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Original research

Lung function trajectories from school age to adulthood and their relationship with markers of cardiovascular disease risk

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/thorax-2023-220485).

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Received 16 May 2023
Accepted 14 April 2024

To cite: Granell R, Haider S, Deliu M, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thorax-2023-220485

ABSTRACT

Rationale Lung function in early adulthood is associated with subsequent adverse health outcomes.

Objectives To ascertain whether stable and reproducible lung function trajectories can be derived in different populations and investigate their association with objective measures of cardiovascular structure and function.

Methods Using latent profile modelling, we studied three population-based birth cohorts with repeat spirometry data from childhood into early adulthood to identify trajectories of forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC). We used multinomial logistic regression models to investigate early-life predictors of the derived trajectories. We then ascertained the extent of the association between the derived FEV_1/FVC trajectories and blood pressure and echocardiographic markers of increased cardiovascular risk and stroke in ~3200 participants at age 24 years in one of our cohorts.

Results We identified four FEV_1/FVC trajectories with strikingly similar latent profiles across cohorts (pooled N=6377): above average (49.5%); average (38.3%); below average (10.6%); and persistently low (1.7%). Male sex, wheeze, asthma diagnosis/medication and allergic sensitisation were associated with trajectories with diminished lung function in all cohorts. We found evidence of an increase in cardiovascular risk markers ascertained by echocardiography (including left ventricular mass indexed to height and carotid intima-media thickness) with decreasing FEV_1/FVC (with p values for the mean crude effects per-trajectory ranging from 0.10 to p<0.001). In this analysis, we considered trajectories as a pseudo-continuous variable; we confirmed the assumption of linearity in all the regression models.

Conclusions Childhood lung function trajectories may serve as predictors in the development of not only future lung disease, but also the cardiovascular disease and multimorbidity in adulthood.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In utero and early-life factors have been shown to influence lung function trajectory through childhood and can influence the lung function attained at the physiological peak in early adulthood.

WHAT THIS STUDY ADDS

⇒ Little is known about the relationship between lung function development during childhood and preclinical markers of cardiovascular and metabolic disease risk. We ascertained the association of lung function trajectories from childhood to early adulthood derived using data-driven methods with objective measures of cardiovascular structure and function ascertained using echocardiogram data and carotid artery scans (which are markers of preclinical cardiovascular risk and can predict subsequent cardiovascular disease).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study highlights the importance of lung growth and its association with adverse respiratory, cardiovascular and metabolic outcomes, and the importance of identifying early life risk factors. Our findings draw attention to the potential importance of measuring lung function from early school age as a marker of future risk, since early lung function optimisation to alter trajectories may help in preventing adverse health outcomes in adulthood.

INTRODUCTION

Spirometry is the most commonly used pulmonary function test for identifying patterns of physiological abnormalities. Spirometric impairments (both airflow obstruction and restrictive ventilatory defect) are related to adverse health outcomes.[1] For example, diminished forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC), which is a hallmark of chronic obstructive pulmonary disease (COPD), is also associated with cardiovascular morbidity and mortality.[2] Low FEV_1 is associated with contemporaneous cardiovascular disease in adults, and similar relationships have been observed for FVC.

In recent years, a substantial effort has been devoted to identifying lifetime lung function trajectories based on different spirometry measures and their associations with early-life risk factors and subsequent health outcomes (reviewed in Okyere *et al*[3]). Potential implementation of this knowledge in clinical practice to detect poor lung health early is attracting increasing attention.[4] Due to limited availability of repeated spirometry measurement in children, relatively few studies extended the modelling of trajectories to childhood lung function (online supplemental table S1).[3] In such studies, in utero and early-life factors have been shown to influence trajectory through childhood and have an important impact on the lung function attained at the physiological peak in early adulthood. Early life factors associated with diminished lung function in early adulthood include preterm birth, respiratory infections, allergic sensitisation, childhood asthma and persistent wheezing, and exposure to tobacco smoke in utero. Poor intrauterine growth and nutritional deficits during pregnancy and childhood precede and predict the development of spirometric restriction in adulthood.[5 6] Importantly, diminished lung function at physiological peak is an independent marker of not only respiratory disease in later adulthood, but also cardiovascular morbidity and early all-cause mortality.[1 7–9] However, little is known about the relationship between lung function development during childhood and preclinical markers of cardiovascular and metabolic disease risk, and whether assessment of spirometry in childhood may be informative about the future cardio-metabolic health.

We hypothesise that diminished childhood lung function trajectories are associated with preclinical markers of cardiovascular and metabolic disease. To address our hypothesis, we first modelled lung function from early school age to physiological peak in the third decade in three UK birth cohorts with repeated spirometry through childhood to ascertain whether stable and reproducible trajectories can be derived in different populations. We focused on modelling FEV_1/FVC as a marker of airway obstruction to facilitate comparison of our findings with previous studies such as TCRS,[10] PELOTAS[11] and RAINE.[12] We then capitalised on the availability of the ultrasound scans of carotid arteries and echocardiograms including carotid artery intima-media thickness (cIMT) and the measurement of pulse wave velocity (PWV), (blood pressure and blood triglycerides) at age 24 years in subjects in the Avon Longitudinal Study of Parents and Children (ALSPAC) without overt clinical cardiovascular and metabolic disease.[13] We ascertained the association of the derived lung function trajectories with these objective measures of cardiovascular structure and function, which are markers of preclinical cardiovascular risk and which predict subsequent cardiovascular disease.[14–16]

METHODS

Detailed description of cohorts, methods and analyses is presented in online supplemental file.

Study design, setting and participants

We used data from three UK population-based birth cohorts in the STELAR/UNICORN consortium: ALSPAC,[17] Isle of Wight (IOW)[18] and Manchester Asthma and Allergy Study (MAAS).[19] Data were integrated in a web-based knowledge management platform to facilitate joint analyses.[20]

Data sources/measurements

Spirometry was available at ages 8, 11, 16 and 20 years in MAAS; 8, 15 and 24 years in ALSPAC; and 10, 18 and 26 years in IOW. Details of clinical follow-up and definitions of outcomes including asthma, wheeze phenotypes from birth to early adulthood,[21] severe asthma exacerbations, lower respiratory tract infections (LRTIs) and environmental exposures are provided in online supplemental file.

Assessment of cardiovascular risk in ALSPAC

Left ventricular (LV) mass indexed to height$^{2.7}$ (LVMI, g/m$^{2.7}$), LV posterior wall (PW) systolic thickness average (LVPW, cm), carotid femoral PWV (m/s), pulse pressure (mm Hg), average cIMT mean (mm), systolic and diastolic blood pressure (BP) (mm Hg), triglycerides (log-transformed) and high-density lipoprotein (HDL, mmol/L) were measured at research clinics at age 25 years.[13]

Ultrasound scans of the left and right common carotid arteries were performed using a CardioHealth Panasonic system with a 13–5 MHz linear array broadband transducer according to a standardised protocol to measure cIMT. Echocardiography was performed using a Philips EPIQ 7G Ultrasound in accordance with American Society of Echocardiography guidelines. PWV was measured using a Vicorder device validated in adolescents.[22] Three PWV measurements were taken with an interval of 1 min between measurements, acceptable PWV measurements were within ≤0.5 m/s of each other. Results were averaged to give a measurement of arterial stiffness. In MAAS, blood pressure was measured at age 20 years.

