ORIGINAL ARTICLE

Plasticity of Individual Lung Function States from Childhood to Adulthood

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Abstract

Rationale: Recent evidence highlights the importance of optimal lung development during childhood for health throughout life.

Objectives: To explore the plasticity of individual lung function states during childhood.

Methods: Prebronchodilator FEV_1 *z*-scores determined at age 8, 16, and 24 years in the Swedish population-based birth cohort BAMSE (Swedish abbreviation for Child [Barn], Allergy, Milieu, Stockholm, Epidemiological study) ($N = 3{,}069$) were used. An unbiased, data-driven dependent mixture model was applied to explore lung function states and individual state chains. Lung function catch-up was defined as participants moving from low or very low states to normal or high or very high states, and growth failure as moving from normal or high or very high states to low or very low states. At 24 years, we compared respiratory symptoms, small airway function (multiple-breath washout), and circulating inflammatory protein levels, by using proteomics, across states. Models were replicated in the independent Dutch population-based PIAMA (Prevention and Incidence of Asthma and Mite Allergy) cohort.

Measurements and Main Results: Five lung function states were identified in BAMSE. Lung function catch-up and growth failure were observed in 74 (14.5%) BAMSE participants with low or very low states and 36 (2.4%) participants with normal or high or very high states, respectively. The occurrence of catch-up and growth failure was replicated in PIAMA. Early-life risk factors were cumulatively associated with the very low state, as well as with catch-up (inverse association) and growth failure. The very low state as well as growth failure were associated with respiratory symptoms, airflow limitation, and small airway dysfunction at adulthood. Proteomics identified IL-6 and CXCL10 (C-X-C motif chemokine 10) as potential biomarkers of impaired lung function development.

Conclusions: Individual lung function states during childhood are plastic, including catch-up and growth failure.

Keywords: asthma; early life risk factors; inflammation; multiple-breath washout; respiratory health

Lung function normally increases from birth to early adulthood and attains its peak at around 20–25 years of age (1). Suboptimal lung development with failure to achieve normal peak lung function in early adulthood occurs in 4–12% of the general population (2) and is associated with a higher prevalence and an earlier incidence of respiratory, cardiovascular, and metabolic diseases, as well as with premature death (3–8). These observations highlight the importance of optimal lung development during childhood and adolescence for health and disease throughout life (2).

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At a Glance Commentary

Scientific Knowledge on the Subject: Recent evidence highlights the importance of optimal lung development during childhood for health and disease through life. However, the plasticity of individual lung function states has not been explored adequately.

What This Study Adds to the Field: Individual lung function states during childhood, adolescence, and early adulthood are plastic, including both catch-up and growth failure.

Evidence from previous longitudinal studies shows that there is a range of different lung function trajectories in the general population, the majority indicating that the level of lung function in later life is already set in early childhood (4, 9, 10). However, the analytical approaches used so far may have been limited in their ability to identify individual-level variations (2, 11) and the potential plasticity of individual lung function states during childhood and adolescence into early adulthood, including both catch-up (moving from low to normal or high lung function) and growth failure (moving from normal or high to low lung function) (*see* Figure E1 in the online supplement). To better identify windows of opportunity for prevention and early intervention of lung function development abnormalities during childhood and adolescence, the use of methods that can accurately detect individual variations is essential. Furthermore, the relationship between lung function development and preventable risk exposures, as well as potential biomarkers, needs to be explored and may yield new pathobiological insights and identify subjects at risk and, potentially, novel pharmacological targets for early intervention (12).

Here we used an unbiased, data-driven, dependent mixture modeling (13) in the birth cohort BAMSE (Swedish abbreviation for Child [Barn], Allergy, Milieu, Stockholm, Epidemiological) study (14) to identify and characterize individual lung function growth from childhood to early adulthood. Models were replicated in the independent Dutch PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort (15, 16). To explore potential determinants and consequences of individual lung function development, we characterized lung function states with respect to early-life risk factors, respiratory symptoms, small airway function, and airway as well as systemic inflammatory biomarkers in early adulthood. Some of the results of these studies have been previously reported in the form of an abstract (17).

Methods

Subjects and Ethics

The Swedish population-based birth cohort BAMSE recruited 4,089 infants from inner-city, urban, and suburban districts of Stockholm (Sweden) between February 1994 and November 1996 and followed them up from birth until around 24 years (14, 18). BAMSE was approved by the Ethics Committee of Karolinska Institutet (Ref 2016/1380-31/2), Stockholm. All parents (at inclusion, 4, and 8 yr) and participants (at age 16 and 24 yr) signed their informed consent, under the Helsinki Declaration.

Measurements

Additional study details, some of which have been published previously, are presented in the online supplement (14). Briefly, information on demographics, lifestyle characteristics, and exposures was obtained from parental questionnaires administered at recruitment, and follow-up questionnaires were answered by parents at ages 1, 2, 4, 8, 12, and 16 years. At age 24 years, participants themselves answered the questionnaire (19). Prebronchodilator spirometry was determined at 8, 16, and 24 years following the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations (details in the online supplement) (20). Post-bronchodilator lung function was measured at 24 years (21). Predicted values and *z*-scores of FEV_1 and FVC were calculated from the Global Lung Function Initiative Equations (22). In 1,186 participants, multiple-breath nitrogen washout was determined (two or more times) at 24 years (Exhalyzer D, Ecomedics Technologies) according to ERS recommendations (23) to measure the lung

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Author Contributions: G.W., J.H., A.A., and E.M. designed the study and outlined the contents of the manuscript. G.W. was responsible for the practical conduct of the study, including the planning, coordination, and analyses of the data, and writing the manuscript under the supervision of A.A. and E.M. G.W., S.K.M., and E.M. verified the data used. J.H. had overall responsibility for the fractional exhaled nitric oxide, multiple-breath nitrogen washout, and lung function measurements at 8, 16, and 24 years. G.P. and O.G. had overall responsibility for the air pollution data. M.v.H. was responsible for the IgE analyses. S.K.M. and M.B. contributed to the analyses of the dependent mixture model. H.-J.K. replicated the models in PIAMA under the supervision of J.M.V. and G.H.K. U.G. contributed to data collection in PIAMA. R.F., S.K., S.B., M.v.H., S.G., A.G., A.B., and I.K. revised the work critically for content. All authors contributed to the interpretation of the data and approved the final manuscript before its submission.

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clearance index (LCI), a sensitive marker of ventilation inhomogeneity (24). Examinations were made and quality checked using the software Spiroware 3.3.1 (25). Fractional exhaled nitric oxide (F_{ENO}) was measured at 24 years according to the ATS/ERS guidelines (26). Data on specific IgE, eosinophil, and neutrophil counts were available from clinical follow-ups (14). Finally, 92 inflammation-related protein biomarkers (Table E10) were measured in plasma by Proseek Multiplex Inflammation I panel (Olink Bioscience) at 24 years (27).

