Trajectories of airflow limitation from childhood to early adulthood: an analysis of six population-based birth cohorts

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Lancet Child Adolesc Health 2025; 9: 172–83

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Summary

Background Lung function during childhood is an important predictor of subsequent health and disease. Understanding patterns of lung function and development of airflow limitation through childhood is necessary to inform lung function trajectories in relation to health and chronic airway disease. We aimed to derive trajectories of airflow limitation from childhood (age 5–8 years) into early adulthood (age 20–26 years) using repeated spirometry data from birth cohorts.

Methods In this study, we drew forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) data from six population-based birth cohorts: the UK-based Avon Longitudinal Study of Parents and Children (ALSPAC), Isle of Wight cohort (IOW), Manchester Asthma and Allergy Study (MAAS), and Aberdeen Study of Eczema and Asthma (SEATON) as well as the Swedish Child (*Barn*), Allergy, Milieu, Stockholm, Epidemiological survey (BAMSE) and the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort. For the discovery analysis, we pooled data from ALSPAC, IOW, MAAS, and BAMSE with spirometry data recorded at middle childhood (age 8–10 years), adolescence (age 15–18 years), and early adulthood (age 20–26 years). For the replication analysis, we pooled middle childhood and adolescence spirometry data from PIAMA and SEATON. We used latent class trajectory modelling to derive trajectory classes based on joint modelling of FEV_1 and FEV_1/FVC ratio regression residuals ascertained from all age groups. The final model was selected using the lowest Bayesian information criterion. Participants were assigned to the trajectory with the highest posterior probability. Weighted random-effect multinomial logistic regression models were used to investigate factors associated with joining each trajectory, the results of which are reported as relative risk ratios (RRRs) with 95% CIs.

Findings The discovery population included 8114 participants: 4710 from ALSPAC, 808 from IOW, 586 from MAAS, and 2010 from BAMSE and was modelled into one of four lung function trajectories that showed normal airflow (6555 [80·8%] of 8114 people), persistent airflow obstruction (1280 [15·8%]), worsening airflow obstruction (161 [2·0%]), and improved airflow obstruction (118 [1·5%]). Both improvement in and worsening airflow obstruction by early adulthood were seen from all initial severity levels. Whereas improvement in airflow obstruction was more prominent between middle childhood and adolescence (57·8%) than between adolescence and early adulthood (13·4%), worsening airflow obstruction was more prominent between adolescence and early adulthood (61·5%) than between middle childhood and adolescence (32·6%). Among current wheezers, higher BMI was associated with a lower relative risk of joining the trajectory with improvement in airflow obstruction (RRR 0·69 [95% CI 0·49–0·95]), whereas among non-wheezers, higher BMI increased the relative risk of being in the improved airflow obstruction trajectory (1·38 [1·04–1·85]). A higher BMI at first lung function assessment was associated with a higher relative risk of joining the trajectory for improvement in airflow obstruction trajectory in participants with low birthweight and no current asthma diagnosis (RRR 2·44 [1·17–5·12]); by contrast, higher BMI is associated with a lower relative risk of joining the trajectory with improvement in airflow obstruction among those with low birthweight and current asthma diagnosis (0·37 [0·18–0·76]). Results in replication cohorts (n=1337) were consistent with those in the discovery cohort.

Interpretation Worsening and improvement in airflow limitation from school age to adulthood might occur at all ages and all airflow obstruction severity levels. Interventions to optimise healthy weight, including tackling overweight and obesity (particularly among children with wheezing) as well as treating underweight among non-wheezers, could help to improve lung health across the lifespan.

Funding UK Medical Research Council and CADSET European Respiratory Society Clinical Research Collaboration.

Introduction

Lungs of full-term, healthy neonates are not yet fully developed at birth, and their growth and development continue until early adulthood, at which point lung function peaks and then steadily declines.[1] The developing lung is susceptible to adverse environmental

Research in context

Evidence before this study

Lung tissue continues to grow and develop from birth until early adulthood, at which point lung function peaks and begins to decline. Diminished lung function at this physiological peak is associated with subsequent poor health, including respiratory, cardiovascular, and metabolic morbidity. The clinical importance of monitoring trajectories of lung function to detect impairment early has been recognised in the literature, but optimal implementation of interventions to improve these trajectories requires understanding of the temporality and determinants of decline or improvement in lung function. In a 2024 review, we summarised progressive research into lung-function trajectories as an innovative approach to detect poor lung health early, monitor respiratory disease progression, and promote lung health. We concluded that lung-function charts could be used for both children and adults to monitor lung health status across the life course. We searched PubMed for original research published in English from database inception to Aug 30, 2024, using the search terms ("trajectories" AND "lung function" AND "spirometry" AND "growth phase") AND ("trajectories" AND "lung function" AND "plasticity" AND "spirometry" AND "growth phase"). Most studies ascertained lung function developmental trajectories through childhood using data-driven methods and found no evidence of trajectories with declining and improving lung function. Studies that have reported lung function improvement and decline have defined these a priori or a posteriori.

Added value of this study

We used data-driven methods to identify trajectories of lung function from middle childhood (ages 8–10 years) to early adulthood (ages 20–26 years) using data from six birth cohorts in the CADSET Clinical Research Collaboration of the European Respiratory Society. Two lung function trajectories were characterised by the lack of change in airflow obstruction (normal and persistent), and two novel trajectories were characterised by a marked change in lung function during the growth phase (worsening and improvement). Changes were observed at all ages and occurred from all initial levels of airflow obstruction severity, but improvement in airflow obstruction was comparatively higher from middle childhood to adolescence, and worsening airflow obstruction was most prominent from adolescence to adulthood. Differences in the risk factors associated with membership of the improvement trajectory were observed between children with and without wheeze. Among those with current wheeze, higher BMI decreased the likelihood of improvement. By contrast, among children who did not wheeze, lower BMI reduced the likelihood of improvement. Maternal smoking during pregnancy raised the relative risk of persistent and worsening airflow obstruction.

Implications of all the available evidence

Among children with wheeze, efforts should be made to derive interventions that prevent wheeze persistence. Interventions to normalise bodyweight might help to preserve lung function and reduce morbidity in later life. Such interventions should be coupled with measures to minimise exposure to tobacco smoke and other adverse environmental exposures as well as societal efforts to reduce inequalities.

exposures, potentially leading to lower maximally attained lung function.[2] Conversely, during postnatal development, recovery from prenatal and early-life insults can occur.[3] This ability to repair and rebuild lung structure is a hallmark of lung health.[2] These dynamic processes should be reflected in the catch-up and growth failure or decline in lung function parameters.