Statistical analysis

We used latent profile modelling to derive trajectory classes based on the development of FEV_1/FVC over time in three cohorts independently. We analysed data from participants who had spirometry on at least two occasions under the assumption that data were missing at random. Briefly, we used two-level random intercept regression models to assign children to their most likely trajectory profile. The models were compared for goodness-of-fit using the Bayesian Information Criterion (BIC). For each child, the posterior probability of belonging to each of the classes was estimated, and children were classified to each trajectory profile based on their maximum posterior probability.

All analyses were repeated for those with complete spirometry data to test the sensitivity and confirm robustness of the derived trajectories.

We used weighted multinomial logistic regression models to ascertain early-life risk factors associated with each lung function trajectory. The posterior probability of membership for each trajectory class was used as weights to reflect uncertainty of class assignment; results are reported as relative risk ratios (RRR) with 95% CIs.

We used linear regression models to assess the associations between lung function trajectories between 8 and 24 years and markers of cardiovascular and metabolic disease risk at 24 years. We report both individual trajectory effects and per-trajectory effects; in this analysis, we considered trajectories as a pseudo-continuous variable; we confirmed the assumption of linearity in all the regression models. All models were weighted by class membership probabilities. Additionally, we performed sex-stratified analyses and further adjustment by low birth weight and tobacco smoke exposure. When considering complete cases in both crude and adjusted analyses, the persistent low trajectory was most affected, with numbers of individuals dropping from 80 to as low as 20–22 in the associations with cardiovascular outcomes.

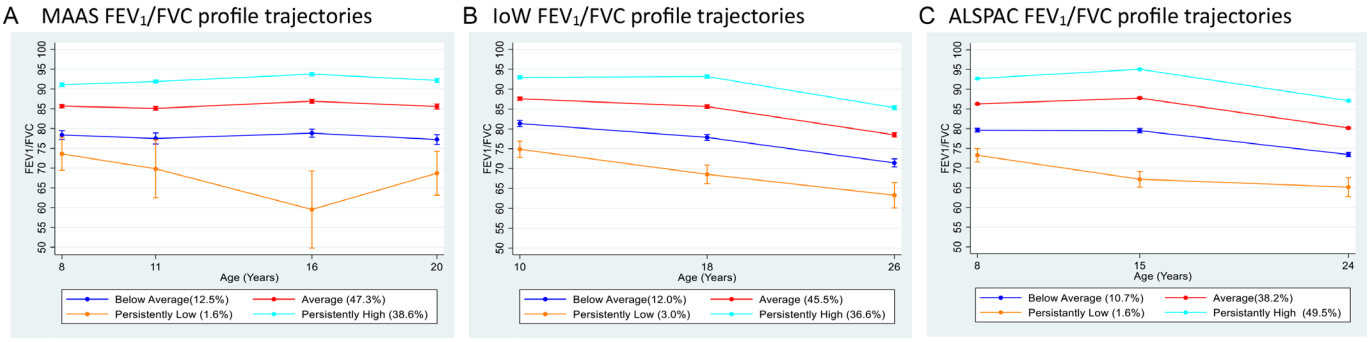

Figure 1 Mean FEV_1/FVC over time in the four trajectory classes. ALSPAC, Avon Longitudinal Study of Parents and Children; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IOW, Isle of Wight; MAAS, Manchester Asthma and Allergy Study.

RESULTS

We included 4874 participants from ALSPAC, 809 from IOW and 801 from MAAS, who had completed spirometry on at least two occasions during the follow-up. Characteristics of the study populations and comparisons between subjects included and excluded from the analyses are shown in online supplemental table S2. In MAAS and IOW, there was a lower prevalence of parental smoking at recruitment and a higher prevalence of breast feeding among included participants. There was a lower proportion of males in the analysed sample in IOW.

FEV_1/FVC trajectories from early school-age to young adulthood

The best-fitting model was selected as four FEV_1/FVC trajectories in all three cohorts (online supplemental table S3 and figure 1). BIC was marginally lower for the 5-class model for MAAS, but we opted for a more parsimonious solution. Based on the developmental pattern of FEV_1/FVC, these trajectories were labelled as: (1) above average; (2) average; (3) below average; and (4) persistently low (figure 1). Study participants within the four trajectories had stable lung function that tracked from early school age to adulthood, with no overlap in FEV_1/FVC between the trajectories at any time (figure 1A–C). The highest within-class variability in the individual FEV_1/FVC trajectories was observed in the persistently low trajectory. Importantly, the proportion of allocated participants and the mean FEV_1/FVC values over time in each of the trajectories were consistent across the cohorts (table 1).

The posterior probability of class membership was high in all cohorts (>0.7), indicating high confidence in class assignment (online supplemental table S4). Class assignments were robust to the presence of missing data, with the proportion of children assigned to the same class in samples with complete and >2 observations exceeding 75% (online supplemental table S5).

Sex, demographic and environmental characteristics of FEV_1/FVC trajectories

Online supplemental table S6 shows results of multinomial logistic regression models weighted for the probability of each individual belonging to each trajectory, using the average class as the reference. Males had a higher risk of being in the persistently low trajectory (MAAS and ALSPAC). Low birth weight was associated with persistently low trajectory in ALSPAC (RRR 2.30, 95% CI 1.05 to 5.06, p=0.038). Maternal smoking during pregnancy and/or the child's first year of life increased the risk of below average (1.30, 1.01 to 1.67, p=0.04) and persistently low (1.60, 0.93 to 2.76, p=0.09) trajectories in ALSPAC, with similar estimates in IOW. Paternal asthma increased the risk of below average in MAAS (2.02, 1.14 to 3.59, p=0.017) and maternal asthma increased the risk of persistently low in ALSPAC (1.88, 1.07 to 3.30, p=0.027). Increasing preschool age body mass index (BMI) was associated with increased risk of below average trajectory in MAAS (1.23, 1.09 to 1.4, p=0.001), while decreasing childhood BMI increased the risk of above average trajectory in MAAS (0.95, 0.89 to 1.02, p=0.03) and ALSPAC (0.92, 0.89 to 0.95, p=1.11E-06), with a similar trend in IOW.

Table 1 The assigned number of children and the mean FEV_1/FVC during the follow-up (with 95% CI) per FEV_1/FVC trajectory

	MAAS		IOW		ALSPAC	
		FEV_1/FVC		FEV_1/FVC		FEV_1/FVC
Trajectories 8–26 years	N (%)	Mean (95% CI)	N (%)	Mean (95% CI)	N (%)	Mean (95% CI)
Above average	309	92.21	320	91.02	2355	91.81
	38.60%	(91.98 to 92.44)	39.60%	(90.68 to 91.37)	49.40%	(91.68 to 91.94)
Average	379	85.78	368	84.61	1816	85.06
	47.30%	(85.53 to 86.03)	45.50%	(84.26 to 84.97)	38.10%	(84.91 to 85.21)
Below average	100	78.01	97	77.53	516	77.94
	12.50%	(77.40 to 78.62)	12.00%	(76.85 to 78.21)	10.80%	(77.61 to 78.27)
Persistently low	13	67.77	24	69.76	80	69.11
	1.60%	(64.28 to 71.35)	3.00%	(67.98 to 71.54)	1.70%	(67.88 to 70.34)

ALSPAC, Avon Longitudinal Study of Pregnancy and Childhood; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IOW, Isle of Wight; MAAS, Manchester Asthma and Allergy Study.