Lung Function States Modeling

We used a data-driven dependent mixture model (13) to assign participants to their most likely lung function states based on FEV_1 *z*-scores. We assumed that there were several different states in the general population and that the FEV_1 *z*-scores that belonged to each of them followed a Gaussian distribution. Participants could move between the states at the following measurement (8–16–24 yr), a process that can be statistically described as a Markov process (details in the online supplement). Models were compared for goodness of fit using the Bayesian information criterion (Table E1). We built the models using data from participants with two or more lung function measures available as well as with participants with one or more measures available, respectively.

After the optimal model had been selected, participants with two or more lung function data available were used to define catch-up and growth failure, a *post hoc* analysis of the individual lung function state chains. Catch-up was defined as participants moving from low states (low or very low) to normal or high states (normal, high, or very high); participants increasing from the very low to low states, or those increasing from normal or high states were not considered to belong to the catch-up group (Figure E1). Growth failure was defined as participants moving from normal or high or very high states to low or very low states; participants who decreased from low state to very low state, or those decreasing from high or very high states to normal were not considered as growth failure (Figure E1).

Sensitivity analyses related to the state assignment of the participants as well as catch-up and growth failure were conducted using the k-means–based longitudinal trajectory analysis (28) as well as participants' moving between lung function quartiles (FEV_1 *z*-scores) at different ages, respectively.

Replication Study

The prospective, population-based Dutch PIAMA birth cohort was used to independently replicate the models (details in the online supplement). Lung function measurements were performed in subsets of participants at ages 8, 12, and 16 years. PIAMA was approved by the respective Medical Ethics Committees; informed (parental or legal guardian) consent was obtained from all participants (Medisch Ethische Toetsings-Commissie (METC) protocol number 07-337/K). The models were built using data from participants with two or more lung function measures available as well as participants with one or more measures available. Models were compared for goodness of fit using the Bayesian information criterion (Table E2). Catch-up and growth failure were calculated subsequently using the model with five lung function states.

Statistical Analyses

Comparisons of early-life risk factors, clinical data, and respiratory symptoms between states were performed using *t* test/ANOVA, Wilcoxon's/Kruskal-Wallis' and chi-square tests, and/or Fisher's exact test, as appropriate. Associations of early-life factors and protein levels with lung function states (including catch-up and growth failure) were investigated using multinomial logistic and linear regression models, respectively, adjusted for potential confounders (details presented in table footnotes and in the online supplement). *P* values were adjusted for false discovery rate by applying the Benjamini-Hochberg method (29). All the analyses were performed using R 4.0.4. with the dependent mixture model using R package depmixS4 version 1.5-0 (13).

Results

Lung Function States

Of the 4,089 participants originally recruited in the BAMSE cohort, we included in the current analysis 3,069 (75.1%) with lung function data available (Figure E2). Spirometry was measured three times in 837, two times in 1,173, and one time in 1,059 subjects. The model including participants with two or more lung function measures and the model including participants with one or more measures available showed overall the same results (Table E3, kappa = 0.99). To increase the power of the analysis of associations with early-life and adulthood factors, the model based on the larger sample size was selected. The data-driven dependent mixture model used here identified five lung function states (Figure E3 and the details shown in Figure E4), which were labeled according to mean FEV_1 *z*-scores as: *1*) very high ($n = 317$, 10.3%); *2*) high ($n = 1{,}014$, 33.0%); *3*) normal ($n = 1{,}031$, 33.6%); *4*) low ($n = 595$, 19.4%); and *5*) very low ($n = 112$, 3.7%) states. Sensitivity analysis showed the assignment of participants to each state to be highly correlated (0.86) to the results obtained using k-means–based longitudinal trajectory analysis (details in the online supplement).

Characteristics of Participants by Lung Function State at Age 24 Years

Male sex was more prevalent in the low states, and some differences in relation to height and body mass index distributions were noted among the five states (Table 1). At 24 years, participants in the very low state had a higher prevalence of respiratory symptoms, asthma, use of inhaled corticosteroids, and chronic bronchitis and were more often smokers than those in the normal state. Airflow limitation (FEV_1/FVC less than the lower limit of normal), reversible or irreversible, occurred in almost 40% of the participants belonging to the very low state. A higher LCI was observed in the very low state, suggesting the presence of small airway dysfunction. No clinically relevant differences in F_{ENO} or circulating neutrophil and eosinophil levels in blood were observed across states.

Factors Associated with Lung Function States

Table 2 presents adjusted associations between early-life factors and lung function states. Compared with participants in the normal state, those included in the very low state were more likely to have been born prematurely, and participants in both the low and very low states were more likely to have suffered respiratory infections in the first years of life, to have been exposed to higher air pollution levels (nitrogen oxides, NO_x), and to have been diagnosed with asthma. A short period of exclusive breastfeeding (<4 mo) was associated with the low state, with similar effect estimates as for the very low state. The very high state was characterized by lack of parental or childhood asthma and low prevalence of IgE sensitization to airborne allergens (Table 2). Finally, the number of

Table 1. Early-Life Exposures and Characteristics of BAMSE Participants at the 24-Year Follow-Up by Lung Function States

