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

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Summary

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

Methods We used six waves of the Tasmanian Longitudinal Health Study (TAHS) to model lung function trajectories measured at 7, 13, 18, 45, 50, and 53 years. We analysed pre-bronchodilator FEV_1 *z*-scores at the six timepoints using group-based trajectory modelling to identify distinct subgroups of individuals whose measurements followed a similar pattern over time. We related the trajectories identified to childhood factors and risk of chronic obstructive pulmonary disease (COPD) using logistic regression, and estimated population-attributable fractions of COPD.

Findings Of the 8583 participants in the original cohort, 2438 had at least two waves of lung function data at age 7 years and 53 years and comprised the study population. We identified six trajectories: early below average, accelerated decline (97 [4%] participants); persistently low (136 [6%] participants); early low, accelerated growth, normal decline (196 [8%] participants); persistently high (293 [12%] participants); below average (772 [32%] participants); and average (944 [39%] participants). The three trajectories early below average, accelerated decline; persistently low; and below average had increased risk of COPD at age 53 years compared with the average group (early below average, accelerated decline: odds ratio 35·0, 95% CI 19·5–64·0; persistently low: 9·5, 4·5–20·6; and below average: 3·7, 1·9–6·9). Early-life predictors of the three trajectories included childhood asthma, bronchitis, pneumonia, allergic rhinitis, 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 immunisation, and avoiding personal smoking, especially in those with smoking parents or low childhood lung function, might minimise COPD risk. Clinicians and patients with asthma should be made aware of the potential long-term implications of non-optimal asthma control for lung function trajectory throughout life, and the role and benefit of optimal asthma control on improving lung function should be investigated in future intervention trials.

Funding National Health and Medical Research Council of Australia; European Union's Horizon 2020; The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; The Victorian, Queensland & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline.

Introduction

Lifetime lung function is related to quality of life and longevity. Recent studies have highlighted that low lung function, especially low 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 through phases of growth and decline[3,4] and individuals have unique lifetime lung function trajectories based on the timing and duration of these phases. Trajectories might have different risk factors and different consequences for chronic lung disease risk, particularly chronic obstructive pulmonary disease (COPD), which is expected to be the 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,

Lancet Respir Med 2018; 6: 535–44

Published Online April 5, 2018 http://dx.doi.org/10.1016/S2213-2600(18)30100-0

See Comment page 482

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Research in context

Evidence before this study

Although accelerated lung function decline has been shown to be associated with development of chronic obstructive pulmonary disease (COPD), 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 from inception 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 on the basis of more than two 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, understanding how child and adult factors interact to determine membership of healthy as well as adverse lifetime trajectories is crucial 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 course of COPD, and show the potential for interventions that promote healthy lung function and reduce 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 risk of COPD and collectively accounted for most COPD cases. Most importantly, moderate–severe COPD cases 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

Reduction of maternal smoke exposure and personal smoking and encouragement of immunisation 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.

only two[6,7] have published lung function trajectories based on more than two timepoints, with one study being restricted to participants with childhood asthma.[7] However, neither study was able to capture the decline phase, vital for lung health outcomes in later life, because they had data only to the fourth decade. Although evidence suggests 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, understanding of how childhood and adult factors interact to determine membership of healthy as well as adverse lifetime trajectories is crucial.

Despite inter-individual variation in lung function trajectories within a general population, distinct sub-populations might follow similar FEV_1 trajectories. The Tasmanian Longitudinal Health Study (TAHS),[9] 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) characterise population FEV_1 trajectories from the first to the sixth decade, (2) investigate their childhood predictors and interaction with adult asthma and personal smoking, and (3) relate trajectories to COPD risk.

Methods

Study design and data collection

Six waves of TAHS[9] were used. TAHS began in 1968 when 8583 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 spirometry and their parents completed a questionnaire. Follow-up assessments were done at 13, 18, 45, and 50 years of age with pre-bronchodilator 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.