Association between FEV_1/FVC trajectories, asthma diagnosis, wheeze and sensitisation

The persistently low FEV_1/FVC trajectory was associated with current wheeze and current asthma diagnosis in all cohorts (online supplemental table S7). For example, current asthma in ALSPAC was strongly associated with persistently low trajectory (RRR 3.62, 95% CI 2.14 to 6.11, $p=1.5\times10^{-6}$), and in general, the likelihood of asthma diagnosis increased with decreasing trajectory.

We capitalised on the availability of data from healthcare records in MAAS to show evidence of an association between diminished lung function trajectories and LRTIs and asthma/wheeze hospital admissions by age 3 years, with markedly increased risks for below average and persistently low trajectories (online supplemental table S7). Respiratory syncytial virus-confirmed bronchiolitis was one of the strongest associates of persistently low trajectory (RRR 6.7, 95% CI 1.30 to 34.88, p=0.023).

We found strong evidence of an association between trajectory membership and allergic sensitisation in all cohorts. Sensitisation in preschool and early school age increased the risk of membership of the persistently low trajectory (ALSPAC age 7, RRR 2.41, 95% CI 1.44 to 4.03, p<0.0001; IOW age 4, RRR 3.84, 95% CI 1.44 to 10.21, p=0.007). In MAAS, children in the Above average lung function trajectory were less likely to be sensitised after age 3 years.

Association between FEV_1/FVC trajectories and wheeze phenotypes

The proportion of participants in the persistent wheeze cluster increased with decreasing lung function trajectory, although it is of note that 5%–6% of those in the above average trajectory had persistent wheeze (figure 2, online supplemental table S8).[21]

Lung function trajectories and cardiovascular and metabolic outcomes in ALSPAC

Table 2 shows the crude and adjusted risk of cardiovascular outcomes at 24 years per-FEV_1/FVC trajectory increase (ie, with decreasing lung function). These analyses were performed on 1422–2759 individuals with data available in ALSPAC.

We found an increase in LVMI (mean 1.14 $g/m^{2.7}$, 95% CI 0.68 to 1.60 per FEV_1/FVC trajectory; $p=1.30\times10^{-6}$), increase in LVPW systolic thickness average (mean 0.03 cm, 95% CI 0.02 to 0.05; $p=2.0\times10^{-7}$), increase in average cIMT mean (mean 0.005 mm, 95% CI 0.001 to 0.008; p=0.008) and increase in pulse pressure (mean 1.10 mm Hg, 95% CI 0.65 to 1.55; $p=1.82\times10^{-6}$), with decreasing lung function. Furthermore, we observed an increase in systolic BP (mean 1.44 mm Hg, 95% CI 0.87 to 2.02 per-lung function trajectory; $p=8.4\times10^{-7}$), higher serum triglycerides (mean 0.03 mmol/L, 95% CI 0.01 to 0.06 per-lung function trajectory; p=0.006), and lower HDL (mean −0.04 mmol/L, 95% CI −0.06 to −0.01, p=0.003),

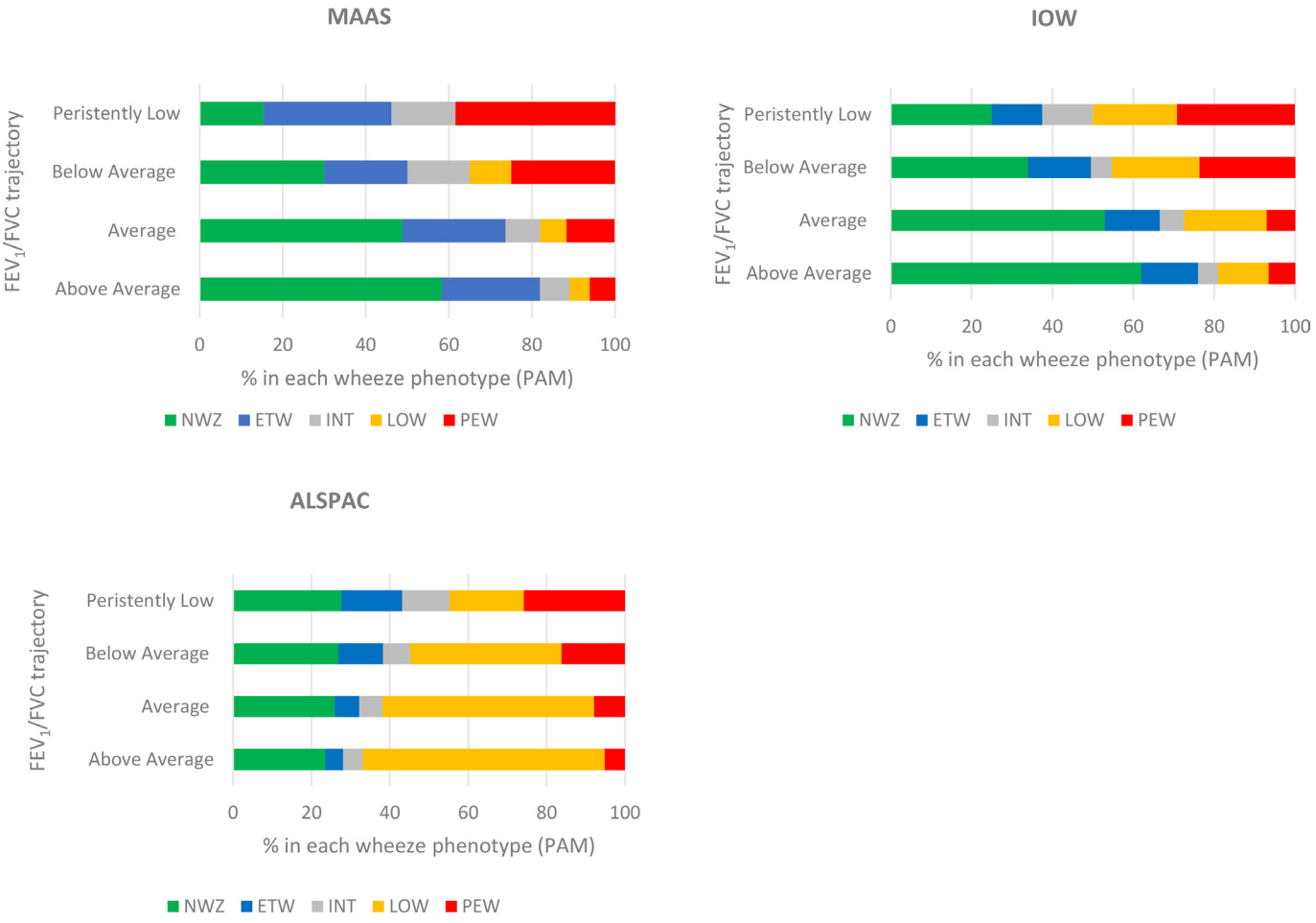

Figure 2 Distribution of partition-around-medoids (PAM) wheeze phenotypes (ETW, INT, LOW, NWZ, PEW) membership[21] by FEV_1/FVC assigned classes. ALSPAC, Avon Longitudinal Study of Parents and Children; ETW, early-transient; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; INT, intermittent; IOW, Isle of Wight; LOW, late-onset; MAAS, Manchester Asthma and Allergy Study; NWZ, never; PEW, persistent wheeze.