	Very High ($n = 317$)	High ($n = 1014$)	Normal ($n = 1031$)	Low ($n = 595$)	Very Low ($n = 112$)	ANOVA *P* Value
Demographics						
Age, yr	22.5 ± 0.48	22.5 ± 0.54	22.4 ± 0.52	22.4 ± 0.50	22.4 ± 0.40	0.185
Sex, male	146 (46.1)	439 (43.3)*	522 (50.6)	303 (50.9)	62 (55.4)	0.0021
Height, m						
Female	1.67 ± 0.06	1.68 ± 0.06	1.68 ± 0.06	1.69 ± 0.06	1.70 ± 0.08	0.034
Male	1.81 ± 0.07†	1.82 ± 0.07	1.82 ± 0.07	1.83 ± 0.08	1.83 ± 0.08	0.018
Weight, kg						
Female	66.54 ± 12.24	65.46 ± 11.06	64.66 ± 11.64	64.56 ± 12.49	65.43 ± 14.56	0.402
Male	78.98 ± 11.76	80.01 ± 13.81	78.22 ± 13.10	78.46 ± 14.07	79.17 ± 19.15	0.449
Body mass index, kg/m^2						
Female	23.74 ± 4.17†	23.08 ± 3.63	22.78 ± 3.98	22.60 ± 4.44	22.55 ± 4.17	0.038
Male	24.08 ± 3.10	24.19 ± 3.96‡	23.47 ± 3.64	23.29 ± 3.72	23.69 ± 5.41	0.020
Exposures						
Current smoking	67 (23.7)	208 (24.1)‡	167 (18.6)	93 (18.1)	24 (25.8)	0.011
Secondhand smoking	13 (4.8)†	32 (3.9)†	18 (2.1)	11 (2.3)	4 (4.6)	0.065
Maternal smoking during pregnancy	34 (10.7)	126 (12.4)	115 (11.2)	74 (12.4)	16 (14.4)	0.724
Parental smoking						
0–1 yr	48 (15.7)	187 (18.9)	171 (17.1)	93 (15.9)	19 (17.6)	0.253
0–4 yr	79 (24.9)	273 (26.9)	281 (27.3)	157 (26.4)	38 (33.9)	0.467
0–8 yr	89 (28.1)	295 (29.1)	293 (28.4)	172 (28.9)	38 (33.9)	0.806
NO_x higher than the median						
0–1 yr	161 (51.8)	495 (49.7)	534 (52.3)	280 (47.4)	58 (52.3)	0.377
1–4 yr	141 (48.3)	473 (51.2)	473 (50.0)	277 (50.8)	58 (56.9)	0.640
4–8 yr	137 (49.8)	432 (51.1)	434 (49.2)	240 (47.6)	53 (55.8)	0.551
Early life events						
Premature birth	14 (4.4)	52 (5.1)	50 (4.8)	34 (5.7)	12 (10.7)‡	0.102
Birth weight, kg	3.54 ± 0.50	3.57 ± 0.53	3.52 ± 0.55	3.50 ± 0.56	3.42 ± 0.65	0.035
Exclusive breastfeeding for >4 mo	249 (81.4)	809 (81.8)	813 (81.3)	447 (76.4)†	83 (76.9)	0.070
Bronchitis during 0–1 yr	25 (8.3)	58 (5.9)	63 (6.3)	59 (10.1)‡	15 (13.9)‡	0.0011
Pneumonia/RSV infections during 0–1 yr	15 (4.9)	60 (6.1)	75 (7.5)	46 (7.9)	16 (14.8)‡	0.0063
Pneumonia during 0–1 yr	4 (1.3)†	27 (2.7)	35 (3.5)	19 (3.2)	8 (7.4)†	0.028
Pneumonia during 0–4 yr	28 (9.0)	101 (10.0)†	114 (11.2)	69 (11.7)	24 (21.6)‡	0.0041
Parental education						
University	167 (52.7)	537 (53.0)	595 (57.8)	314 (52.9)	57 (50.9)	0.129
Primary school/high school	150 (47.3)	476 (47.0)	434 (42.2)	280 (47.1)	55 (49.1)	
Asthma and sensitization history						
Parental asthma	49 (15.6)†	190 (18.9)	223 (21.8)	111 (18.7)	25 (22.5)	0.107
Childhood asthma during 0–8 yr	55 (17.4)*	229 (22.7)†	277 (27.1)	185 (31.3)	51 (45.9)*	<0.001
Childhood asthma during 0–8 yr						
Never	262 (82.6)‡	780 (77.3)	744 (72.9)	406 (68.7)†	60 (54.1)*	<0.001
Transient	49 (15.5)‡	214 (21.2)	256 (25.1)	162 (27.4)†	43 (38.7)*	
Persistent	6 (1.9)‡	15 (1.5)	21 (2.1)	23 (3.9)†	8 (7.2)*	
Airborne allergen sensitization						
4 yr	31 (12.8)	108 (14.9)	122 (16.3)	75 (17.4)	17 (21.0)	0.309
8 yr	49 (19.3)‡	181 (25.0)	214 (27.7)	130 (30.2)	28 (31.5)	0.016
Food allergen sensitization						
4 yr	39 (16.0)	121 (16.6)	113 (15.1)	73 (16.9)	16 (19.8)	0.800
8 yr	46 (18.1)	153 (21.2)	151 (19.6)	90 (21.0)	25 (28.1)	0.319

(*Continued*)

Table 1. (*Continued*)

	Very High ($n = 317$)	High ($n = 1014$)	Normal ($n = 1031$)	Low ($n = 595$)	Very Low ($n = 112$)	ANOVA *P* Value
Symptoms at age 24 yr (in the previous 12 mo)						
Respiratory symptoms	57 (20.1)	202 (23.3)	228 (25.4)	138 (26.8)	34 (36.6)†	0.014
Wheezing >3 times	26 (9.2)	103 (11.9)	114 (12.7)	78 (15.2)	22 (23.7)‡	0.0027
Any wheezing	57 (20.1)	201 (23.2)	228 (25.4)	137 (26.7)	34 (36.6)†	0.014
Current asthma	20 (7.1)†	81 (9.4)†	111 (12.4)	72 (14.0)	24 (25.8)*	<0.001
ICS usage	9 (3.2)†	46 (5.3)	61 (6.8)	41 (8.1)	16 (17.6)*	<0.001
Respiratory infections						
Never	40 (14.5)	103 (12.4)	113 (13.0)	68 (13.7)	8 (9.0)	0.699
1–3 times	183 (66.3)	530 (63.6)	559 (64.5)	310 (62.4)	57 (64.0)	
>4 times	53 (19.2)	200 (24.0)	194 (22.4)	119 (23.9)	24 (27.0)‡	
Chronic bronchitis symptoms						
Only cough	6 (2.2)	22 (2.7)	25 (2.9)	23 (4.7)	8 (9.0)	0.0079
Only mucus	17 (6.2)	86 (10.4)	86 (10.0)	44 (9.0)	12 (13.5)	
Cough and mucus	12 (4.4)	46 (5.6)	47 (5.5)	27 (5.5)	9 (10.1)	
Lung function at age 24 yr						
Pre-bronchodilator spirometry						
% Predicted FEV_1	113.8 ± 5.5*	103.4 ± 3.7*	94.05 ± 3.35	85.4 ± 3.7*	75.7 ± 5.5*	<0.001
% Predicted FVC	113.0 ± 8.0*	104.1 ± 7.2*	97.06 ± 7.23	91.1 ± 7.7*	83.4 ± 9.5*	<0.001
FEV_1/FVC, %	86.3 ± 5.0*	85.2 ± 5.1*	82.93 ± 5.90	80.3 ± 6.6*	78.1 ± 8.8*	<0.001
Post-bronchodilator spirometry						
% Predicted FEV_1	116.1 ± 6.1*	106.1 ± 4.2*	97.32 ± 3.98	89.3 ± 4.6*	80.4 ± 6.8*	<0.001
% Predicted FVC	112.8 ± 8.1*	103.6 ± 7.1*	96.49 ± 7.41	90.6 ± 8.0*	83.8 ± 10.4*	<0.001
FEV_1/FVC, %	88.2 ± 4.3*	87.7 ± 4.5*	86.29 ± 5.35	84.3 ± 5.7*	82.4 ± 7.4*	<0.001
AL	*	*		*	*	
Reversible AL	1 (0.5)	12 (1.9)	34 (5.0)	42 (11.4)	14 (22.6)	<0.001
Irreversible AL	0 (0.0)	0 (0.0)	12 (1.8)	17 (4.6)	10 (16.1)	
Lung clearance index§	6.01 ± 0.38‡	6.01 ± 0.41*	6.10 ± 0.40	6.13 ± 0.40	6.33 ± 0.58‡	<0.001
F_{ENO}, neutrophils, eosinophils, and IgE sensitization at age 24 yr						
F_{ENO}, ppb	11 (8–17)‡	11 (8–18)‡	13 (9–19)	12 (9–18)	14 (11–21)*	<0.001
Neutrophils in blood (% total cell count)	55.3 (50.0–61.6)	55.7 (50.0–62.7)	55.9 (50.0–62.5)	56.2 (49.3–62.5)	56.4 (49.0–62.1)	0.895
Eosinophils in blood (% total cell count)	1.4 (0.0–3.0)	1.3 (0.0–2.7)	1.4 (0.0–2.9)	1.5 (0.0–3.2)	1.9 (0.0–3.8)‡	0.033
Airborne allergen sensitization‖	95 (41.7)	286 (42.2)	329 (43.6)	183 (43.5)	36 (50.7)	0.701
Food allergen sensitization¶	14 (6.1)	59 (8.7)	61 (8.1)	47 (11.2)	9 (12.7)	0.150