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

Procedures

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

Definition of variables

We defined childhood factors (asthma, bronchitis, eczema, allergic rhinitis, food allergy, pneumonia, breast feeding, weight status, parental asthma, and parental smoking) using the information provided by parents in 1968 (see appendix for further details). COPD was defined as post-bronchodilator FEV_1:forced vital capacity (FVC) less than the lower limit of normal at 53 years.

We defined other adulthood factors (appendix) using information provided by participants at age 53 years.

Statistical analysis

We analysed pre-bronchodilator FEV_1 *z*-scores at six timepoints (7, 13, 18, 45, 50, and 53 years) 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 (appendix).[14,15] This method allows handling of missing data for each individual, and produces asymptotically unbiased parameter estimates. As well as model fit, we also considered interpretation of trajectories 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).

To investigate the 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 likelihood ratio test with five degrees of freedom. Then we employed two modelling approaches in parallel. For the first approach, we used logistic regression to investigate associations between each childhood predictor and lung function trajectories, where each trajectory was compared with the average trajectory—ie, the so-called non-disease group. For each childhood predictor, a specific minimal sufficient set of potential confounders was selected on the basis of causal diagrams (directed acyclic graphs).[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 smaller than 0·10 was retained in the final model. For comparison, we used a second approach in which all childhood predictors with a p value smaller than 0·15, computed using the likelihood ratio test, were included in a single multivariable multinomial logistic regression model adjusted simultaneously for all childhood predictors. 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), we used penalised maximum likelihood logistic regression to reduce bias in estimates of regression coefficients.[17] Population-attributable fractions of COPD were estimated for trajectories.[18] All analyses were done using Stata version 13.0 (Stata Corp, College Station, TX, USA) with a GBTM plug-in.[15]

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

Of 8583 participants from the original cohort, pre-bronchodilator and post-bronchodilator spirometry were done at 53 years in 2689 participants. 2438 participants had at least two waves of lung function data at age 7 years and 53 years and comprised the study population (appendix). The participants included had similar baseline characteristics to those not included except for more female participants, more participants with eczema, and fewer smoking parents among those included (appendix). Those included and those deceased by 53 years also had similar baseline characteristics (appendix).

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] On the basis of lung function at age 7 years and growth and decline rates, trajectories were given the following labels: early below average, accelerated decline (97 [4%] participants); persistently low (136 [6%] participants); early low, accelerated growth, normal decline (196 [8%] participants); persistently high (293 [12%] participants); below average (772 [32%] participants); and average (944 [39%] participants; appendix). The average trajectory had lung function consistently around the population mean over time. The means of the raw values of FEV_1 at six timepoints among trajectories are presented in the appendix. In a sensitivity analysis, exclusion of the datapoint with the smallest number of observations (at 18 years) yielded six very similar lung function trajectories (appendix).

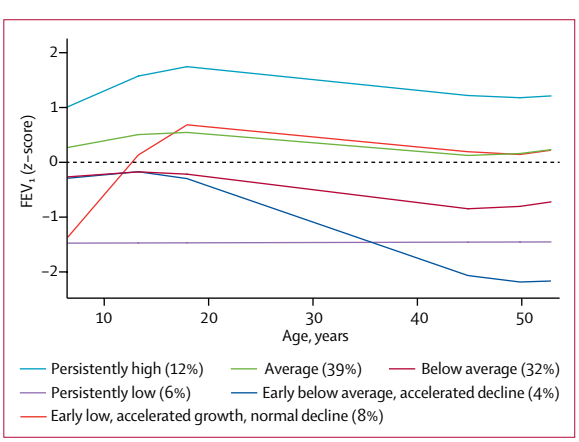

Figure 1: **Trajectories of lung function (FEV_1 *z*-score) from 7 to 53 years of age**
The six trajectories represent the latent growth patterns of lung function. The group prevalences do not add up to 100% because of rounding.