Low peak lung function in early adulthood is associated with a high risk of chronic obstructive pulmonary disease and other adverse health outcomes[4,5] such as cardiovascular and cerebrovascular events,[6] sudden cardiac death,[7] and premature death from all causes through adulthood.[8] Lung function measured in children and young adults can therefore be used to identify individuals at risk of unhealthy ageing.[9] The importance of lung function trajectories and the potential implementation of this knowledge in clinical practice to detect impairment early and monitor its progression have recently been recognised, with the proposal to use a Lung Function Tracker to monitor lung health across the life course.[10] However, the ability to identify a potential problem by measuring spirometry in childhood does not automatically extend to actionable interventions to address it, and an understanding of temporality and determinants of decline or improvement in lung function is key for the development of interventions to promote lung health.[10]

Data-driven research of adult lung function described trajectories characterised by low peak lung function and accelerated decline and catch-up in later adulthood.[11,12] By contrast, most such analyses of lung function development through childhood revealed no evidence of clusters with declining or improving lung function (appendix pp 3–5).[11–19] A study published in 2023 used descriptive statistics and regression modelling to suggest that worsening and improvement in spirometry can be observed at two transition points from school age to adulthood.[17] However, these changes in lung function were defined a priori, and data-driven analyses of the same dataset identified three longitudinal clusters (normal, restrictive, and obstructive lung function) but no clusters characterised by improvement or decline in lung function.[17] Another recent analysis using data-driven Markovian models identified five cross-sectional lung function states (ranging from very low lung function to very high lung function) at three points through

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See **Online** for appendix

childhood. A subsequent exploratory analysis in which catch-up and growth failure were defined a posteriori suggested that such defined growth failure can predict respiratory symptoms, airflow limitation, and small-airway dysfunction in adulthood.[20] Another study used group-based trajectory modelling (ages 4–18 years) and identified three parallel trajectories (high, normal, and low), and a catch-up, but not declining trajectory.[19]

We propose that patterns of change in lung function characterised by improvement and decline can be identified using data-driven methodologies, but this would require large sample size and collaboration involving multiple cohorts.[17,20,21] A data-driven approach is important because it allows identification of potentially important hidden patterns (clusters) in complex traits across the entire data space, which would not be apparent when using investigator-led a priori[17] or a posteriori[20] definitions. In subsequent steps, it is possible to probe associates of such discovered clusters.[22] This approach recently enabled identification of the novel mechanisms of persistence of wheezing that were not apparent when using investigator-proposed definitions.[23] Discovery of such patterns and their associates might allow identification of temporal windows of opportunity and potential targets for early intervention to preserve or improve lung function. To test this, we explored trajectories of airflow limitation from childhood (age 5–8 years) into early adulthood (age 20–26 years) in a unique dataset across six birth cohorts with repeated spirometry.

Methods

Study design and population

We used data from six population-based birth cohorts. The Avon Longitudinal Study of Parents and Children (ALSPAC),[24] Isle of Wight (IOW),[25] Manchester Asthma and Allergy Study (MAAS),[26] and Aberdeen Study of Eczema and Asthma (SEATON)[27] cohorts are contained within the UK STELAR consortium,[28] whereas the Child (*Barn*), Allergy, Milieu, Stockholm, Epidemiological (BAMSE) survey [29] is a Swedish birth cohort and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA)[30] cohort is Dutch. Sex, race, and ethnicity data were obtained via parental report. Further details about the cohorts are provided in the appendix (pp 6–7). Research ethics committees approved all studies, and written informed consent was obtained from parents or study participants, or both, when applicable .

Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines[31,32] at ages 8 years, 15 years, and 24 years in ALSPAC; ages 10 years, 18 years, and 26 years in IOW; ages 8 years, 11 years, 16 years, and 20 years in MAAS; ages 8 years, 16 years, and 24 years in BAMSE; ages 5 years, 10 years, and 15 years in SEATON; and ages 8 years, 12 years, and 16 years in PIAMA (appendix pp 8–9). Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were recorded for all cohorts. This analysis includes participants with at least two spirometry assessments.

Discovery and replication populations

For the discovery analysis, we pooled data from four cohorts with lung function until early adulthood (ALSPAC, IOW, MAAS, and BAMSE). We defined shared time intervals—ie, the common age at which lung function was assessed across cohorts—as middle childhood (ages 8–10 years), adolescence (15–18 years), and early adulthood (20–26 years).

For replication, we pooled data from cohorts with lung function to adolescence (PIAMA and SEATON). We defined shared time intervals as early school age (5–8 years), middle childhood (10–12 years), and adolescence (15–16 years).

Statistical analysis

We aimed to identify growth trajectories of spirometry parameters extending from childhood into physiological peak in adulthood. A detailed description of the statistical analysis and approach to missing data is provided in the appendix (pp 12–13). Missing data patterns for spirometry are shown in the appendix (p 13). Briefly, we did not impute missing data on spirometry because the model used to derive trajectories could handle missing data. Because gender was related to attrition in spirometry, we added gender into the model when driving trajectories as a sensitivity analysis. We imputed missing data on risk factors (only for the discovery cohort) to check how sensitive the association analysis was to missing data. Weighted κ and Rand index were calculated to measure the agreement between trajectory allocation on the basis of complete and incomplete data (appendix p 11). The rationale for joint modelling of the FEV_1/FVC ratio and FEV_1 and for using regression residuals is described in the appendix (pp 39–40).

To estimate standardised regression residuals for the trajectory derivation, we performed regression analysis for FEV_1 and for the FEV_1/FVC ratio on age (linear and quadratic), height, and race or ethnicity after stratification by sex.

We considered three levels of airflow limitation severity relative to the lower limit of normal (LLN) FEV_1 (ie, the lower fifth percentile), corresponding to standardised regression residuals of around –1·645). Mild airflow limitation was defined as standardised regression residuals less than LLN but greater than or equal to –2. Moderate airflow limitation was defined as standardised regression residuals less than –2 but greater than or equal to –3. Severe airflow limitation was defined as standardised regression residuals less that –3.[33] In addition, very mild airflow limitation was defined as a FEV_1/FVC ratio regression residuals less than or equal to LLN and FEV_1 regression residuals greater than or equal to LLN.[33]

We used latent class trajectory modelling[34] to derive trajectory classes based on joint modelling of FEV_1 and