Definition of abbreviations: AL = airflow limitation; F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroids; IQR = interquartile range; kUA = Kilounits of allergen-specific IgE; NO_x = nitrogen oxides; RSV = respiratory syncytial virus.

The data are presented as mean ± SD, number (proportion), or median (IQR).

*$P < 0.001$ for comparisons between each lung function state and the normal state.

†$P < 0.05$ for comparisons between each lung function state and the normal state.

‡$P < 0.01$ for comparisons between each lung function state and the normal state.

§Multiple-breath nitrogen washout analyses between each state and the normal state were adjusted for age, sex, height, and body mass index.

‖Sensitization to a mix of common airborne allergens with Phadiatop (ImmunoCAP System; ThermoFisher. A positive test was defined as specific IgE ⩾0.35 kUA/L).

¶Sensitization to a mix of common food allergens with fx5 (ImmunoCAP System; ThermoFisher. A positive test was defined as specific IgE ⩾0.35 kUA/L).

Table 2. Multivariable Adjusted Associations between Early-Life Factors and Lung Function States with the Normal State as Reference

	Very High ($n = 317$)	High ($n = 1014$)	Low ($n = 595$)	Very Low ($n = 112$)
Demographics				
Sex, male	0.84 (0.65–1.08)	**0.76 (0.63–0.90)***	1.02 (0.84–1.25)	1.22 (0.82–1.81)
Parental education				
University	Ref	Ref	Ref	Ref
Primary school/high school	1.25 (0.96–1.62)	1.19 (1.00–1.43)	1.21 (0.99–1.49)	1.3 (0.87–1.94)
Early-life events				
Premature birth	0.94 (0.51–1.73)	1.12 (0.75–1.68)	1.18 (0.75–1.87)	**2.26 (1.13–4.50)†**
Birth weight, per 1 kg	1.09 (0.86–1.38)	**1.18 (1.00–1.39)†**	0.92 (0.77–1.11)	0.75 (0.53–1.06)
Exclusive breastfeeding for more than 4 mo	1.00 (0.72–1.4)	1.07 (0.85–1.35)	**0.75 (0.58–0.97)†**	0.84 (0.52–1.38)
Bronchitis during 0–1 yr	1.45 (0.89–2.36)	0.95 (0.65–1.37)	**1.69 (1.16–2.45)***	**2.47 (1.34–4.55)***
Pneumonia/RSV infections during 0–1 yr	0.66 (0.37–1.17)	0.82 (0.57–1.17)	1.05 (0.71–1.55)	**2.04 (1.12–3.71)†**
RSV infections during 0–1 yr	0.78 (0.40–1.53)	0.73 (0.46–1.15)	1.03 (0.64–1.67)	1.39 (0.61–3.18)
Pneumonia during 0–1 yr	0.37 (0.13–1.06)	0.79 (0.47–1.33)	0.93 (0.53–1.66)	**2.28 (1.02–5.07)†**
Pneumonia during 0–4 yr	0.80 (0.52–1.25)	0.91 (0.69–1.22)	1.07 (0.78–1.48)	**2.21 (1.34–3.63)***
Exposures				
Maternal smoking during pregnancy	0.89 (0.58–1.35)	1.08 (0.82–1.42)	1.10 (0.80–1.51)	1.21 (0.67–2.18)
Parental smoking				
0–1 yr	0.95 (0.64–1.40)	1.09 (0.84–1.43)	0.82 (0.60–1.12)	0.87 (0.47–1.59)
0–4 yr	0.87 (0.63–1.20)	0.89 (0.71–1.11)	0.87 (0.67–1.13)	1.22 (0.76–1.97)
0–8 yr	0.97 (0.71–1.33)	0.96 (0.77–1.19)	0.95 (0.74–1.23)	1.14 (0.71–1.83)
NO_x higher than the median‡				
0–1 yr	1.26 (0.82–1.95)	0.93 (0.70–1.25)	0.93 (0.66–1.29)	1.40 (0.74–2.64)
1–4 yr	0.93 (0.64–1.36)	1.22 (0.94–1.59)	**1.43 (1.04–1.95)†**	**2.08 (1.07–4.03)†**
4–8 yr	1.10 (0.77–1.56)	1.08 (0.85–1.37)	1.00 (0.76–1.32)	1.63 (0.90–2.97)
Allergies and asthma				
Parental asthma	**0.66 (0.47–0.93)†**	0.84 (0.68–1.05)	0.82 (0.64–1.06)	1.05 (0.65–1.68)
Childhood asthma during 0–8 yr (any vs. never)	**0.62 (0.44–0.86)***	0.84 (0.68–1.03)	**1.28 (1.02–1.61)†**	**2.20 (1.45–3.34)§**
Childhood asthma during 0–8 yr				
Never	Ref	Ref	Ref	Ref
Transient	**0.60 (0.42–0.84)***	0.85 (0.68–1.05)	1.21 (0.96–1.54)	**2.09 (1.36–3.22)§**
Persistent	0.87 (0.35–2.2)	0.72 (0.37–1.42)	**2.09 (1.13–3.85)†**	**3.52 (1.35–9.18)†**
Airborne allergen sensitization‖				
4 yr	0.81 (0.53–1.25)	0.92 (0.69–1.23)	1.09 (0.79–1.50)	1.34 (0.75–2.38)
8 yr	**0.66 (0.46–0.95)†**	0.92 (0.73–1.16)	1.15 (0.88–1.49)	1.16 (0.71–1.89)
Food allergen sensitization¶				
4 yr	1.08 (0.72–1.62)	1.10 (0.83–1.47)	1.10 (0.79–1.52)	1.28 (0.71–2.31)
8 yr	0.93 (0.65–1.35)	1.11 (0.86–1.43)	1.09 (0.82–1.47)	1.55 (0.94–2.57)