See Online for appendix

	Early below average, accelerated decline (n=97)	Persistently low (n=136)	Early low, accelerated growth, normal decline (n=196)	Persistently high (n=293)	Below average (n=772)	Average (n=944)
Childhood characteristics at 7 years						
Female	45 (46%)	64 (47%)	123 (63%)	167 (57%)	380 (49%)	479 (51%)
Male	52 (54%)	72 (53%)	73 (37%)*	126 (43%)	392 (51%)	465 (49%)
Ever asthma	36 (37%)*	38/135 (28%)*	32 (16%)	48/291 (16%)	137/766 (18%)	137/940 (15%)
Asthma phenotype						
Transient	3/96 (3%)	8/133 (6%)	8/193 (4%)	16/287 (6%)	36/758 (5%)	39/935 (4%)
Late onset	11/96 (11%)	7/133 (5%)	7/193 (4%)	12/287 (4%)	43/758 (6%)	43/935 (5%)
Persistent	21/96 (22%)	21/133 (16%)	14/193 (7%)	16/287 (6%)	50/758 (7%)	50/935 (5%)
Ever bronchitis	68 (70%)*	75/135 (56%)	97 (49%)	132/291 (45%)	386/765 (50%)	449/942 (48%)
Ever eczema	18 (19%)*	27/123 (22%)*	24/195 (12%)	28/291 (10%)	75/765 (10%)	98/937 (10%)
Ever allergic rhinitis	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 (7%)	21/291 (7%)	55/762 (7%)	60/940 (6%)
Ever pneumonia or pleurisy	21/96 (22%)*	19/134 (14%)	18 (9%)	29/287 (10%)	120/760 (16%)*	116/931 (12%)
Weight status at 7 years						
Underweight	3/95 (3%)	7/134 (5%)	13 (7%)*	5/290 (2%)	30/766 (4%)	25/937 (3%)
Normal	77/95 (81%)	116/134 (87%)	165 (84%)	241/290 (83%)	665/766 (87%)	803/937 (86%)
Overweight	15/95 (16%)	11/134 (8%)	18 (9%)	44/290 (15%)	71/766 (9%)	109/937 (12%)
Breastfeeding						
Breastfed only	36 (37%)	56/134 (42%)	73/195 (37%)	136/290 (47%)	309/763 (40%)	427/941 (45%)
Breast and bottle	32 (33%)	36 (26%)	66/195 (34%)	95/290 (33%)	248/763 (33%)	293/941 (31%)
Socioeconomic status						
1st quintile (highest)	18/94 (19%)	28/123 (23%)	45/182 (25%)	74/278 (27%)	185/732 (25%)	226/908 (25%)
2nd quintile	7/94 (7%)	14/123 (11%)	11/182 (6%)	17/278 (6%)	47/732 (6%)	73/908 (8%)
3rd quintile	32/94 (34%)	34/123 (28%)	53/182 (29%)	80/278 (29%)	210/732 (29%)	276/908 (30%)
4th quintile	29/94 (31%)	30/123 (24%)	53/182 (29%)	78/278 (28%)	190/732 (26%)	248/908 (27%)
5th quintile (lowest)	8/94 (9%)	17/123 (14%)	20/182 (11%)	29/278 (10%)	91/732 (12%)	85/908 (9%)
Mean FEV_1 at 7 years						
z-score	−0·23 (0·64)*	−1·66 (0·61)*	−1·57 (0·57)*	1·15 (0·70)*	−0·33 (0·62)*	0·31 (0·60)
% predicted	97 (8)*	79 (8)*	80 (7)*	114 (9)*	96 (8)*	104 (8)
FEV_1:FVC at 7 years	88·4% (0·1)	87·7% (0·1)	87·3% (0·1)	92·6% (0·1)	90·7% (0·1)	92% (0·1)
Parental characteristics						
Parental asthma	19/94 (20%)	37/131 (28%)*	30/189 (16%)	58/283 (20%)	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 (31%)	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%)

Data are n (%), n/N (%), median (IQR), or mean (SD). Denominators are shown where data are missing. FVC=forced vital capacity. *Significantly different from the average trajectory (p<0·05).