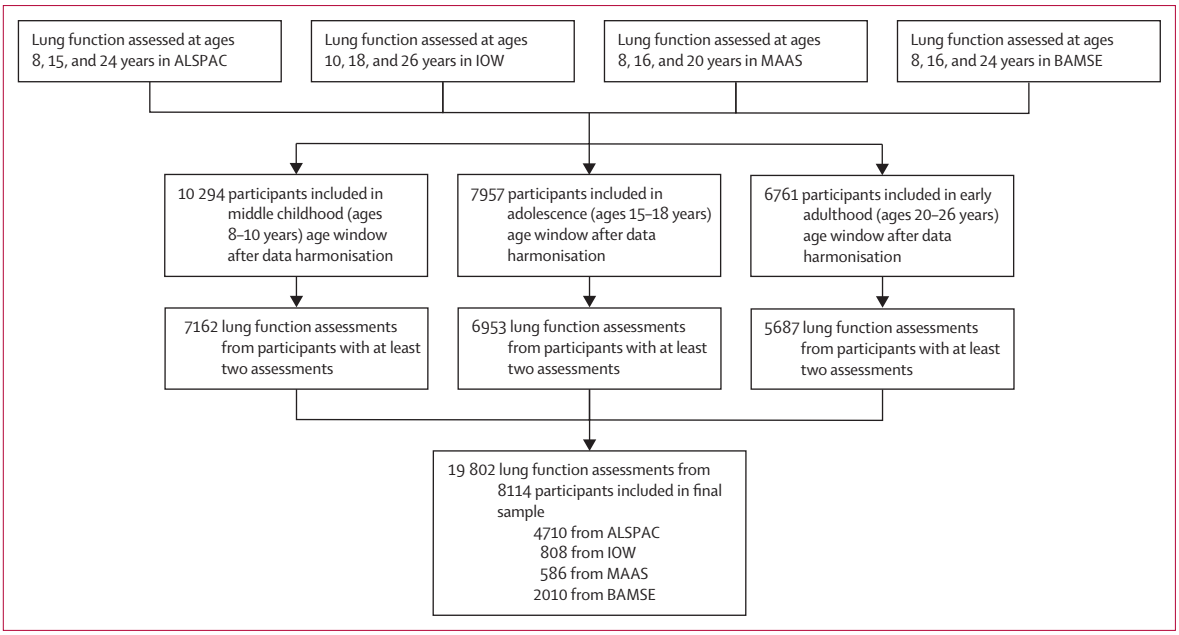

Figure 1: **Data harmonisation and sample sizes in the discovery population**
ALSPAC=Avon Longitudinal Study of Parents and Children. BAMSE=Child (*Barn*), Allergy, Milieu, Stockholm, Epidemiological survey. IOW=Isle of Wight. MAAS=Manchester Asthma and Allergy Study.

	Discovery cohorts				Replication cohorts	
	ALSPAC (n=4710)	IOW (n=808)	MAAS (n=586)	BAMSE (n=2010)	PIAMA (n=909)	SEATON (n=428)
Sex						
Male	2370 (50·3%)	402 (49·8%)	310 (52·9%)	914 (45·5%)	429 (47·2%)	216 (50·5%)
Female	2340 (49·7%)	406 (50·2%)	276 (47·1%)	1096 (54·5%)	480 (52·8%)	212 (49·5%)
White European ancestry	4629 (98·3%)	808 (100%)	563 (96·1%)	2010 (100%)	876 (96·4%)	428 (100%)
Gestational age, weeks	39·46 (1·86)	39·92 (1·54)	39·93 (1·57)	39·79 (1·86)	39·95 (1·53)	39·21 (2·52)
Maternal age at pregnancy, years	29·12 (4·56)	26·97 (5·24)	30·69 (4·80)	30·99 (4·43)	30·80 (3·72)	29·41 (5·58)
Birthweight centiles	63·32 (27·89)	56·80 (29·39)	61·72 (28·46)	66·42 (27·04)	53·01 (29·00)	62·99 (28·43)
Parental asthma	621/3721 (16·7%)	159/802 (19·8%)	173 (29·5%)	412/1997 (20·6%)	183/900 (20·3%)	117/428 (27·3%)
Maternal smoking during pregnancy	887/4329 (20·5%)	178/797 (22·3%)	74/584 (12·7%)	228/2009 (11·3%)	124/904 (13·7%)	127 (29·7%)
Breastfeeding during first 6 months	3447/4225 (81·6%)	604/754 (80·1%)	419/565 (74·2%)	1661/1958 (84·8%)	787 (86·6%)	296/417 (71·0%)
Early childhood wheeze*	2194/4441 (49·4%)	229/794 (28·8%)	257 (43·9%)	317 (15·8%)	350 (38·5%)	93/419 (22·2%)
Pet ownership first year of life†	2931/4251 (68·9%)	416/758 (54·9%)	194/519 (37·4%)	214/1972 (10·9%)	444 (48·8%)	148/422 (35·1%)

Data are n (%), n/N (%) or mean (SD). ALSPAC=Avon Longitudinal Study of Parents and Children. BAMSE=Child (*Barn*), Allergy, Milieu, Stockholm, Epidemiological. IOW=Isle of Wight. MAAS=Manchester Asthma and Allergy Study. PIAMA=Prevention and Incidence of Asthma and Mite Allergy. SEATON=Study of Eczema and Asthma. *Current wheeze at age 5 years or younger. †Pet inside the house or contact with pets most of the time in the first year of life.

Table 1: **Cohort characteristics of the study populations**

FEV_1/FVC ratio regression residuals. By joint modelling, we mean modelling these two markers simultaneously in a single model. We fitted latent class growth analysis (also known as grouped-based trajectory modelling)[35] and a latent growth mixture model. The final model was selected using the lowest Bayesian information criterion (BIC), the average posterior membership probability, class size, relative entropy, and interpretation. We aimed to select a model that achieved at least 70% average posterior probability for all classes and with the highest relative entropy (at least 80%). For the resulting trajectories to be clinically meaningful, we included classes with at least 1% population capture.[36] More details about latent class trajectory modelling and different model specifications and definitions are given in the appendix (pp 14–15). To confirm regression residuals-based trajectories, we calculated percentage-predicted values using Global Lung Function Initiative (GLI)

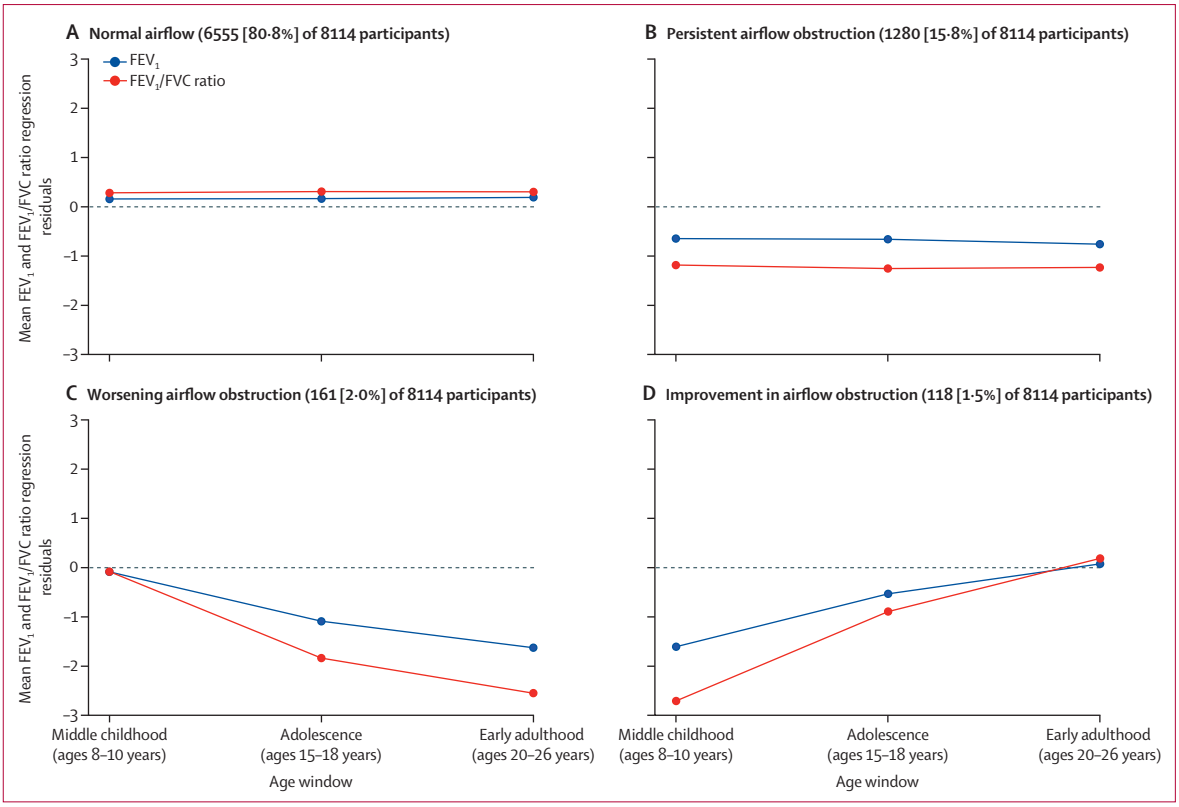

Figure 2: **Change in mean FEV_1 and FEV_1/FVC ratio regression residuals with age, by airflow limitation trajectory, using pooled data from the discovery population (n=8114)**

FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

reference equations. Model parameters were estimated using a maximum likelihood framework. Participants were assigned to the trajectory with the highest posterior probability. For final model selection and reporting, we followed the Guidelines for Reporting Latent Trajectory Studies[37] (appendix pp 42–44).

Association analysis was done independently in each of the UK cohorts and in BAMSE (discovery analysis), and in each of the SEATON and PIAMA cohorts (replication). Variables included in the analyses are listed in the appendix (pp 15–16). Briefly, we considered early-life factors and data collected at the time of the first lung function test. We investigated early-life factors as well as demographic characteristics associated with each trajectory using weighted random-effect multinomial logistic regression models. The posterior probability of trajectory membership was included as weights to reflect the uncertainty of assignment, and the cohort was used as a random effect to account for between-study heterogeneity. Results are reported as relative risk ratios (RRRs) with Wald 95% CIs and Wald χ^2 p values. We pooled RRRs from cohorts and used fixed-effect or random-effect models for meta-analysis, depending on the results of Cochran's Q test for heterogeneity used in meta-analysis (appendix p 11). To investigate the impact of known risk factors with repeated-measure data, such as wheeze and BMI, we have presented the prevalence or mean values as appropriate across different ages. We have also reported the prevalence of asthma medication usage across ages by trajectories to assess the potential benefits of treatments on lung function trajectories. We conducted two meta-analyses in the discovery cohort to identify risk factors associated with trajectory membership. In the first meta-analysis, we estimated RRRs by merging risk factors data from STELAR cohorts and pooled them with RRRs from the BAMSE cohort. In the second meta-analysis, we pooled RRRs from each STELAR cohort individually as well as BAMSE. The results from both approaches were identical; thus, we only report findings from the first meta-analysis. A priori chosen interaction terms for wheeze and BMI Z score, as well as for asthma diagnosis, BMI Z score, and birth weight percentiles were included in the multinomial logistic regression model. If any interaction was statistically significant ($p<0·05$), we reported the stratified relative risk ratios (RRRs) along with their 95% CIs. Further details are available in the appendix (p 16). Analyses were performed using SAS (version 9.4) and R (version 4.2.2).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The discovery analysis included 8114 participants (4710 from ALSPAC, 808 from IOW, 586 from MAAS, and 2010 from BAMSE (figure 1). The replication population included 909 children from PIAMA and 428 from SEATON (1337 participants in total). Cohorts were comparable in sex, gestational age, maternal age, birthweight, and breastfeeding (table 1). Parental asthma was most prevalent in the MAAS and SEATON cohorts, whereas maternal smoking was most prevalent in the SEATON cohort. Pet ownership was most common in ALSPAC.

The four-class latent class growth analysis model offered the best balance between the lowest BIC score and class sizes (appendix p 17). The average posterior probabilities of trajectory membership and relative entropy were high (>0·70), showing confidence in the class assignment (appendix p 18). The four trajectories of change in mean FEV1 and FEV_1/FVC ratio regression residuals with age in the discovery population are shown in figure 2 (mean FEV1 and FEV_1/FVC ratio regression residuals in individual cohorts are shown in the appendix pp 19–20). Based on the patterns of spirometry parameters, we labelled trajectories as normal, persistent airflow obstruction, worsening airflow obstruction, and improvement in airflow obstruction. Individual participant lung function in each trajectory is shown in the appendix (p 21). The addition of sex to the model showed similar patterns (appendix p 22).

Participants in the worsening airflow obstruction trajectory had a mean GLI percentage-predicted FEV_1 of 99·51% (SD 13·81) in middle childhood, which decreased to 77·07% (12·93) by early adulthood (figure 3; appendix p 23). Participants in the improvement in airflow obstruction trajectory had mean FEV_1 of 80·98% (SD 12·32) in middle childhood, which increased to 96·61% (12·24) by early adulthood. The mean GLI percentage-predicted FEV_1/FVC ratio decreased from 99·16% (SD 9·57) in middle childhood to 77·37% (7·87) in early adulthood in the worsening airflow obstruction trajectory, and increased from 80·60% (7·00) in middle childhood to 98·03% (10·19) by early adulthood in the improvement in airflow obstruction trajectory (figure 3; appendix p 23).

As a sensitivity analysis, we ran modelling among 3574 individuals in the discovery cohort with spirometry at all three timepoints. We obtained a similar four-trajectory optimal solution (appendix pp 24–25). There was a strong agreement between analyses on complete and incomplete data (weighted κ 0·82; adjusted Rand index 0·81). Trajectory assignments were robust to missing data, with the proportion of children assigned to the same trajectory in the two analyses exceeding 70% (appendix p 25).

The distribution of obstructive phenotypes and severity at each timepoint across the four trajectories is shown the appendix (p 26). The transition pattern for improvement and worsening trajectories is shown in figure 4. In the worsening airflow trajectory, the transition rate from non-obstructive to obstructive spirometry was higher from adolescence to early adulthood than from middle childhood to adolescence (61·5% *vs* 32·6%; appendix p 27). By contrast, in the trajectory with improvement in airflow obstruction, the transition rate from obstructive to non-obstructive spirometry was substantially higher from middle childhood to adolescence than from adolescence to early adulthood (57·8% *vs* 13·4%; appendix p 27).

To identify factors associated with FEV_1 and FEV_1/FVC trajectories, we applied random-effect multinomial logistic regression models for the UK-based discovery cohorts ALSPAC, IOW, and MAAS, and separately for the BAMSE cohort using the normal airflow trajectory as the reference (appendix pp 28–30). The associations were similar in the two analyses. The pooled RRRs after meta-analysis from UK-based discovery cohorts and BAMSE cohort are given in table 2. Older gestational age was associated with a reduced relative risk of persistent airflow obstruction; in other words, a 1-week increase in gestational age was associated with reduced relative risk of joining the persistent airflow obstruction