Definition of abbreviations: kUA = Kilounits of allergen-specific IgE; NO_x = nitrogen oxides; Ref = reference; RSV = respiratory syncytial virus.
Data are shown as odds ratio (95% confidence interval). The multinomial logistic regression models were adjusted for sex, maternal smoking during pregnancy, asthma heredity, and socioeconomic status. Statistically significant values are highlighted using bold text.
*$P < 0.01$ for regression analysis between each state and the normal states (Ref).
†$P < 0.05$ for regression analysis between each state and the normal states (Ref).
‡The multinomial logistic regression models for air pollution were adjusted for municipality at birth, sex, maternal smoking during pregnancy, asthma heredity, and socioeconomic status.
§$P < 0.001$ for regression analysis between each state and the normal states (Ref).
‖Sensitization to a mix of common airborne allergens with Phadiatop (ImmunoCAP System; ThermoFisher. A positive test was defined as specific IgE ⩾0.35 kUA/L).
¶Sensitization to a mix of common food allergens with fx5 (ImmunoCAP System; ThermoFisher. A positive test was defined as specific IgE ⩾0.35 kUA/L).

coexisting risk factors was cumulatively associated with very low and very high states (vs. the normal state; Figure E7).

Plasma Inflammatory Proteins

Out of the 92 plasma inflammatory markers tested, 25 (27%) were different between lung function states (Table E4). After adjustment for multiple testing and potential confounders, 17 of the proteins were associated with the very low state (vs. normal and/or vs. very high; Table E5). When FEV_1 *z*-scores at 24 years were analyzed as a continuous trait, we identified four associated proteins: IL-6, TNF (tumor necrosis factor)-related weak inducer of apoptosis, stem cell factor, and CXCL10 (C-X-C motif chemokine 10) (Table E6). IL-6 and CXCL10 emerged as potential biomarkers for impaired lung function development, as they both were negatively associated with FEV_1 *z*-score (independently of states) and the very low state.

Catch-Up and Growth Failure

In general, individual lung function states were remarkably stable over time, but 16.8% and 6.3% of the participants moved between states between 8 and 16 years and 16 and 24 years, respectively (Figure 1 and Table E7).

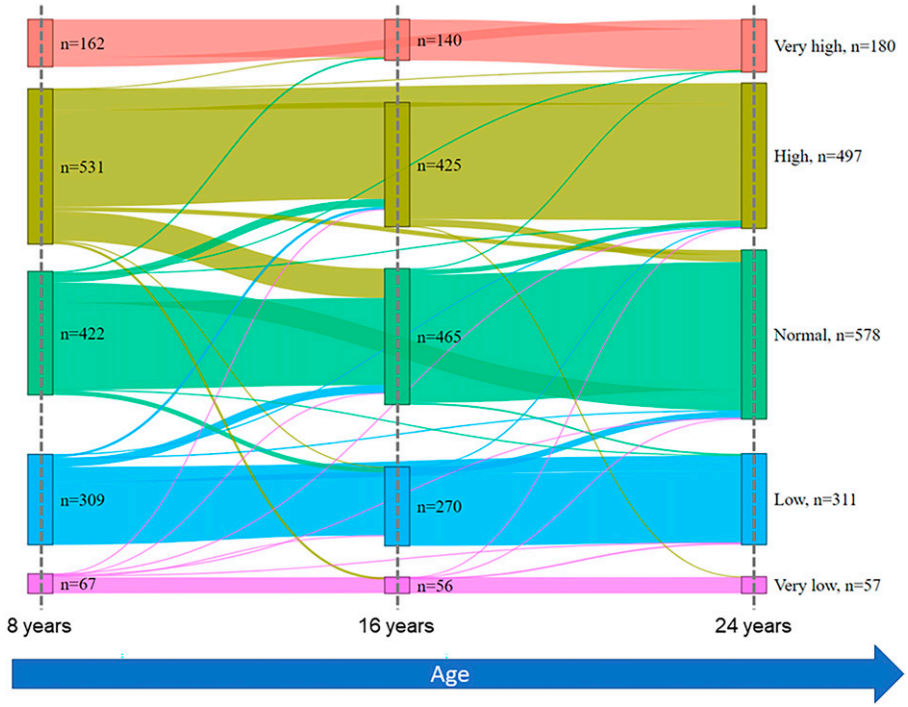

Figure 1. Alluvial plot that illustrates transition of lung function states from childhood to early adulthood. Participants with two or more lung function measures recorded were included. The width of each line is proportional to the number of participants included. The numbers behind Figure 1 are available in Table E6.

Overall, 14.5% of the participants with low or very low states showed lung function catch-up, and 2.4% of the participants with normal or high or very high states showed growth failure (Figures 2, 3A, and 3B and Table E8). Both catch-up and growth failure appeared to occur at any age but were more common in the 8–16 years age bin (13.1% and 3.0%, respectively; Figure 2).

Similar catch-up and growth failure trends were observed in FEV_1 *z*-score quartile-based moving patterns (as complementary analysis), albeit not with complete overlap with the state-based patterns (kappa = 1.0 for catch-up and 0.53 for growth failure, respectively; online supplement).

Table E9 summarizes the main characteristics of participants with catch-up or growth failure. Compared with participants persistently in the low or very low lung function states, those with catch-up were characterized by a lower prevalence of bronchitis in the first year of life, maternal smoking during pregnancy, or parental smoking exposure (both of borderline significance). At 24 years, spirometry was fully recovered in the catch-up group, and no differences in LCI were found.

Compared with participants persistently in the normal or high or very high states, children with growth failure were predominantly females, born prematurely, suffered pneumonia/respiratory syncytial virus infections during the first year of life, were more often diagnosed with asthma, were treated with inhaled corticosteroids more often, and were frequently sensitized to food allergens. Participants with growth failure had a higher prevalence of airflow limitation and worse LCI at age 24 years compared with those who remained in the high states (Table E9). Biomarker association with catch-up and growth failure was not explored because of limited study power.