Table 1: **Childhood characteristics of participants according to lung function trajectories from first to sixth decade**

Childhood characteristics of participants according to lung function trajectories are shown in table 1. The results of our two modelling approaches were almost identical, thus we only present results for the first approach. Adjusted associations between childhood factors and lung function trajectories compared with the average trajectory show that individuals with the early below average, accelerated decline trajectory were more likely to have childhood asthma (p<0·0001), bronchitis (p=0·0080), allergic rhinitis (p=0·012), pneumonia or pleurisy (p=0·0080), and a heavy-smoking mother (p=0·038; table 2).

The persistently low trajectory was associated with childhood asthma—in particular, frequent asthma symptoms and early asthma onset—eczema, and parental asthma. Borderline associations were seen between this trajectory and food allergy, and childhood underweight.

	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 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
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 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<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 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
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 or pleurisy||	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)
Allergic rhinitis**	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§§					
Bottle only	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
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 and 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					
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
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)

Data are odds ratio (95% CI). *For asthma, model is adjusted for parental asthma, childhood pneumonia or pleurisy, infantile eczema, parental smoking, sex, breastfeeding, and childhood socioeconomic status. †p<0·01. ‡p<0·05. §p<0·001. ¶For bronchitis, model is adjusted for childhood asthma, childhood pneumonia or pleurisy, infantile eczema, parental smoking, and childhood socioeconomic status. ||For pneumonia or pleurisy, model is adjusted for breastfeeding, and childhood socioeconomic status. **For eczema, allergic rhinitis, and food allergy, models are adjusted for childhood asthma, parental asthma, parental smoking, sex, and childhood socioeconomic status. ††For parental asthma, models adjusted for sex, parental smoking, and childhood socioeconomic status. ‡‡For parental smoking, models are adjusted for parental asthma, childhood asthma, and childhood socioeconomic status. §§For breastfeeding, model is adjusted for parental asthma, parental smoking, and childhood socioeconomic status. ¶¶For childhood weight status, model is adjusted for childhood pneumonia or pleurisy, sex, breastfeeding, and childhood socioeconomic status.

Table 2: **Associations between childhood clinical factors and each of five lung function trajectories compared with the average trajectory**

There were synergistic effects between childhood asthma and eczema (p=0·068) and allergic rhinitis (p=0·062). Participants with childhood asthma, eczema, and allergic rhinitis had a 4·9-times (95% CI 1·9–12·1) risk increase for the persistently low trajectory.

The below average trajectory was associated with childhood pneumonia (table 2). The effects of the childhood factors were independent of adult personal smoking on the three trajectories early below average, accelerated decline; persistently low; and below average.

Female and underweight children were more likely to have the early low, accelerated growth, normal decline trajectory (table 2). The effect of underweight on this trajectory became non-significant when weight gain during ages 7–11 years was added to the model (odds ratio [OR] 2·0, 95% CI 0·9–4·5).