Table 2 Associations between FEV_1/FVC trajectories (8–24 years) and markers of cardiovascular disease risk at 24 years in 1700–3200 individuals in Avon Longitudinal Study of Parents and Children

	N	Mean 95% CI Per-FEV_1/FVC trajectory 8–24 years Crude effect	P value	Mean 95% CI Per-FEV_1/FVC trajectory 8–24 years Adjusted effect†	P value	Attenuating confounders
Cardiovascular outcomes at 24 years						
Left ventricular mass indexed to height 2.7 ($g/m^{2.7}$)	1460	1.14 (0.68 to 1.60)	<0.001	0.58 (0.14 to 1.02)	0.009	Sex and BMI
Left ventricle posterior wall systolic thickness average (cm)	1422	0.033 (0.020 to 0.045)	<0.001	0.014 (0.002 to 0.025)	0.02	Sex
Carotid femoral pulse wave velocity (m/s)	1702	0.058 (–0.011 to 0.13)	0.10	–0.012 (–0.079 to 0.056)	0.73	Sex
Pulse pressure (mm Hg)	2759	1.10 (0.65 to 1.55)	<0.001	0.005 (–0.38 to 0.39)	0.98	Sex
Average carotid intima-media thickness-mean (mm)	1451	0.005 (0.001 to 0.008)	0.008	0.003 (–0.001 to 0.006)	0.12	Sex and BMI
Blood pressure measures at 24 years						
Systolic (mm Hg)	2759	1.44 (0.87 to 2.02)	<0.001	0.07 (–0.43 to 0.58)	0.77	Sex
Diastolic (mm Hg)	2759	0.34 (–0.06 to 0.74)	0.09	0.07 (–0.33 to 0.47)	0.73	Sex, BMI
Fasting lipids at 24 years						
Triglycerides (mmol/L, log)	2269	0.032 (0.009 to 0.056)	0.006	0.016 (–0.007 to 0.039)	0.18	Sex, BMI
HDL (mmol/L)	2269	–0.035 (–0.059 to –0.012)	0.003	–0.006 (–0.029 to 0.016)	0.58	Sex

Lung function trajectories treated as continuous: (1) above average (49.5%); (2) average (38.3%); (3) below average (10.6%); and (4) persistently low (1.7%). Linear regression crude and adjusted analyses weighted by class membership probabilities. We tested the assumption of linearity in all the regression models using lrtest command in Stata. P values from likelihood ratio tests were ≥0.05.
*Adjusted by sex, maternal lower education level (educated to the General Certificate of Education level 'school-leaving certificate' or lower) and child's BMI at 7 years. Note: 'per-class increase' is equivalent to 'with decreasing lung function'.
BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL, high-density lipoprotein.

with decreasing lung function. After adjustment by sex, maternal education level and child's BMI, the only remaining associations were for LVMI (mean 0.58 $g/m^{2.7}$, p=0.009) and LVPW systolic thickness average (mean 0.01 cm, p=0.02); with small evidence for residual associations for average cIMT mean.

We observed similar effect in relation to systolic BP in MAAS, with an increase in BP with decreasing lung function (mean 2.05 mm Hg, 95% CI 0.63 to 3.47 per trajectory; p=0.005) (online supplemental table S9). This difference was completely attenuated after adjustment for sex and BMI.

Results for individual effects for each lung function trajectory (average as reference category) are reported in online supplemental tables S10–S12. Sex-stratified analyses (online supplemental table S13) show similar effects for LVMI (males: mean 0.79 $g/m^{2.7}$ per-lung function trajectory, p=0.03; females: mean 0.59 $g/m^{2.7}$, p=0.06) but an attenuation of the effect for LVPW systolic thickness average in females (males: mean 0.02 cm, p=0.08; females: mean 0.01 cm, p=0.17).

Online supplemental table S14 compares associations using predicted FEV_1/FVC trajectories (which are adjusted by age, ethnicity, height and gender) vs raw FEV_1/FVC adjusted by sex, maternal education level and child's BMI in ALSPAC. While some of the associations between trajectories and CV markers failed to reach formal statistical significance, this was not the case for all of them (associations with LVMI and LVPW, with a trend for cIMT remained significant).

DISCUSSION

In this study, we used data-driven analyses in three independent birth cohorts to identify four FEV_1/FVC trajectories extending from early school age into early adulthood (above average, average, below average and persistently low). Results were highly consistent across the populations, with no overlap in FEV_1/FVC at any follow-up time in all cohorts. Membership of the persistently low trajectory was associated with male sex, wheeze and allergic sensitisation in all cohorts. Individuals assigned to the persistently low trajectory were at an increased risk of having an asthma diagnosis through childhood, adolescence and early adulthood. Decreasing BMI in preschool and early school age was associated with increasing probability of allocation to above average trajectory. Importantly, our results provide evidence of the association of diminished lung function trajectories with objective echocardiographic markers of the propensity to cardiovascular diseases (including heart failure and stroke). Our results add weight to the emerging concept in the field of assessing lung function in childhood (eg, at school) as a marker of subsequent risk of respiratory, cardiovascular and metabolic diseases.[4]

LVMI and cIMT are indicators of future cardiovascular disease risk. For example, cIMT has been extensively validated as a predictor of cardiovascular disease-risk in adults, and LVMI is a measure that independently predicts adverse cardiovascular events and premature death.[13 16] We observed a relationship between decreasing lung function trajectory and an increase in both markers. Coronary Artery Risk Development in Young Adults (CARDIA) study was the first to investigate the interplay between early adulthood lung function and late cardiac changes demonstrated on an echocardiogram.[23] A decline in FEV_1/FVC was associated with decreased left heart chamber size and lower cardiac output, whereas a decline in FVC with a preserved FEV_1/FVC (a precursor to a restrictive pathology) was associated with left heart hypertrophy, increased cardiac output, and diastolic dysfunction, irrespective of race, sex, age, height, cigarette smoking, diabetes or BMI.[23] Although FEV_1 and FVC are highly correlated, the fact that the pattern of airway pathology in young adulthood seems to differently influence future cardiovascular phenotypes could suggest an underlying mechanism which is independent of a systemic inflammatory response. However, while CARDIA aimed to identify factors in young adulthood that contribute to the development of cardiovascular disease, our studies followed participants from the antenatal period,

allowing for more precise assessment of early-life risk factors, and the association with childhood lung function patterns.

The association between lung and cardiac disease has been long established in patients with COPD.[24] There is a reduction in both cardiac chamber size and the left atrial and ventricular filling in those with severe COPD, with the degree of hyperinflation showing the strongest correlation with heart size. The mechanism behind this is unknown, but few studies have postulated that lung hyperinflation increases intrathoracic pressure, which decreases venous return,[24] or increases LV wall stress leading to increased LV stroke work and eventual increased LV mass and LV remodelling.[25] Indeed, the Multi-Ethnic Study of Atherosclerosis study found that an increase in LV mass-to-volume ratio as well as end-diastolic volume was associated with an increase in cardiovascular events, which is consistent with a load effect that induces chamber remodelling and hypertrophy.[26] Other studies discussed a possible role of haemodynamic effects of hypoxia and vascular remodelling leading to pulmonary hypertension with subsequent effect on RV and LV interdependence as a cause of altered cardiac chamber size.[27] Using CT scans, findings suggestive of 'early emphysema' in an otherwise healthy population were associated with lower LV end-diastolic volume, stroke volume and cardiac output, implying that the interaction between heart and lung seen in advanced disease initiates earlier in life and at subclinical levels of disease,[28] likely prior to any of the proposed mechanisms in those with severe lung disease like COPD. This is supported by our findings. However, the above data come from cross-sectional studies in older populations, and our results take this one step further by identifying that lung function patterns starting in school age predict cardiac effect in adulthood.