Figure 3C shows that the prevalence of catch-up decreased and that of growth failure increased cumulatively in relation to the number of early-life risk factors present. Likewise, the odds ratios for catch-up or

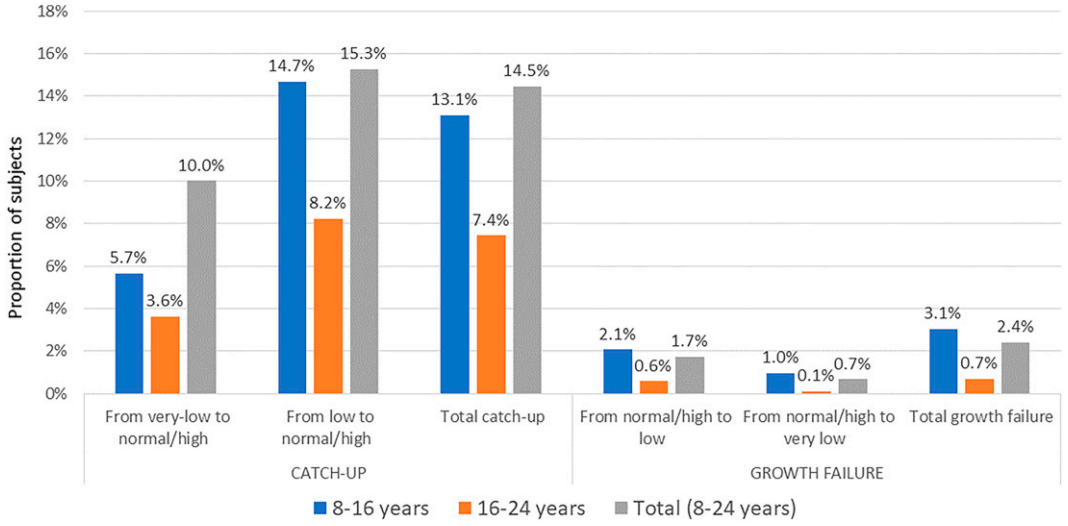

Figure 2. Prevalence of catch-up (left) and growth failure (right) at different age bins (8–16 yr, 16–24 yr, and 8–24 yr). A subgroup of participants contributed lung function data only at 8 and 24 years (but not 16 yr); therefore, the total proportion of subjects (gray) does not always match the sum of 8–16 (blue) and 16–24 (orange) year proportions. The numbers behind Figure 2 are available in Table E7.

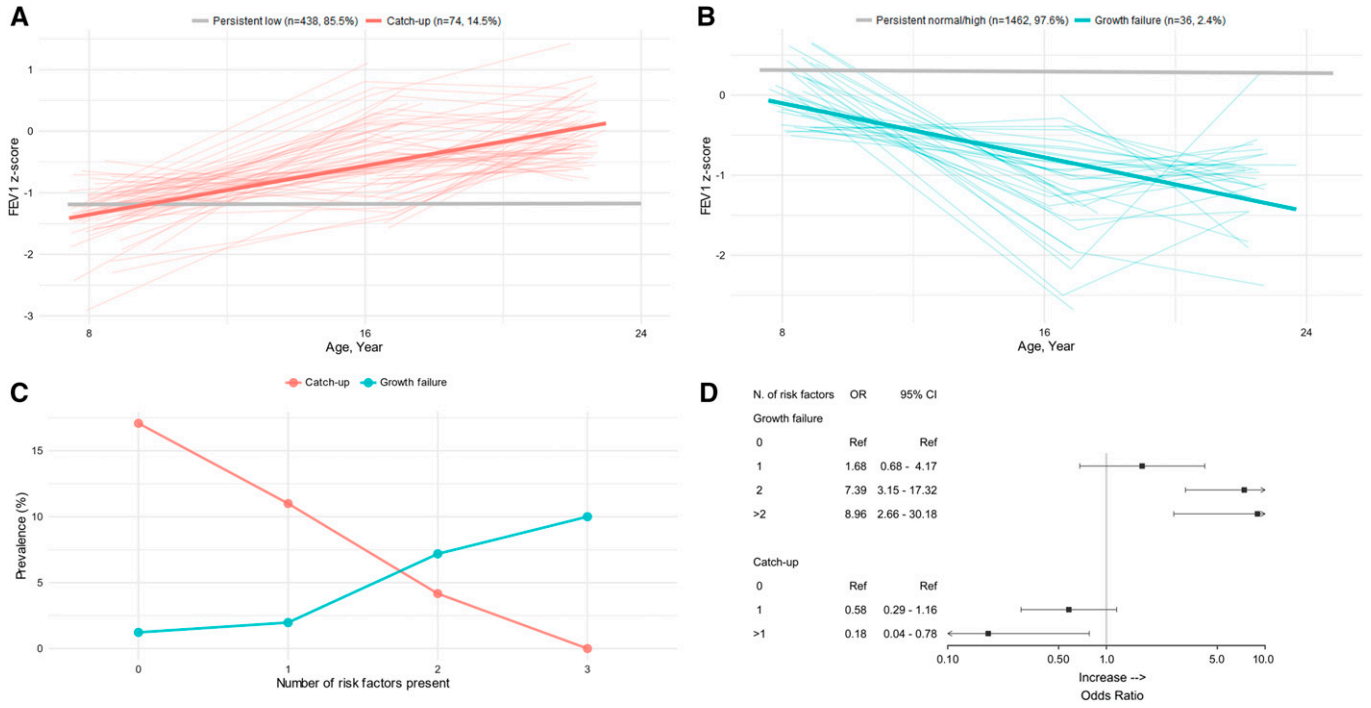

Figure 3. Individual FEV_1 *z*-scores in participants with lung function (*A*) catch-up and (*B*) growth failure. (*C*) Prevalence and (*D*) OR of catch-up and growth failure by the number of associated risk factors coexisting in the same participants. The risk factors included in the association with catch-up were maternal smoking during pregnancy, parental smoking during 0–1 years, and early bronchitis. The risk factors included in the association with growth failure were preterm birth, early bronchitis, respiratory syncytial virus/pneumonia during infancy, sensitization to food allergens during 4–8 years, and childhood asthma during 0–8 years. CI = confidence interval; OR = odds ratio; Ref = reference.

growth failure decreased or increased, respectively, with increased number of risk factors (Figure 3D).

Replication in an Independent Dataset

There were 1,484 participants in PIAMA with lung function data available for replication analysis. Spirometry was measured three times in 252, two times in 379, and one time in 853 subjects. The five lung function states (Figure E5 and the details showed in Figure E6) were labeled according to mean FEV_1 *z*-scores as: *1*) very high ($n = 94$, 6.3%); *2*) high ($n = 446$, 30.1%); *3*) normal ($n = 501$, 33.8%); *4*) low ($n = 407$, 27.4%); and *5*) very low ($n = 36$, 2.4%) states. Individual lung function states were found stable over time also in PIAMA, although 13.6% of participants changed their states between 8 and 16 years. Specifically, 4.1% (7/172) of participants with low or very low states showed lung function catch-up, and 5.7% (26/459) of participants with normal or high or very high states showed growth failure. In BAMSE, 13.1% (40/305) and 3.0% (28/919) of participants experienced catch-up and growth failure between 8 and 16 years.