	Early below average, accelerated decline (n=97)	Persistently low (n=136)	Early low, accelerated growth, normal decline (n=196)	Persistently high (n=293)	Below average (n=772)	Average (n=944)
COPD	44/95 (46%)*	17 (13%)*	1/194 (1%)	1/289 (<1%)	44/765 (6%)*	12/936 (1%)
Active asthma at 53 years	56 (58%)*	53/135 (39%)*	35 (18%)	41/291 (14%)	179/771 (23%)*	153 (16%)
Atopic asthma	28 (29%)	21/135 (16%)	18 (9%)	12/291 (4%)	77/771 (10%)	69 (7%)
Non-atopic asthma	28 (29%)	32/135 (24%)	17 (8%)	29/291 (10%)	103/771 (13%)	84 (9%)
Asthma-COPD phenotypes						
Neither	21/95 (22%)	79/135 (59%)	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%)	0/194	1/287 (<1%)	30/764 (4%)	9/936 (1%)
Overlap	25/95 (26%)*	14/135 (10%)*	1/194 (1%)	0/287	14/764 (2%)	3/936 (<1%)
Chronic cough	41/96 (43%)*	40/135 (30%)	35 (18%)	46/291 (16%)*	198/770 (26%)	219/941 (23%)
Chronic sputum production	32/95 (34%)*	32/133 (24%)*	16 (8%)	20/291 (7%)	95/769 (12%)	96/942 (10%)
Shortness of breath at rest in past year	17/96 (18%)*	16/133 (12%)*	13/195 (7%)	11/292 (4%)	61/768 (8%)	59/938 (6%)
Shortness of breath after exercise in past year	50 (52%)*	53/134 (40%)*	20/195 (10%)	34/292 (12%)	136/769 (18%)*	117/940 (12%)
Wheezing in last year	57 (59%)*	54/135 (40%)*	28 (14%)	33 (11%)	184/768 (24%)*	140/942 (15%)
Pre-bronchodilator lung function at 53 years						
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)*	104·2 (6·8)	112·1 (7·5)*	88·9 (6·4)*	104·0 (6·8)
FEV_1:FVC	66·5% (0·1)*	73·0% (0·1)*	79·8% (0·1)	79·5% (0·1)	75·6% (0·1)*	78·5% (0·1)
Post-bronchodilator lung function at 53 years						
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 past year	41/88 (47%)*	38/132 (29%)*	15/191 (8%)	21/290 (7%)	103/755 (14%)*	79/933 (8%)
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 (45%)	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	14 (0–29)*	<1 (0–20)*	0 (0–10)	0 (0–6)	1 (0–18)*	0 (0–9)

Data are n (%), n/N (%), median (IQR), or mean (SD). Denominators are shown where data are missing. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. *Significant difference from the average trajectory (p<0·05).

Table 3: **Clinical characteristics at 53 years according to lung function trajectories from first to sixth decade**

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

We found that adult active asthma and personal smoking were independently associated with three trajectories: early below average, accelerated decline; below average; and persistently low (appendix).

We observed a significant interaction between heavy maternal smoking and personal smoking defined using pack-years (p<0·0001) for the risk of belonging to the early below average, accelerated decline trajectory. The adverse effect of maternal smoking increased with increasing personal smoking (appendix).

We found evidence of potential interaction between childhood asthma and adult active asthma for the risk of the early below average, accelerated decline trajectory (p=0·077) with the effect of childhood asthma mainly evident in participants with adult active asthma.

At 53 years, participants in the early below average, accelerated decline trajectory had the highest prevalence of COPD (46%), followed by the persistently low trajectory (13%) and the below average trajectory (6%; table 3, figure 2). Compared with the average trajectory, these three trajectories had 35·0-times (95% CI 19·5–64·0), 9·5-times (4·5–20·6), and 3·7-times (1·9–6·9) increased risk of COPD, respectively (appendix). 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—more than 75% of all COPD cases at 53 years. For moderate–severe COPD (an addition of FEV_1 <80% predicted values), all cases in our sample only arose from these three trajectories (early below average, accelerated decline; persistently low; and below average).

We replicated the analysis by defining COPD using FEV_1:FVC less than 0·7 and findings were not materially different to those using the lower limit of normal (appendix). We found similar results using a clinical definition of COPD (appendix).

In addition to the higher prevalence of respiratory conditions (table 3), we found that these three trajectories (early below average, accelerated decline; persistently low; and below average) had higher prevalences of diabetes and obstructive sleep apnoea compared with the average trajectory (appendix). Higher prevalences of hypertension and heart attack or myocardial infarction were also seen for the below average and persistently low trajectories.

