group-based approach. *Psychol Methods* 1999;**4**:139–57.

14. Heather A, Natasha C, Amanda T, Patrick G, Benoît L. Latent Class Growth Modelling: A Tutorial. *Tutor Quant Methods Psychol* 2009;**5**:11–24.

15. Jones BL, Nagin DS. A Note on a Stata Plugin for Estimating Group-based Trajectory Models. *Sociol Methods Res* 2013;**42**:608–613.

16. Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. *Respirology* 2014; **19**: 303–11.

17. Firth D. Bias Reduction of Maximum Likelihood Estimates. *Biometrika* 1993; 80: 27–38.

18. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998;**88**:15–9.

19. Nagin DS, Odgers CL. Group-Based Trajectory Modeling in Clinical Research. *Annu Rev Clin Psychol* 2010;**6**:109–138.

20. Belgrave DC, Granell R, Turner SW, et al. Lung function trajectories from pre-school age to adulthood. Submitted 2017.

21. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med* 2013;**1**:728–42.

22. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. *N Engl J Med 2016*;**375**:871–8.

23. James AL, Palmer LJ, Kicic E, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005;**171**:109–14.

24. Lodge CJ, Lowe AJ, Allen KJ, et al. Childhood wheeze phenotypes show less than expected growth in FEV1 across adolescence. *Am J Respir Crit Care Med* 2014;**189**:1351–8.

25. Hallberg J, Thunqvist P, Schultz ES, et al. Asthma phenotypes and lung function up to 16 years of age-the BAMSE cohort. *Allergy* 2015;**70**:667–73.

26. Chan JY, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. *Pediatrics* 2015;**135**:607–16.

27. Johnston ID, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 1998;**338**:581–7.

28. Wang X, Wypij D, Gold DR, et al. A longitudinal study of the effects of parental smoking on pulmonary function in children 6-18 years. *Am J Respir Crit Care Med* 1994;**149**:1420–5.

29. Turner S, Fielding S, Mullane D, et al. A longitudinal study of lung function from 1 month to 18 years of age. *Thorax* 2014;**69**:1015–20.

30. Edwards CA, Osman LM, Godden DJ, Douglas JG. Wheezy bronchitis in childhood: a distinct clinical entity with lifelong significance? *Chest* 2003;**124**:18–24.

31. Svanes C, Sunyer J, Plana E, et al. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;**65**:14–20.

32. Dratva J, Zemp E, Dharmage SC, et al. Early Life Origins of Lung Ageing: Early Life Exposures and Lung Function Decline in Adulthood in Two European Cohorts Aged 28-73 Years. *PloS one* 2016;**11**:e0145127.

33. Guerra S, Stern DA, Zhou M, et al. Combined effects of parental and active smoking on early lung function deficits: a prospective study from birth to age 26 years. *Thorax* 2013;**68**:1021–8.

34. Upton MN, Smith GD, McConnachie A, Hart CL, Watt GC. Maternal and personal cigarette smoking synergize to increase airflow limitation in adults. *Am J Respir Crit Care Med* 2004;**169**:479–87.

35. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined Impact of Smoking and Early Life Exposures on Adult Lung Function Trajectories. *Am J Respir Crit Care Med* 2017; DOI: 10.1164/rccm.201703-0506OC

36. Lodrup Carlsen KC, Mowinckel P, Hovland V, Haland G, Riiser A, Carlsen KH. Lung function trajectories from birth through puberty reflect asthma phenotypes with allergic comorbidity. *J Allergy Clin Immunol* 2014;**134**:917–23.e7.

37. Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S. Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. *Am J Respir Crit Care Med* 2010;**181**:969–74.

38. Australian Bureau of Statistics. Death rates, Summary, States and territories - 2004 to 2014. (accessed Jan 10 2018, at http://www.abs.gov.au 1997)

39. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of COPD, 2016. (Accessed April 10 2016, at http://www.goldcopd.org.)