Discussion

This study explored the plasticity of individual lung function states from childhood to early adulthood in two population-based birth cohorts, BAMSE and PIAMA. Although most individual lung function states were stable over time, some participants in the low lung function states displayed catch-up to normal lung function, and growth failure occurred in some participants with initial normal or high lung function. Our results also highlight a cumulative effect of several risk factors and identify novel state-associated inflammatory biomarkers to consider in future preventive and/or interventional strategies.

Previous Studies

Previous studies have identified four (10) to six (4) lung function trajectories from school age to adulthood; our methodology identified five parallel states (Figures 1 and E3). Differences in population type and size, quality, and frequency of lung function measures, as well as the different analytical tools used, can account for these relatively minor discrepancies in the number of trajectories/states identified.

Multiple host factors (genetics/epigenetics) and environmental exposures can contribute to membership in a lung function state or trajectory group up to adolescence (30, 31). In line with previous studies (4, 10, 14, 18, 30, 32), we found that preterm birth, childhood asthma, bronchitis, respiratory infections, and air pollution exposure during early life were associated with low lung function states and that parental asthma, sensitization to airborne allergens, and childhood asthma decreased the likelihood of a high state. Importantly, we could also show that there is a cumulative effect of these risk factors on the likelihood of belonging to a lower state. These are important findings from a public health point of view because several of the risk factors are avoidable.

Interpretation of Novel Findings

Our study provides several novel findings of interest. First, we show that individual lung function states are remarkably stable over time, but individual catch-up and growth failure can indeed occur, particularly in the 8–16 years age range. The overall estimates of subjects moving among the five states were quite similar in BAMSE and the replication

cohort PIAMA (16.8% vs. 13.6%, respectively, between 8 and 16 yr), whereas the catch-up and growth failure estimates differed somewhat (catch-up 13.1% vs. 4.1% and growth failure 3.0% vs. 5.7%). Differences in population type and size, environmental exposures, as well as the different data points available may contribute to these discrepancies. However, the PIAMA results confirm the concept that at the group level, the lung function states are rather stable over time, whereas at the individual level, the lung function states may be plastic, including both catch-up and growth failure. The finding that lung function changes occur rather early during childhood, also confirmed using FEV_1 quartile data in both cohorts, strongly argues in favor of early detection and follow-up of lung function deviations in children and adolescents (33, 34).

Lung function catch-up has previously been observed in subjects born preterm (11). We did not observe this in the current study (presumably due to few children born extremely preterm) but found that early bronchitis was associated with a permanent low state, suggesting that early viral infections may decrease the chance of lung function catch-up. Although catch-up was rare in children in the very low state, the possibility of such development should encourage research aimed at understanding the molecular basis of catch-up to help children regain normal lung function.

We also observed participants who had a lower-than-expected growth rate in FEV_1 (i.e., growth failure). In a previous study (35), growth failure has been observed in very young children with persistent wheezing. Our results extend this finding by demonstrating that growth failure can also occur during school age (Figure 2) and that female sex, preterm birth, early respiratory infections, childhood asthma, and sensitization to food allergens play a role. Finally, we could show that the combination of several risk factors greatly increases the risk of growth failure and, conversely, reduces the likelihood of catch-up, in an additive manner (Figure 3).

In our analysis, lung function states were determined based on FEV_1 only. However, almost 40% of participants in the lowest state showed airflow limitation (FEV_1/FVC less than lower limit of normal) at 24 years and were often symptomatic (Table 1). Furthermore, FVC levels gradually decreased from the very high to the very low states, but the lack of total lung capacity measurements prevents determining whether this is an effect of air trapping related to increasing airflow limitation or a sign of a restrictive lung impairment. Further studies are needed to jointly model more lung function parameters together, such as FEV_1 and FVC. Finally, we could show that the low lung function state, as well as growth failure, was associated with ventilation inhomogeneity measured as LCI at the age of 24 years. Higher values of LCI have been reported to associate with disease severity in adults with chronic obstructie pulmonary disease (36) or bronchiectasis (37) but have to our knowledge not been assessed in large, younger populations. Whether earlier respiratory insults, such as viral/bacterial respiratory infections also linked to severe childhood wheeze (38), relate to small airway pathophysiology remains to be formally evaluated, but, as discussed below, several of our biomarker observations support it.

The plasma levels of IL-6 and CXCL10 were associated with the very low lung function state, as well as negatively with FEV_1 (independently of states). These two pleiotropic factors are associated with a wide range of biological processes, including IFN-γ pathways (39, 40). Interestingly, respiratory infections early in life (known activators of IFN pathways) were strongly associated with a very low state and growth failure, so the prevention of respiratory infections during childhood may help to improve the peak lung function achieved at early adulthood. Further exploration of IFN-driven pathways may identify potentially new pharmacological targets for prevention and/or early intervention during early childhood.

Potential Limitations

We acknowledge that our definitions of catch-up and growth failure are arbitrary with regard to capturing participants moving from relatively higher-risk to lower-risk subgroups (or relatively lower-risk to higher-risk subgroups) of future diseases. Yet, with this study, we are introducing the concept of plastic individual lung function states during childhood, which includes catch-up and growth failure. We acknowledge, though, the complexity of modeling age-dependent lung development using clinical endpoints like lung function and that further efforts are needed to evaluate the optimal statistical approaches, data input (single vs. multiple lung function measures, age categories, etc.), and validation in other ethnic groups and in other environmental contexts. In addition, our observations on related inflammatory biomarkers are needed to be validated in other populations, and other omics layers such as epigenetics need to be further explored (41). Large-scale collaboration involving multiple cohorts, such as the CADSET (Chronic Airway Disease Early Stratification) collaboration (42), would be needed for such analyses. Also, we do not have lung function data earlier than 8 years of age. Although reliable spirometry data are very challenging to achieve in preschool children, lung function assessed by alternative methods could assist in the evaluation of when early lung function changes may have occurred.