Other major risk factors for cardiovascular disease include dyslipidaemia (defined as either high triglycerides, high low-density lipoprotein or low HDL). Of note, such metabolic abnormalities have also been associated with asthma[29–31] and airway obstruction in children[32].

Several studies have shown that poorer lung function in early adulthood is associated with stroke and hypertension in later adulthood. Lung function in young adulthood in CARDIA was independently associated with cardiovascular and cerebrovascular events into middle age,[33] and within-individual change in lung function (including low normal and deterioration from peak health) was independently associated with a greater incidence of hypertension and blood pressure variability.[34]

In our study, low birth weight and maternal asthma were associated with persistently low FEV_1/FVC trajectory. Similarly, we have previously demonstrated that low birth weight identified children with a persistently low FEV_1 trajectory,[35] as well as the restrictive phenotype.[6] Both the IOW[36] and the Pelotas cohorts[11] showed that low birth weight was associated with low FEV_1 and FEV_1/FVC trajectories. Exact pathophysiological mechanisms have not been ascertained, but it has been suggested that adverse early life risk factors such as maternal smoking,[37] poor maternal nutrition,[38] restricted intrauterine growth[39] and gestational age[40] could contribute to this. This adds to the evidence that low birth weight acts as a proxy for adult health and that it is associated with chronic disease including coronary artery disease and hypertension.

Our study has several limitations. One limitation which is common to most analyses of longitudinal data which involve multiple follow-up measurements over a long period of time is missing values due to drop-out. Both analyses (complete dataset and at least two spirometry measures) gave consistent optimal goodness-of-fit using the BIC, and the child class assignments were stable across the two analyses. This suggests that the missing-at-random assumption was plausible, given that if children with missing datapoints were not missing at random, we would have observed a higher mismatch between classes.

A further limitation of our study is the heterogeneity between cohorts (minor differences in data collection ages, wording of questions, etc). However, the lung function trajectories were remarkably consistent across the cohorts. Another limitation is that missing data limits assessment of risk factors. Given a relatively small sample size in the persistently low trajectory, we may not have enough power to detect clinically important effects and may lack precision. Strengths of our study include the longitudinal nature of the data coming from multiple sources and covering different age ranges and screening intervals, the long duration of the follow-up (up to 26 years of age) and similar methodology applied for determining participants' health status.

Our study highlights the importance of lung growth in general as the associate of adverse respiratory, cardiovascular and metabolic outcomes, and the importance of early life factors, particularly deprivation. Childhood lung function trajectories may serve as important predictors in the development of not only future lung disease, but also the interplay and multimorbidity of lung, cardiovascular and metabolic diseases. Our findings draw attention to the potential importance of measuring lung function from early school age as a marker of future risk, since early lung function optimisation to alter trajectories may help in preventing adverse health outcomes in adulthood. However, being able to identify a potential problem does not automatically extend to actionable interventions to address it. The question remains as to whether the age at which the majority of children in the community can perform reliable forced expiratory manoeuvres (usually around age 6 years) is already too late to intervene to improve lung growth.[41] However, we have previously shown in ALSPAC that catch-up growth in FEV_1 and FVC is possible around puberty, and that later onset and higher velocity of pubertal growth are associated with higher maximally attained lung function at age 24 years.[42] Given the global trends towards earlier puberty[43] and a significant relationship between the early onset of puberty with child's obesity[44] and maternal obesity and gestational weight gain,[45] a combination of intervention tackling childhood obesity to protect current generations, and obesity in pregnancy to protect future generations (particularly among women with impaired lung function),[41] may have substantial impact on overall health. This should be coupled with measures to minimise exposure to tobacco smoke, air pollution and other adverse environmental exposures. Among children with recurrent wheeze, every effort should be made to reduce the number of severe exacerbations. However, all these measures must be paralleled with societal efforts to reduce inequalities and social deprivation if the nation's health is to be improved.

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Acknowledgements The authors of all cohorts would like to 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 would also like to acknowledge the hard work and dedication of the study teams (post-doctoral scientists, physiologists, research fellows, nurses, technicians and clerical staff). This article is dedicated to the memory of our wonderful colleague and friend Professor John Henderson (1958–2019), whose contribution to our work cannot be overstated. Rainbow-chasers and UNICORN riders forever.

Collaborators STELAR/UNICORN investigators: Professor John Ainsworth (School of Health Sciences, The University of Manchester). Dr Andrew Boyd (University of Bristol). Dr Philip Couch (School of Health Sciences, The University of Manchester). Professor Paul Cullinan (Imperial College London). Professor Graham Devereux (Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool). Dr Ibrahim Emam (Department of Computing, Imperial College London). Francesca Riccioli (Department of Computing, Imperial College London). Professor Yi-ke Guo (Department of Computing, Imperial College London). Professor Steve Turner (Child Health, University of Aberdeen, Aberdeen, UK). Professor Ashley Woodcock, The University of Manchester.

Contributors AC, SH and RG conceived the study and initial draft. RG and SH run all the analyses. RG, SH, MD, AU, OM, SF, LL, AS, JWD, SHA, CSM, GR, AH, CP, JWH and AC made substantial contributions to interpretation of results, drafting and final approval of the paper. SH and RG verified the underlying data. RG will serve as guarantor for the contents of this paper.

Funding Supported by the MRC Programme Grant MR/S025340/1. The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. This publication is the work of the authors and Raquel Granell & Adnan Custovic will serve as guarantors for the contents of this paper. A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf). The funders had no role in conception, design, data analysis or interpretation.

Competing interests RG, SH, MD, AU, OM, SF, LL, AS, CP, CSM and GR declare no conflicts of interest. AS has received research grants. JWD has received research and charity grants and declares pharmaceutical support for lectures and attending conferences/meetings. AH has received support from Research Institutions and declares an unpaid fiduciary role. JWH has received research grant and support for travel to congress. AC has received research grants, consulting fees, honoraria for lectures and declares unpaid fiduciary role.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and ALSPACAll self-completion questionnaire content is approved by the ALSPAC Ethics and Law Committee. Bristol and Weston Health Authority: E1808 Children of the Nineties: Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). (28 November 1989) Southmead Health Authority: 49/89 Children of the Nineties -'ALSPAC'. (5 April 1990) Frenchay Health Authority: 90/8 Children of the Nineties. (28 June 1990) MAASERP/94/032 up to 5 years. Allergen avoidance, Primary Prevention, genetics, sRaw age 3 and 5; SOU/00/259 5 years; ERP/95/137 exposure to pet allergens, atopy, genetics; ERP/97/023 IFWIN, genetics 03/SM/400 8 years; 06/Q1403/142 10–12 years; 11/NW/0228 13–15 years; 14/NW/1309 18+ years. IoW Ethics approval for the IoW cohort was originally given by the Isle of Wight local research ethics committee in 1989 and at each subsequent follow up (1, 2 and 4 years) (this is pre 'numbers'). Age 10 follow-up (including DNA and genotyping): Isle of Wight Health Authority Local Research Ethics Committee 18/98. Age 18 follow-up (including DNA and genotyping): Isle of Wight, Portsmouth & South East Hampshire Research Ethics Committee 06/Q1701/34. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The informed consent obtained from all included participants does not allow the data to be made freely available through any third party maintained public repository. However, data used for this submission can be made available on request to the corresponding cohort executive. The ALSPAC website provides information on how to request and access its data (http://www.bristol.ac.uk/alspac/researchers/access/). For queries regarding access of data from MAAS, IoW, SEATON or Ashford contact Philip Couch philip.couch@manchester.ac.uk).