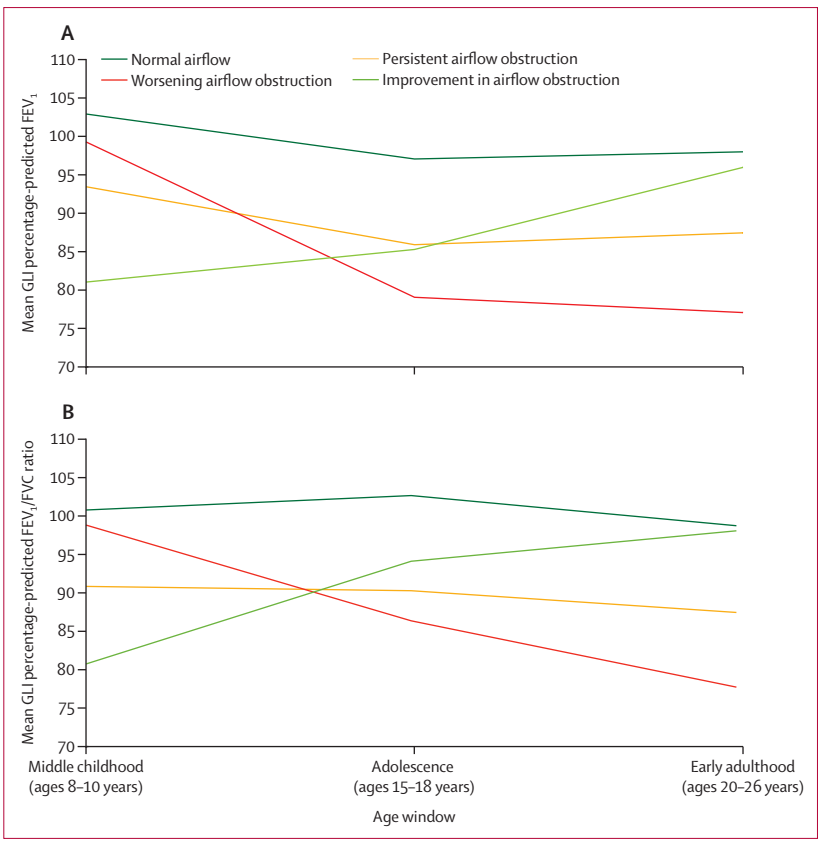

Figure 3: **Change in GLI percentage-predicted FEV_1 and FEV_1/FVC ratio with age, by airflow limitation trajectory**

Age-specific percentage-predicted FEV_1 and FVC values were calculated from pooled data of the discovery population (n=8114) using GLI reference equations. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. GLI=Global Lung Function Initiative.

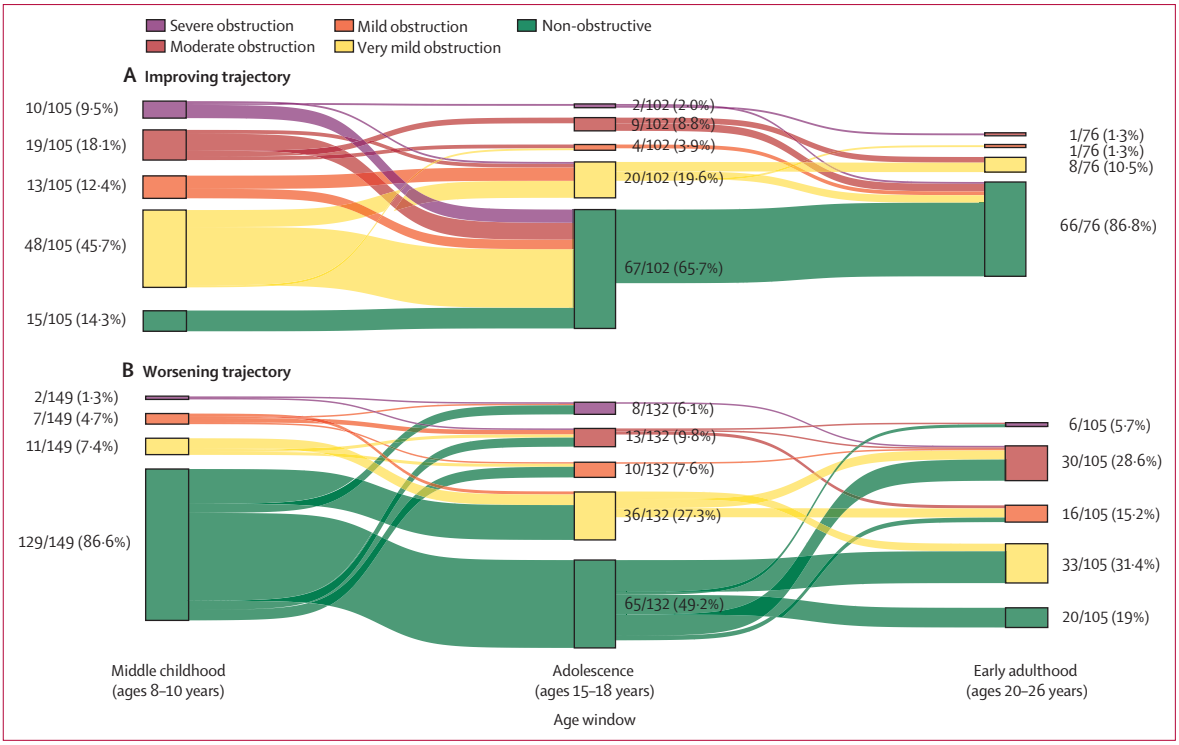

Figure 4: **Change in prevalence of airflow limitation severity with age and its transitional patterns for the improvement in airflow obstruction trajectory (A) and worsening airflow obstruction trajectory (B)**
Denominators for each age group represent the number of individuals with available lung function assessments for that age. At each timepoint, individuals who do not have data have been removed. The improvement in obstruction trajectory includes all improvers, irrespective of where they started. Similarly, the worsening obstruction trajectory includes all decliners, regardless of where they started.

	Persistent obstruction		Worsening obstruction		Improvement in obstruction	
	Univariate relative risk ratio (95% CI)	p value	Univariate relative risk ratio (95% CI)	p value	Univariate relative risk ratio (95% CI)	p value
Male	1·04 (0·97–1·11)	0·26	0·94 (0·80–1·11)	0·49	0·98 (0·81–1·18)	0·81
Gestational age, weeks	0·93 (0·91–0·96)	<0·0001	0·96 (0·88–1·04)	0·33	0·96 (0·87–1·06)	0·42
Maternal age	1·00 (0·98–1·02)	0·81	0·99 (0·96–1·02)	0·49	0·98 (0·94–1·02)	0·26
Birthweight centiles	1·00 (0·99–1·00)	0·99	1·00 (0·99–1·00)	0·92	0·99 (0·99–0·99)	<0·0001
Parental asthma	1·24 (0·86–1·79)	0·25	1·05 (0·83–1·33)	0·68	1·31 (1·01–1·71)	0·043
Maternal smoking during pregnancy	1·25 (1·15–1·36)	<0·0001	1·32 (1·08–1·61)	0·011	1·19 (0·93–1·52)	0·18
Breastfeeding first 6 months	0·99 (0·90–1·08)	0·81	1·01 (0·80–1·28)	0·92	1·01 (0·78–1·33)	0·91
Pet ownership first year of life*	1·00 (0·92–1·08)	0·99	1·07 (0·89–1·29)	0·49	1·23 (0·98–1·54)	0·076
Early childhood wheeze†	1·59 (1·16–2·17)	0·0041	1·36 (1·15–1·60)	<0·0001	1·96 (1·57–2·44)	<0·0001
BMI Z score at first lung function‡	1·13 (1·06–1·20)	<0·0001	0·95 (0·80–1·13)	0·59	1·00 (0·83–1·22)	0·96
Current wheeze at first lung function	1·56 (1·28–1·90)	<0·0001	1·49 (1·22–1·80)	<0·0001	2·31 (1·89–2·83)	<0·0001
Current asthma diagnosis at first lung function	1·50 (1·23–1·81)	<0·0001	1·57 (1·30–1·89)	<0·0001	2·38 (1·94–2·93)	<0·0001
Current sensitisation at first lung function	1·17 (1·08–1·28)	<0·0001	1·29 (1·05–1·58)	0·015	1·34 (1·07–1·69)	0·013
Current parental smoking at first lung function	1·10 (1·02–1·18)	0·021	1·22 (1·03–1·45)	0·023	0·98 (0·78–1·23)	0·87