Discussion

Our study is unique in that, to our knowledge, it is the first to characterise lung function trajectories in a large general population sample from early childhood to the sixth decade. This analysis is of considerable importance because understanding lifetime lung function is crucial for population-based interventions to promote healthy trajectories and prevent unhealthy ones. We identified six distinct FEV_1 trajectories including two novel trajectories: 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. 75% of COPD cases at 53 years were attributable to these three trajectories. Most importantly, moderate–severe COPD cases arose only from these three trajectories. Childhood asthma, bronchitis, pneumonia, allergic rhinitis, 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 led 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, because they had data only into early adulthood. One study[7] describes four FEV_1 trajectories from ages 7 to 26 years in 684 patients with asthma. 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 ages 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 might include smaller sample size and shorter follow-up.

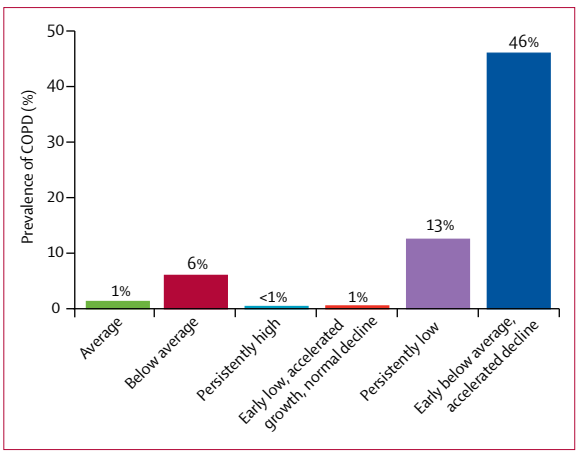

Figure 2: **Prevalence of COPD among six lung function trajectories at 53 years**
COPD=chronic obstructive pulmonary disease.

Using similar statistical methodology to ours, a study[20] from three population-based birth cohorts (Manchester Asthma and Allergy Study [MAAS], the Avon Longitudinal Study of Parents and Children [ALSPAC], and the Perth Infant Asthma Follow-up Study [PIAF]) found four FEV_1 trajectories between ages 5 and 24 years (persistently high, average, below average, and persistently low). We also found these trajectories, and identified two further trajectories. Our study's ability to tease out more trajectories might 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 of the COPD cases in our study. This result was supported by a study[8] in which half of the 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 could lead to poorer lung growth and adult risk factors contributing to accelerated decline.[21–23]

We believe that this is the first study to establish the early life factors determining FEV_1 trajectories into the sixth decade. Previous studies have investigated the influence of early life factors only on single phases of lung function trajectories—ie, impaired growth[24–29] or accelerated decline.[30–32] Maternal smoking and childhood 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 affects early lung function, but predisposes children to more rapid lung function decline if they later smoke. Expressed another way, personal smoking not only accelerated FEV_1 decline but also amplified the effect 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, and parental asthma, with borderline associations with food allergy and childhood underweight. Additionally, asthma in combination with either eczema or allergic rhinitis had a multiplicative rather than additive effect on the risk of following this trajectory. Consistent with our findings, the MAAS, ALSPAC, and PIAF study[20] found that their persistently low trajectory was associated with asthma or wheeze and allergic sensitisation. Similarly, a birth cohort study in Oslo[36] reported a persistently impaired lung function pattern from birth to 16 years in asthma with eczema and allergic rhinitis.[36] These findings suggest that arresting the atopic march, believed to drive these early allergic comorbidities, might help to 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, ALSPAC, and PIAF study.[20] We found that participants 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 MAAS, ALSPAC, and PIAF study.[20] Although some infants with poor lung function in the PIAF cohort continued in the low FEV_1 trajectory, most 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 might be related to birthweight, given that weight catch-up was reported in children with low birthweight and those with catch-up growth showed improved lung function.[37] We did not have full birthweight information to explore this effect. However, we found that childhood underweight predicted the early low, accelerated growth, normal decline trajectory; the association between childhood underweight and this trajectory became non-significant when controlled for weight gain between 7 and 11 years. This result suggests that childhood underweight followed by accelerated weight gain might be related to accelerated lung growth in this group. The persistently low trajectory had more than twice the prevalence of persistent childhood asthma than did the early low, accelerated growth, normal decline trajectory. Although the two trajectories had similar early acquired lung function deficits, it is possible that persistent asthma prevented the catch-up in the persistently low trajectory.