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Lung function trajectories from school age to adulthood and their relationship with markers of cardiovascular disease risk

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Online Data Supplement

Granell R, *et al. Thorax* 2024;0:1–8. doi: 10.1136/thorax-2023-220485

SUPPLEMENTARY INTRODUCTION

Table S1. *Summary of existing studies to derive lung function trajectories in childhood*

Name of study	MAAS[1]	ALSPAC[1]	PIAF[1]	TCRS[2]	IOW[3]	CAMP[4]	RAINE[5]	PELOTAS[6]	TAHS[7]
Year of Publication	2018	2018	2018	2016	2019	2016	2022	2020	2018
Locations	U.K.	U.K.	Australia	Arizona	UK	USA/Canada	Australia	Brazil	Tasmania/ Australia
No. of subjects	1046	1390	196 (spirometry on at least one occasion)	599 participants	981 have LF at age 10, 839 have LF at age 18 and 547 individuals have LF at age 26	684	1512	2917 individuals who had measurements in all follow-up visits	2438
			253 (infant lung function)	with 2,142 observations					
Time points	5, 8, 11, and 16 years	8, 15, and 24 years	6, 12, and 18 years & 1, 6, and 12 months	11, 16, 22, 26, and 32 years	10,18 and 26 years	23 - 30 years	6 – 22 years	15,18 and 22 years	7, 13, 18, 45, 87 50 and 53 years
Spirometry Measures	Forced expiratory volume in one second (FEV_1) and Forced vital capacity	Forced expiratory volume in one second (FEV_1) and Forced vital capacity	FEV_1 as % predicted at 6, 12, and 18 years.	Ratio of FEV_1 to FVC (FEV_1/FVC)	FVC, FEV_1, FEV_1 and FVC ratio and	Pre-BD FEV_1	FEV_1, FVC, FEV_1/FVC	FEV_1, FVC and FEV_1 and FVC ratio	Pre- and post-BD spirometry
			Rapid thoracoabdo						

	(FVC) were recorded and the data expressed as FEV_1 % predicted and FEV_1/FVC ratio.	(FVC) were recorded and the data expressed as FEV_1 % predicted and FEV_1/FVC ratio.	minal compression test to determine the maximal flow at functional residual capacity (V'maxFRC) at 1, 6, and 12 months.		FEF25-75				
Type of Spirometry Measures	FEV1 as % predicted at each age (*2)	FEV1 as % predicted at each age (*2)	(1) Mean % predicted FEV_1 (95% CI) over time by FEV_1 trajectory (196 children).	Percent of predicted FEV_1 values.	Raw (Male and Female)	Pre-BD FEV_1	Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC (z-scores)	Z-scores	Pre-BD FEV_1 z-scores at six time points
			(2) Mean % predicted V'maxFRC (95% CI) over time by V'maxFRC trajectory (253 children).	Ratio of FEV_1 to FVC (FEV1/FVC), adjusting for sex.					

			(3) Membership of FEV_1 trajectory (from 6 to 18 years of age) in relation to the V'maxFRC trajectories (from 1 to 12 months of age), evaluated in 196 children.	V9maxFRC was measured at age 6 years.					
Number of trajectories	4	4	(1) 3; (2) 3; (3) 2	2	2 (FVC, FEV1, ratio) and 3 (FEF)	4	4	3	6
Derived trajectories	Persistently high, n=46; 4%,	Persistently high, n=52; 4%,	(1) Persistently high, n=24; 12%,	(1) Low: n = 56; 9.3%	Male FEV1:	Normal growth, n=70; 25%	FEV_1 and FVC trajectories Very Low (n=51 3%, FEV_1, n=61 4% FVC)	Low: 15.5%,	(1) Early below average accelerated decline: 4%, n=97,
	Normal n=468; 45%,	Normal n=632; 45%,	Normal n=133; 68%,	(2) Normal: 543;	Low: 57.2%,	Normal growth, early decline, n=178; 26%	Low (n=746 49%, FEV_1, n=855 56% FVC)	Average: 59.6%,	(2) Persistently low: 5·6%, n=136,

	Below average n=496; 47%,	Below average n=613; 44%,	Below average n=39; 20%.		High: 42.8%.	Reduced growth, n=160; 23%	Average (n=611 40%, FEV_1, n=457 30% FVC)	High: 24.9%.	(3) Below average: 31·6%, n=772,
	Persistently low n=36; 3%.	Persistently low n=93; 7%.	(2) Above average n=62; 25%,		Female FEV1:	Reduced growth, early decline, n=176; 26%	Above Average (n=104 7%, FEV_1, n=139 9% FVC)		(4) Above average: 12·1%, n=293,
			Below average n=191; 75%.		Low: 47.9%,		FEV_1/FVC trajectories		(5) Early low, accelerated growth, normal decline: 8%, n=196,
							Very Low (n=131, 9%)		
			(3) V´max FRC: above average 25%		High: 52.1%.		Low Average (n=198, 13%)		(6) Average: 38·7%, n=944
							Average-Low (n=529, 35%)		
			V´max FRC: below average 75%				Average (n=654, 43%)		

Methods used	Two-level random intercept and random coefficients regression models	Two-level random intercept and random coefficients regression models	Two-level random intercept and random coefficients regression models	Latent class linear mixed effects model with subject specific random effects for slope and intercept and a fixed effect for sex.	Finite mixture models	Subjective expert classification using NHANES III, Kaplan-Meier	Group based trajectory modeling	Group based trajectory modeling	Group-based trajectory modelling

SUPPLEMENTARY METHODS

The Avon Longitudinal Study of Parents and Children (ALSPAC)

ALSPAC is a birth cohort study established in 1991 in Avon, UK[8-10]. Pregnant women with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541. Of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age.

When the oldest children were approximately 7 years of age, an attempt was made to bolster the study with eligible cases who had failed to join originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 24 is 913 (456, 262 and 195 recruited during Phases II, III and IV respectively), resulting in an additional 913 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper and its update. The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 foetuses. Of these 14,901 were alive at 1 year of age.

Study data were collected and managed using REDCap Research Electronic Data Capture) electronic data capture tools[11] hosted at University of Bristol.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The study website contains details of available data through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

The Manchester Asthma and Allergy Study (MAAS)

MAAS is an unselected birth cohort study established in 1995 in Manchester, UK[12]. It consists of a mixed urban-rural population within 50 square miles of South Manchester and Cheshire, located within the maternity catchment area of Wythenshawe and Stepping Hill Hospitals. All pregnant women were screened for eligibility at antenatal visits (8-10th week of pregnancy). Of the 1499 couples who met the inclusion criteria (≤10 weeks of pregnancy, maternal age ≥18 years, and questionnaire and skin prick data test available for both parents), 288 declined to take part in the study and 27 were lost to follow-up between recruitment and the birth of a child. A total of 1184 children were born into the study between February 1996 and April 1998. They were followed prospectively for 20 years to date and attended follow-up clinics for assessments, which included lung function measurements, skin prick testing, biological samples (serum, plasma and urine), and questionnaire data collection. The study was approved by the North West – Greater Manchester East Research Ethics Committee.