Data are pooled relative risk ratio (Wald 95% CI) from STELAR cohorts (ALSPAC, IOW, MAAS) and BAMSE after meta-analysis (n=8114) and Wald χ^2 p values. For all continuous variables, the relative risk ratios are per unit increase, whereas for categorical variables the relative risk ratios are for "yes", with "no" as a reference. ALSPAC=Avon Longitudinal Study of Parents and Children. BAMSE=Child (*Barn*), Allergy, Milieu, Stockholm, Epidemiological survey. IOW=Isle of Wight. MAAS=Manchester Asthma and Allergy Study. *Pet inside the house or contact with pets most of the time in first year of life. †Current wheeze at age 5 years or younger. ‡Based on the British 1990 and WHO Growth Reference, more details about WHO Growth Reference calculation are given the appendix (p 15).

Table 2: **Parental and childhood risk factors associated with obstructed lung function relative to normal lung function**

trajectory compared with the normal airflow trajectory (RRR 0·93 [95% CI 0·91–0·96], p<0·0001; table 2). Lower birthweight was associated with a higher relative risk of joining the trajectory with improvement in airflow obstruction than in the normal airflow trajectory (table 2). Maternal smoking during pregnancy was associated with a higher relative risk of joining the persistent airflow obstruction trajectory and worsening airflow obstruction trajectory than the normal airflow trajectory. A higher BMI Z score at the time of first lung function assessment was associated with a higher relative risk of joining the persistent airflow obstruction trajectory; in other words, for one Z-score increase in BMI at the time of first lung function assessment, the relative risk of joining the persistent airflow obstruction trajectory compared with the normal airflow trajectory increased (1·13 [1·06–1·20], p<0·0001; table 2). The presence of wheeze, an asthma diagnosis, and allergic sensitisation at the first lung function assessment compared with no such diagnosis at first lung function assessment, was associated with a higher relative risk of joining the trajectories for persistent, worsening, and improvement in airflow obstruction respectfully than the normal airflow trajectory (table 2). Parental asthma was linked to a higher relative risk of joining the improvement in airflow obstruction trajectory than the normal trajectory. Early childhood wheezing was also associated with a higher relative risk of joining the trajectories for persistent, worsening, and improvement in airflow obstruction relative to the normal airflow trajectory. Additionally, current parental smoking at the first lung function assessment was associated with an increased risk of joining the trajectories for persistent and worsening airflow obstruction compared with the normal airflow trajectory (table 2). No other factors were found to be significantly linked to trajectory membership.

The point prevalence of wheezing and mean BMI with age in the four trajectories are shown in the appendix (p 31). Compared with other trajectories, participants in the trajectory with improvement in airflow obstruction had persistently lower mean BMI and higher incidence of early childhood wheezing, but importantly, wheezing in this trajectory declined sharply with age (appendix p 31). Asthma medication usage was notably higher among participants in the trajectory with improvement in airflow obstruction, and medication use decreased with age in this trajectory (appendix p 32).

The adjusted RRRs with 95% CIs from multinomial logistic regression model, adjusted for sex, gestational age, maternal smoking during pregnancy, and asthma heredity, are shown in the appendix (p 33). After adjustment, the presence or absence of parental asthma had no effect on trajectory membership, whereas a pattern similar to the univariate association was observed for other risk factors. Consistent results were observed among the multivariable-adjusted associations between parental characteristics, childhood characteristics, and characteristics measured at first lung function using imputed data for risk factors (appendix p 34).

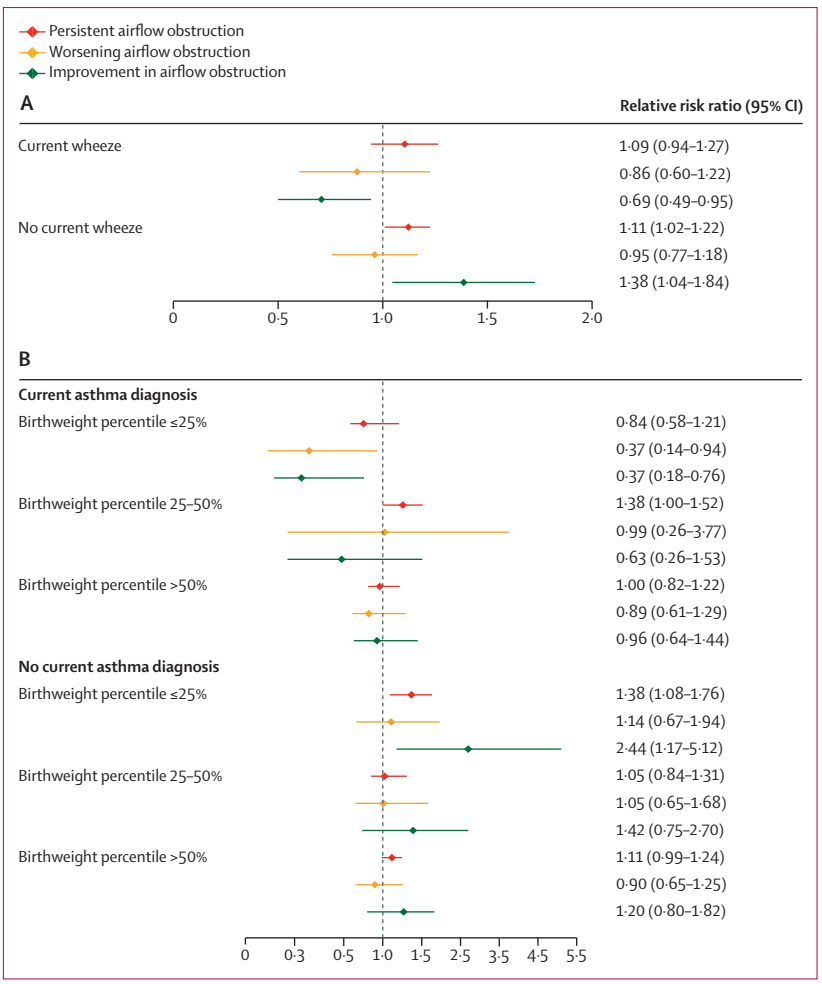

Figure 5: **Interaction between BMI and current wheeze (A), and between BMI, birthweight, and asthma diagnosis (B)**

(A) Relative risk ratios per 1 Z score increase with Wald 95% CI for current BMI Z score at first lung function assessment stratified by current wheezing at first lung function assessment, estimated from multinomial logistic regression with Normal trajectory as a reference, showed a significant interaction between BMI Z score and current wheeze ($p_{interaction}$=0.017). (B) Relative risk ratios per 1 Z score increase with Wald 95% CI for current BMI Z score at first lung function assessment stratified by birthweight centiles and current asthma diagnosis at first lung function assessment, estimated from multinomial logistic regression with Normal trajectory as a reference, showed a significant interaction between birthweight centiles, BMI Z score at first lung function assessment, and current asthma diagnosis at first lung function assessment ($p_{interaction}$=0·016).