Conclusions

Individual lung function states from 8 to 24 years of age are remarkably stable over time, but catch-up or lung growth failure can indeed occur in a population-based setting. Our study identifies risk factors and blood biomarkers associated with impaired lung function development. Collectively, these results contribute to a better understanding of the determinants, consequences, and implications of abnormal lung development and open new research avenues of great relevance to promote respiratory and global health starting during childhood and continuing throughout life. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009;180:3–10.
2. Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019;7:358–364.
3. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017;5:935–945.
4. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, *et al.* Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535–544.
5. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, *et al.* Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015;373:111–122.
6. Buhr RG, Barjaktarevic IZ, Quibrera PM, Bateman LA, Bleecker ER, Couper DJ, *et al.* Reversible airflow obstruction predicts future chronic obstructive pulmonary disease development in the SPIROMICS cohort: an observational cohort study. *Am J Respir Crit Care Med* 2022;206:554–562.
7. Marott JL, Ingebrigtsen TS, Çolak Y, Vestbo J, Lange P. Trajectory of preserved ratio impaired spirometry: natural history and long-term prognosis. *Am J Respir Crit Care Med* 2021;204:910–920.
8. Marott JL, Ingebrigtsen TS, Çolak Y, Vestbo J, Lange P. Lung function trajectories leading to chronic obstructive pulmonary disease as predictors of exacerbations and mortality. *Am J Respir Crit Care Med* 2020;202:210–218.
9. Berry CE, Billheimer D, Jenkins IC, Lu ZJ, Stern DA, Gerald LB, *et al.* A distinct low lung function trajectory from childhood to the fourth decade of life. *Am J Respir Crit Care Med* 2016;194:607–612.
10. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souëf PN, *et al.* Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018;6:526–534.
11. Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. *Thorax* 2012;67:54–61.
12. Martinez FJ, Agusti A, Celli BR, Han MK, Allinson JP, Bhatt SP, *et al.* Treatment trials in young patients with chronic obstructive pulmonary disease and pre-chronic obstructive pulmonary disease patients: time to move forward. *Am J Respir Crit Care Med* 2022;205:275–287.
13. Visser I, Speekenbrink M. depmixS4: an R package for hidden Markov models. *J Stat Softw* 2010;36:1–21.
14. Wang G, Hallberg J, Um Bergström P, Janson C, Pershagen G, Gruzieva O, *et al.* Assessment of chronic bronchitis and risk factors in young adults: results from BAMSE. *Eur Respir J* 2021;57:2002120.
15. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, *et al.* The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13:55–60.
16. Wijga AH, Kerkhof M, Gehring U, de Jongste JC, Postma DS, Aalberse RC, *et al.* Cohort profile: the prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol* 2014;43:527–535.
17. Wang G, Hallberg J, Merid SK, Klevebro S, Björkander S, Gruzieva O, *et al.* Longitudinal modelling of lung function trajectories from childhood to early adulthood in the BAMSE cohort [abstract]. *Eur Respir J* 2021;58:OA1318.
18. Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van Hage M, *et al.* Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J Allergy Clin Immunol* 2010;125:1013–1019.
19. Melén E, Bergström A, Kull I, Almqvist C, Andersson N, Asarnoj A, *et al.* Male sex is strongly associated with IgE-sensitization to airborne but not food allergens: results up to age 24 years from the BAMSE birth cohort. *Clin Transl Allergy* 2020;10:15.
20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.*; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
21. Wang G, Kull I, Bergström A, Hallberg J, Bergström PU, Guerra S, *et al.* Early-life risk factors for reversible and irreversible airflow limitation in young adults: findings from the BAMSE birth cohort. *Thorax* 2021;76:503–507.
22. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, *et al.*; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–1343.
23. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, *et al.* Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J* 2013;41:507–522.
24. Horsley A. Lung clearance index in the assessment of airways disease. *Respir Med* 2009;103:793–799.
25. Sandvik RM, Gustafsson PM, Lindblad A, Robinson PD, Nielsen KG. Improved agreement between N_2 and SF_6 multiple-breath washout in healthy infants and toddlers with improved EXHALYZER D sensor performance. *J Appl Physiol (1985)* 2021;131:107–118.
26. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912–930.
27. Klevebro S, Björkander S, Ekström S, Merid SK, Gruzieva O, Mälarstig A, *et al.* Inflammation-related plasma protein levels and association with adiposity measurements in young adults. *Sci Rep* 2021;11:11391.
28. Genolini C, Falissard B. KmL: a package to cluster longitudinal data. *Comput Methods Programs Biomed* 2011;104:e112–e121.
29. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995;57:289–300.
30. Breyer-Kohansal R, Faner R, Breyer M-K, Ofenheimer A, Schrott A, Studnicka M, *et al.* Factors associated with low lung function in different age bins in the general population. *Am J Respir Crit Care Med* 2020;202:292–296.
31. Agustí A, Melén E, DeMeo DL, Breyer-Kohansal R, Faner R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. *Lancet Respir Med* 2022;10:512–524.
32. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, *et al.* Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842–1852.
33. Agusti A, Alcazar B, Cosio B, Echave JM, Faner R, Izquierdo JL, *et al.*; Scientific Committee of the ANTES programme. Time for a change: anticipating the diagnosis and treatment of COPD. *Eur Respir J* 2020;56:2002104.
34. Agusti A, Fabbri LM, Baraldi E, Celli B, Corradi M, Faner R, *et al.* Spirometry: a practical lifespan predictor of global health and chronic respiratory and non-respiratory diseases. *Eur J Intern Med* 2021;89:3–9.
35. Belgrave DCM, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. *Am J Respir Crit Care Med* 2014;189:1101–1109.
36. Bell AS, Lawrence PJ, Singh D, Horsley A. Feasibility and challenges of using multiple breath washout in COPD. *Int J Chron Obstruct Pulmon Dis* 2018;13:2113–2119.
37. Verbanck S, King GG, Zhou W, Miller A, Thamrin C, Schuermans D, *et al.* The quantitative link of lung clearance index to bronchial segments affected by bronchiectasis. *Thorax* 2018;73:82–84.
38. Robinson PFM, Fontanella S, Ananth S, Martin Alonso A, Cook J, Kaya-de Vries D, *et al.* Recurrent severe preschool wheeze: from prespecified diagnostic labels to underlying endotypes. *Am J Respir Crit Care Med* 2021;204:523–535.
39. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *Int J Biol Sci* 2012;8:1237–1247.
40. Liu M, Guo S, Hibbert JM, Jain V, Singh N, Wilson NO, *et al.* CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications. *Cytokine Growth Factor Rev* 2011;22:121–130.
41. Lee M, Huan T, McCartney DL, Chittoor G, de Vries M, Lahousse L, *et al.* Pulmonary function and blood DNA methylation: a multiancestry epigenome-wide association meta-analysis. *Am J Respir Crit Care Med* 2022;206:321–336.
42. Agusti A, Faner R, Donaldson G, Heuvelin E, Breyer-Kohansal R, Melén E, *et al.*; on behalf of the CADSET Clinical Research Collaboration; Current members of the CADSET Clinical Research Collaboration. Chronic Airway Diseases Early Stratification (CADSET): a new ERS Clinical Research Collaboration. *Eur Respir J* 2019;53:1900217.