The early below average and accelerated decline trajectory had the highest prevalence and intensity of smoking. Thus, this trajectory resembles the lung function pattern among so-called susceptible smokers, as originally framed by Fletcher and Peto.[3] Although 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 might have prevented an accelerated decline in lung function. By contrast, the prevalence and intensity of smoking were extremely low in what we found to be the three most favourable trajectories—ie, persistently high; early low, accelerated growth, normal decline; and average. These trajectories 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, the three unfavourable lung function trajectories had higher prevalences of diabetes and obstructive sleep apnoea compared with the average trajectory. Higher prevalences of hypertension and heart attack or myocardial infarction were also seen for the below average trajectory and the 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 their consequences has been a 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 small sample sizes with few 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 that 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 that could mean we have missed trajectory transitions around peak lung function. However, insufficient data at this peak lung function period would be unlikely to substantially affect the trajectories we calculated for childhood and middle age. In a sensitivity analysis, when the datapoint 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 logistical difficulties, results from such studies might 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 that 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 because most patients with COPD are diagnosed in their sixties. The effect of adverse lung function trajectories on COPD risk might 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 years; hence, there is a high attrition rate. Importantly, however, the death rate for TAHS participants by age 53 years 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 participants 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 or 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 can present with asthma-like symptoms, whereas airway inflammation associated with asthma can 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 might help to elucidate this issue.

Our findings have clinical and public health implications. Visual presentations of lung function trajectory scenarios could be useful in educational programmes on the dangers of smoking. Routine spirometry measurements in school students to identify those with low lung function might help early identification of high risk groups. Although not directly tested, our findings raise the possibility that reducing maternal smoke exposure, encouraging immunisation, and avoiding personal smoking, especially for those with parents who smoke 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 the role and benefit of optimal asthma control should be investigated in future intervention trials.

In conclusion, this characterisation of lung function change from the first to the sixth decade revealed six distinct trajectories that might 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 might amplify the effect of maternal smoking and adult asthma might amplify the effect of childhood asthma to determine membership of the worst lung function trajectory.

Contributors

SCD, EHW, GGG, and MJA contributed to the study concept and design. SCD, EHW, MJA, and SCM obtained funding. SCD, EHW, MCM, JAB, PST, and SCM acquired the data. DSB, SCD, and JAB did the statistical analysis. DSB, SCD, JAB, and MCM analysed and interpreted the data. DSB, SCD, JAB, and MCM drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Declaration of interests

We declare no competing interests for this work. MJA holds investigator-initiated grants from Pfizer and Boehringer Ingelheim, outside of the submitted work.

Acknowledgments

We acknowledge the TAHS study participants and previous investigators. We thank Mark Jenkins (Centre for Epidemiology & Biostatistics, The University of Melbourne, VIC, Australia), a TAHS investigator, but not a coauthor of this manuscript, for his assistance with obtaining funds and data collection. We also acknowledge all the respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland, and New South Wales; and the research interviewers, data entry operators, and research officers. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 TAHS questionnaires. This study was supported by the National Health and Medical Research Council (NHMRC) of Australia under NHMRC project grant scheme (299901, 1021275) and NHMRC European collaborative grant scheme (1101313) as part of ALEC (Ageing Lungs in European Cohorts funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 633212); The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline.

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