We observed a significant interaction between BMI and current wheeze at the time of the first lung function assessment ($p_{interaction}$=0·017; figure 5A). Among children with current wheeze, one Z-score increase in BMI was associated with a reduced relative risk of joining the trajectory with improvement in airflow obstruction than in the normal airflow trajectory. By contrast, among those without current wheeze, a one Z-score increase in BMI was associated with an increased relative risk of joining the trajectory with improvement in airflow than in the normal airflow trajectory.

A significant interaction was also observed between birthweight and BMI and current asthma diagnosis at the first lung function assessment($p_{interaction}$=0·016). A higher BMI was associated with a higher relative risk of joining the trajectory with improvement in airflow obstruction in participants with low birthweight and no current asthma diagnosis; by contrast, higher BMI is associated with a lower relative risk of joining the trajectory with improvement in airflow obstruction among those with low birthweight and current asthma diagnosis (figure 5B).

An optimal solution with almost identical set of four trajectories was evident in the replication cohorts (n=1337; appendix p 35). A detailed modelling summary of the replication cohorts along with risk factor association results is shown in the appendix (pp 36–38). The results were consistent with those obtained in the discovery cohorts.

Discussion

Using data from four population-based birth cohorts, we identified four growth trajectories of spirometry parameters extending from childhood into physiological peak in adulthood. Two of the trajectories were characterised by lack of change (normal and persistent airflow obstruction), and two characterised by a marked change in lung function during the growth phase (worsening and improvement in airflow obstruction). Results were replicated in two cohorts with spirometry measured from early school age to adolescence. Importantly, improvement in and worsening airflow were observed at all ages from early school age to early adulthood and occurred from all airflow obstruction severity levels. Lung function improvement was higher from middle childhood to adolescence; by contrast, worsening was higher from adolescence to early adulthood.

Most previous longitudinal models of lung function from school age into early adulthood have identified between two and four trajectories, which are characterised by stable lung function through childhood, and graphically represented by parallel lines (usually interpreted as so-called tracking of lung function through childhood and into adulthood[21]). However, clinical experience and visualisation of individual lung function trajectories suggest variability between children, with improvement in some and decline in others. To our knowledge, this is the first data-driven analysis to identify both worsening and improvement trajectories during the growth phase (of note, other approaches identified only catch-up[19] or suggested the presence of catch-up and growth failure[17,20]). In the current study, assignment to the improvement and worsening trajectories was rare (overall rate 1·5% and 2·0%, respectively), which is consistent with the population-level estimates of the catch-up and growth failure rates when using investigator-derived definitions[20] (2·4% and 1·2%, respectively), and the catch-up rates of 2% for FEV_1 trajectories.[19]

In contrast to two previous studies that used investigator-derived definitions of the change in lung function,[17,20] the worsening trajectory in the current analysis included participants with a declining pattern irrespective of their initial lung function, comprising both those who declined from normal lung function (86·6%), and from low lung function (13·4%). Similarly, the improvement trajectory included all improvers, some of whom started with low lung function (85·7%), and others with normal lung function (14·3%). In comparison, in previous analyses, only individuals moving from the low or very low lung function to normal or high lung function were assigned to a catch-up group, and those transitioning from normal or high lung function to low or very low lung function were assigned to the growth failure group.[20] This is important, as any reduction in growth might result in a lower maximally attained lung function, which might be clinically relevant, and vice versa, improvement in lung function from normal to supernormal might contribute to healthy ageing.

Importantly, the transition rate towards deterioration in airflow limitation in the worsening trajectory was higher from adolescence to early adulthood than from middle childhood to adolescence. By contrast, in the improvement trajectory, the transition rate towards improvement was significantly higher from middle childhood to adolescence. This finding is consistent with observations that catch-up growth in lung function might be possible around puberty, in association with later onset of puberty and higher velocity of pubertal growth.[38] Taken together, these data suggest that the likelihood of worsening seems to be higher later in life, whereas improvement tends to occur more frequently earlier, in school-aged children. This provides potentially important information on how and when to identify individuals who could benefit from intervention, as well as the nature of the intervention required.

The likelihood of being in the improvement trajectory was significantly higher for participants with wheezing and asthma diagnoses, which might appear to be counterintuitive. However, children with asthma or wheeze have the highest probability of impaired lung function at early school age and hence also the highest potential for improvement.[33] Of note, among participants in the improvement trajectory, wheezing declined sharply over time, whereas in those with worsening obstruction wheezing persisted. However, at symptom onset in early childhood, clinical presentation among transient and persistent wheezers is similar, and it is difficult to predict the course of wheezing.[22] This emphasises the need to develop methods to accurately identify preschool children with wheeze who will stop wheezing and differentiate them from children whose wheezing will persist and lead to a decline in lung function[39] because the management of these two groups might be different. Of note, the use of asthma medications in childhood was higher among those in

the improvment trajectory and started decreasing by adolescence.

Differences in the associated risk factors (and by extension in the possible interventions that might be applied to preserve or improve lung function) were observed between children with and without wheeze at the time of the first lung function assessment. Among children with a current wheeze diagnosis, higher BMI significantly decreased the likelihood of improvement. By contrast, among children without a wheeze diagnosis, lower BMI significantly increased the likelihood of improvement. These finding are consistent with a study showing that higher BMI at age 4 years is associated with a greater likelihood to be assigned to catch-up.[19] Similarly, a significant interaction was observed between birthweight, BMI, and current asthma diagnosis, in that an increase in BMI increased the chance of improvement in participants with low birthweight and no current asthma diagnosis. Conversely, an increase in BMI decreased the chance of improvement among children with a low birthweight and current asthma diagnosis. These results suggest that every effort should be made to decrease overweight among children with asthma diagnosis and current wheeze, whereas healthy ways to gain and maintain an optimal weight should be encouraged among those without wheeze (particularly those with low birthweight).

Unsurprisingly, maternal smoking during pregnancy was associated with higher risk of being in the persistent airflow obstruction and worsening airflow obstruction trajectories. Similar to most previous studies, the persistent obstruction trajectory was associated with lower gestational age, maternal smoking during pregnancy, early childhood wheeze, BMI, current wheeze, asthma diagnosis, allergic sensitisation, and parental smoking at middle childhood age.