We capitalized on a unique feature of the health care system in the UK in that, General practitioners (GPs) maintain primary care records of all health care encounters of their patients, including hospital admission, and outpatient appointments. A trained paediatrician extracted and transcribed data from GP-held medical records including AD diagnosis and prescriptions for topical treatments. Timing, type of visit, symptoms, indication and prescriptions for each encounter were noted. A total of 987 participants

provided informed consent for medical data collection. We reviewed 925 study participants due to GPs' lack of response for data collection or participants moving away. Nine of these were partially accessed due to missing paper or electronic records and were excluded.

Data on lower respiratory tract infections (LRTI), hospital admissions, bronchiolitis, and RSV-positive bronchiolitis were extracted from electronic and paper-based primary care medical records, including emergency department admissions, and hospital admissions. Age in days at the time of each event was documented63. This data was available from birth to age 8 years.

Atopic sensitization was ascertained by skin prick testing (SPT) at age 8, 11, 16, and 20 years and measurement of sIgE at each clinical follow-up to a mix of common inhalant and food allergens by ImmunoCAPTM (Phadia, Uppsala, Sweden).

We thank study participants and their parents for their continued support and enthusiasm, and greatly appreciate the commitment they have given to the project. We also acknowledge the hard work and dedication of the study teams (post-doctoral scientists, physiologists, research fellows, nurses, technicians, and clerical staff).

The Isle of Wight (IOW) cohort

IOW is an unselected birth cohort study established in 1989 on the Isle of Wight, UK[13-15]. After the exclusion of adoptions, perinatal deaths, and refusal for follow-up, written informed consent was obtained from parents to enrol 1,456 newborns (of 1536 born between 1st January 1989 and 28th February 1990). Follow-up-up assessments were conducted to 26 years of age to prospectively study the development of asthma and allergic diseases. At each follow-up, validated questionnaires were completed by the parents. Additionally, the Skin Prick Test (SPT) was performed on 980, 1036 and 853 participants at 4, 10 and 18 years of age to check allergic reactions to common allergens. Ethics approvals were obtained from the Isle of Wight Local Research Ethics Committee (now named the National Research Ethics Service, NRES Committee South Central – Southampton B) at recruitment and for the subsequent follow-ups.

The IOW research team are grateful to all the participants and their families for their support over the years and also to the many fellow researchers who have contributed to the cohort's follow up.

Spirometry

ALSPAC

Spirometry tests were were conducted at $8^{1/2}$, 15 and 24 years according to American Thoracic Society/European Respiratory Society guidelines[16,17] using a Vitalograph pneumotachograph system with animated incentive software (Spirotrac, Vitaograph, UK) in a dedicated research clinic by trained technicians. Calibration checks were performed with a standard 3L calibration syringe according to the manufacturer's instructions at the start of each half-day clinic session. Subjects were seated with a nose clip in place and were asked to inhale to total lung capacity (TLC), then instructed to perform a forced expiration, through a mouthpiece, to residual volume (RV). The test was repeated at intervals of 30 seconds until 3 technically acceptable traces were obtained from a maximum of eight attempts. Forced expiratory volume in one second (FEV_1) and Forced vital capacity (FVC) were recorded and the data expressed as FEV_1 % predicted and FEV_1/FVC ratio.

MAAS

Spirometry was performed at ages 8, 11, 16 and 20 years according to American Thoracic Society/European Respiratory Society guidelines[16,17] using a Lilly pneumotachograph system with animated incentive software (Jaeger, Germany). For home visits, we used a flow turbine spirometer

(Micro Medical, UK). Subjects were asked to inhale to total lung capacity (TLC), then instructed to perform a forced expiration, through a mouthpiece, to residual volume (RV). The test was repeated at intervals of 30 seconds until 3 technically acceptable traces were obtained. Forced expiratory volume in one second (FEV_1) and Forced vital capacity (FVC) were recorded and the data expressed as FEV_1 % predicted and FEV_1/FVC ratio. Short-acting β2-agonists were withheld for at least four, and long-acting for at least 24 hours prior to testing. Participants were symptom-free at the time of assessment.

IOW

Pre-bronchodilator lung function tests were conducted at 10, 18, and 26 years of age. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) were measured using a Koko Spirometer and software with a portable desktop device (both PDS Instrumentation, Louisville, KY, USA). Spirometry was performed and evaluated according to the American Thoracic Society (ATS) criteria. The children or adults, respectively, were required to be free of respiratory infection for 2 weeks and not to be taking any oral steroids and were advised to abstain from any β-agonist medication for 6 h and from caffeine intake for at least 4 h.

Assessment of cardiovascular risk in ALSPAC

Participants fasted for 6 h before the clinic, with the exception of those with a diagnosis of diabetes or a condition that would not allow fasting. Ultrasound scans of the left and right common carotid arteries were performed using a CardioHealth Panasonic system with a 13–5 MHz linear array broadband transducer according to a standardised protocol to measure cIMT. Participants lay on a couch with their arms by their side, while a trained researcher performed the ultrasound test on both sides of their neck. Right and left carotid intima-media thickness measurements were taken to be the average of 3 end-diastolic measurements of the far-wall of the common carotid artery over a length of 5–10 mm, and 10 mm adjoining the bifurcation. The mean of both right and left cIMT measures was calculated.

Right and left carotid intima-media thickness measurements were taken to be the average of 3 end-diastolic measurements of the far-wall of the common carotid artery over a length of 5–10 mm, and 10 mm adjoining the bifurcation. The mean of both right and left cIMT measures was calculated.

Echocardiography was performed by two experienced echocardiographers using a Philips EPIQ 7G Ultrasound System equipped with a X5-1 transducer and methods and calculation were performed in accordance with American Society of Echocardiography guidelines; these techniques are described elsewhere[18]. PWV was measured using a Vicorder device (Skidmore Medical, Bristol, UK) which has been validated in previous studies in adolescents [19]. Three pulse wave velocity measurements were taken with an interval of 1 minute between measurements, acceptable PWV measurements were within ≤ 0.5 m/s of each other. Results were averaged to give a measurement of arterial stiffness. Resting blood pressure was measured with the subject in a sitting position using an Omron 705-IT machine using an appropriately sized cuff [18] as the average of the final two of three consecutive measurements.

Resting blood pressure (BP) was measured in a sitting position as the average of the final two of three consecutive measurements.

Definitions of variables (demographic, exposures and outcomes)

Postal questionnaires were used in ALSPAC, while interviewer-administered questionnaires were employed in MAAS and IOW available on multiple occasions from infancy to adolescence.

Wheezing reports were available at 14 time points in ALSPAC over 16.5 years, 7 in MAAS over 20 years, and 6 in IOW over 26 years.

Parental history of asthma, eczema and hay fever were assessed by questionnaires and were defined based on the responses given to the question "have you (and/or your partner) ever had asthma/eczema/hay fever".

Maternal and paternal smoking were defined based on the response given to the question "do you (or does your partner) smoke", administered during pregnancy or 1st year of study child.

Low birth weight was defined as birth weight less than 2500 g based on NHS birth records.

Current wheeze: Current wheeze was defined as a positive response to either the question "Has your child had wheezing in the last 12 months" or "Has your child had wheezing with whistling in the last 12 months" in ALSPAC, and in the other three cohorts to the question "Has your child had wheezing or whistling in the chest in the last 12 months?".