Our study has both strengths and potential limitations. Among the strengths, features of the present study that enabled data-driven identification of both catch-up and decline trajectories, as well as the interaction between birthweight, BMI, and asthma diagnosis in relation to the membership of these two important trajectories include the large sample size, and that we modelled FEV_1 and the FEV_1/FVC ratio jointly. Conversely, we acknowledge that when analysing lung function data from multiple cohorts, a systematic bias might exist in recording spirometry (including the use of different equipment and operators). We used internal reference—ie, regression residuals—to provide an alternative approach and account for potential bias, but this might limit the generalisability of our findings. For trajectory derivation, we used pooled data, and an ideal option was to do the association analysis using pooled data on risk factors. However, because of individual-level data governance restrictions, the association analysis was done independently in the UK-based cohorts ALSPAC, IOW, MAAS and in BAMSE, and the results were pooled using meta-analysis. To check and account for the potential bias of this approach, first, at the meta-analysis stage, we checked for heterogeneity and used random-effect meta-analysis where appropriate; second, as a sensitivity analysis, we performed the analysis in each cohort independently, and the results of subsequent meta-analyses were consistent between the two approaches. Data are available on request, but we have chosen not to report the findings here. Furthermore, there might be between-study heterogeneity. We used cohort as a random effect in all models to address this. Another limitation is that the populations were not ethnically diverse (>95% of participants were of White European ancestry) and so the results might not be transferable to other ethnic groups. Likewise, early-life pulmonary or airway function tests were not performed, which limits the inference to the potential role of preschool lung function.[40] Like most other studies investigating longitudinal lung function, we used pre-bronchodilator spirometry. Postbronchodilator spirometry might more accurately predict subsequent respiratory diseases, but longitudinal data on post-bronchodilator lung function during childhood is rarely collected in birth cohorts. Finally, although multiple early-life risk factors and those contemporaneous with the first assessment of lung function were considered, residual confounding—eg, diet or physical activity, and unexplored risk factors—cannot be excluded.

In conclusion, our results show that improvement and worsening of lung function during childhood can occur at all ages and obstruction severity levels, with likelihood of improvement being higher from childhood to adolescence and worsening from adolescence to adulthood. Our observations open the possibility that a combination of interventions to normalise bodyweight, both tackling overweight and obesity (particularly among children with wheeze and asthma diagnosis) and underweight in children without wheeze, might help to preserve lung function and reduce morbidity in later life. These should be coupled with measures to minimise exposure to tobacco smoke and other adverse environmental exposures. Among children with early wheeze, every effort should be made to derive interventions to prevent wheeze persistence. Given that many of the risk factors for airflow limitation through childhood are related to inequality, all of these measures must be parallelled with societal efforts to reduce inequalities.

Contributors

AC, GR AS, AU, RG, and JWH conceived and planned the study and wrote the manuscript. AC, HA, CSM, ST, JWH, AS, EM, GHK, AA, RF, and GR were responsible for the acquisition of the financial support for the project leading to this publication. AU, RG, GW, JMV, and SF developed and applied statistical, mathematical, and computational techniques to analyse and synthesise data. AU, RG, and SF were responsible for the annotation and maintenance of the research data (including software code for interpreting the data). AU, RG, and SF were responsible for visualisation of data and data presentation. AC, HA, CSM, ST, JWH, LL, AS, EM, and GR conducted investigation process. LL performed longitudinal lung function measurements in MAAS. HJLK, GW, GHK, JMV, JAW, RF, AA, and EM directly or indirectly provided with

the resources and data necessary for this project. All authors contributed to the interpretation of the results. All authors provided critical feedback and helped to shape the research, analysis, and report. AU, RG, and SF directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AC reports personal fees from Sanofi, La Roche-Posay, and Reacta Healthcare. EM has received consulting fees from ALK and AstraZeneca and lecture fees from ALK, AstraZeneca, Chiesi, and Sanofi. GHK reports grant support from the Netherlands Lung Foundation, TEVA the Netherlands, GSK, Vertex, Ubbo Emmius Foundation, the EU (H2020), and Zon-MW and lecture and advisory fees from GSK, AstraZeneca, and Pure-IM, paid to their institution. AA reports research grants, consulting fees, and lecture honoraria from GlaxoSmithKline, AstraZeneca, Menarini, Chiesi, and Sanofi and unpaid roles as Chair of the Board of Directors of GOLD and co-chair of CADSET. RF reports grants, paid to her institution, for research projects from ISC-III, AstraZeneca, GSK, and Menarini; fees for participation in the Novelty study scientific community and for being co-chair from AstraZeneca; and fees for speaking at symposiums from AstraZeneca and Chiesi. JAW report grants from Astra Zeneca, Boehringer, Chiesi, GSK, Novartis, Genentech, and 37Clinical, paid to her institution; fees for advisory boards from AstraZeneca, Epiendo, GSK, Gilead, Novartis, Pieris, Pulmatrix, and Empiricio; and speaker fees from AstraZeneca, GSK, Boehringer, Recipharm, and Novartis. GR reports funding, paid to his institution, from the Medical Research Council and follow-up funding for the Isle of Wight birth cohort from David Hide Asthma & Allergy Research Centre. AS reports grants or contracts from the UK National Institute for Health and Care Research and JP Muton Charitable Foundation, paid to her institution. JWH reports grants from the Medical Research Council UK, paid to their institution. All other authors declare no competing interests.

Data sharing

De-identified participant data and data dictionary are available; each cohort has its own policies and procedure to share the data and can be contacted for data request.

Acknowledgments

We thank the study participants and their parents for their continued support and enthusiasm. We greatly appreciate the commitment they have given to the project. We acknowledge the hard work and dedication of the study teams (post-doctoral scientists, physiologists, research fellows, nurses, technicians, and clerical staff). The CADSET European Respiratory Society (ERS) Clinical Research Collaboration has been supported by financial and other contributions from the following consortium partners: ERS, AstraZeneca, Chiesi Farmaceutici, GlaxoSmithKline, the Menarini Group, and Sanofi-Genzyme. This study was supported by the UK Medical Research Council (MRC) programme grant MR/S025340/1 and grants G0601361 and MR/K002449/1. RG was in part funded through the Wellcome Trust Strategic Award 108818/15/Z. The UK MRC and Wellcome Trust (grant reference 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. MAAS was supported by Asthma UK grant numbers 301 (1995–98), 362 (1998–2001), 01/012 (2001–04), and 04/014 (2004–2007); the British Medical Association James Trust (2005); the JP Moulton Charitable Foundation (2004–16); the North West Lung Centre Charity (1997–current); and the UK MRC grant MR/L012693/1 (2014–18). The IOW assessments were supported by the US National Institutes of Health (grant number R01 HL082925), Asthma UK (grant number 364), British Medical Association James Trust grant, and the David Hide Asthma and Allergy Research Trust. This research was in part supported by the UK National Institute for Health and Care Research (NIHR) Imperial Biomedical Research Centre and Manchester Biomedical Research Centre. The PIAMA study was supported by project grants from the Netherlands Organisation for Health Research and Development; the Netherlands Organisation for Scientific Research; the Lung Foundation Netherlands (formerly Netherlands Asthma Fund, grant number 4.1.20.003); the Netherlands Ministry of Spatial Planning, Housing, and the Environment; the Netherlands Ministry of Health, Welfare, and Sport; and the Dutch National Institute for Public Health and the Environment. BAMSE was supported by the Swedish Research Council (2022-06340), the Swedish Heart-Lung Foundation (20210546), and Region Stockholm (ALF and database maintenance). The views expressed are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care.

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