Current asthma[20]*:* Presence of any two of the following three features: 1) Current wheeze; 2) Current use of asthma medication; 3) Physician-diagnosed asthma ever.

BMI (kg/m^2): weight and height were measured at annual clinic visits

Skin prick test (SPT): The atopic status of the children was determined (at an annual clinic when the children were 7–8 years of age in ALSPAC[21], at ages 4-5, and 7-8 years in MAAS and IOW) by skin prick test responses to a panel of up to 12 common allergens including house dust mite, mixed grasses and cat. Sensitisation to one of these three allergens has been shown to identify 95% of all sensitised children in this population. A positive response was defined as a mean weal diameter of >3 mm (>2 mm for ALSPAC) with an absent response to negative control solution, and atopy was defined as a positive response to one or more of house dust mite, cat or grass pollen.

MAAS transcribed healthcare records[22]

LRTI hospitalisation: Lower respiratory tract infection hospital admission by 3rd year of life.

RSV positive bronchiolitis: ever RSV positive bronchiolitis in the first 8 years of life.

Asthma/wheeze hospital admission: asthma or wheee hospital admission by 3rd year of life.

Data-driven phenotype allocation

Cluster allocation of our study participants into latent wheeze phenotypes has previously been performed using machine learning methods for latent variable analysis.

Spell-based wheeze phenotypes[23]*:* Based on prospectively collected current wheeze data from five pooled birth cohorts birth to age 16 years , children were assigned as:

1. Never wheezing: no or low prevalence of wheeze throughout observation period.
2. Early-transient wheeze: high prevalence of wheeze during infancy, with decrease to mid-childhood.
3. Intermittent wheeze: wheeze from infancy to adolsence interspersed with periods of no wheeze.
4. Late-onset wheezing: low prevalence until mid-childhod age, increasing rapidly to a peak prevalence in adolescence.
5. Persistent wheeze*:* high prevalence of wheeze throughout.

Statistical Analysis

Latent profile modeling[1,24] *to derive trajectory classes based on the development of FEV_1/FVC over time*

We used two-level random intercept regression models to assign children to their most likely trajectory profile; we assumed that each child belonged to one of a set of *k* latent profiles, the number or size of

which were unknown a priori. The models were compared for goodness-of-fit using the Bayesian Information Criterion (BIC). For each child, the posterior probability of belonging to each of the classes was estimated from the model, and children were classified to each trajectory profile based on their maximum posterior probability. Latent profile modelling was undertaken using the *gllamm* (generalised linear latent and mixed models) package implemented in Stata 15 (StataCorp, College Station, TX, USA).

Associations between lung function trajectories and early–life risk factors

The following potential predictors, as evidenced in the literature, were considered in analyses with the derived lung function trajectories: gender, low birthweight, maternal smoking during pregnancy, parental history of asthma, cat/dog ownership in first year of life, current wheeze and current asthma reports from birth to age 8 years, LRTI/asthma/wheeze hospitalizations by age 3 and RSV positive bronchiolitis (MAAS only), BMI and allergic sensitization from early life to age 8 years.

Associations between lung function trajectories and markers of cardiovascular and metabolic disease risk

We used linear regression models to assess the associations between lung function trajectories between 8 and 24 years and markers of cardiovascular and metabolic disease risk at 24 years, before and after adjustment by gender, maternal lower education level (Educated to the General Certificate of Education level (school-leaving certificate) or lower) and child's BMI at 7 years. We report both individual trajectory effects using average as the reference category and per-trajectory effects treating lung function trajectories as a continuous variable (1. Above average; 2. Average; 3. Below average; and 4. Persistently low).

All cardiovascular outcomes were normally distributed except for Triglycerides, which was log-transformed.

All analyses were carried out using Stata 16/17 (StataCorp, College Station, Tex).

SUPPLEMENTARY RESULTS

Table S2. *Characteristics of the study populations: MASS, IOW, and ALSPAC*

	Whole population	Included: Children with data on lung function at 2-3 points	Excluded: Children with data on lung function at <2 time points	P-value included vs excluded
MAAS	**N=1184**	**N=801**	**N=383**	
Parental characteristics				
Maternal age (mean/SD)	30.4 (4.78)	30.8 (4.58)	29.58 (5.12)	0.0001
Maternal asthma	19.9% (235/1184)	20.0% (160/801)	19.6% (75/383)	0.874
Paternal asthma	13.8% (163/1182)	13.6% (109/800)	14.1% (54/382)	0.812
Perinatal characteristics				
Male gender	54.2% (642/1184)	52.4% (420/801)	58.0% (222/383)	0.074
Low birth weight (≤2500 gr)	3.0% (34/1136)	3.1% (24/773)	2.6% (10/363)	0.747
Environmental characteristics				
Breastfeeding	70.0% (780/1115)	73.8% (569/771)	61.3% (211/344)	P<0.0001
Maternal smoking during pregnancy	14.8% (174/1177)	12.2% (97/798)	20.3% (77/379)	P<0.0001
Paternal smoking during pregnancy	29.4% (347/1181)	28.0% (224/799)	32.2% (123/382)	0.142
Presence of cat (recruitment)	20.7% (240/1160)	20.5% (161/787)	21.2% (79/373)	0.777
Presence of dog (recruitment)	17.3% (201/1160)	15.3% (120/787)	21.7% (81/373)	0.007
Isle of Wight (IoW)	**N=1536**	**N=809**	**N=727**	
Parental characteristics				
Maternal age (mean/SD)	26.8 (5.54)	27.1 (5.27)	26.39 (5.43)	0.009
Maternal asthma	10.9% (165/1517)	10.5% (84/802)	11.3% (81/715)	0.593
Paternal asthma	9.9% (149/1504)	10.2% (81/798)	9.6% (68/706)	0.737
Perinatal characteristics				
Male gender	51.2% (786/1536)	46.6% (377/809)	56.3% (409/727)	P<0.0001
Low birth weight (≤2500 gr)	4.1% (62/1501)	3.8% (30/791)	4.5% (32/710)	0.487
Environmental characteristics				
Breastfeeding	77.% (1047/1346)	82.8% (625/755)	71.4% (422/591)	P<0.0001
Maternal smoking during pregnancy	26.0% (393/1509)	19.9% (159/798)	32.9% (234/711)	P<0.0001
Paternal smoking during pregnancy	40.5% (608/1503)	34.4% (275/802)	47.3% (333/704)	P<0.0001

Table S2 continue

	Whole population	Included: Children with data on lung function at 2-3 points	Excluded: Children with data on lung function at <2 time points	P-value included vs excluded
Presence of cat (recruitment)	32.6% (494/1514)	33.8% (271/802)	31.3% (223/712)	0.306
Presence of dog (recruitment)	29.2% (442/1514)	28.3% (227/802)	30.2% (215/712)	0.419
ALSPAC	**N=15,645**	**N=4,767**	**N=10,878**	
Parental characteristics				
Maternal age (mean/SD)	28.0 (5.0), N=14049	29.4 (4.5), N=4559	27.3 (5.0), N=9490	P<0.0001
Maternal asthma ever	11.4% (1435/12590)	11.7% (521/4437)	11.2% (914/8153)	0.37
Paternal asthma ever	12.7% (1092/8568)	12.9% (436/3381)	12.6% (656/5187)	0.74
Perinatal characteristics				
Male gender	51.2% (7706/15061)	46.0% (2193/4767)	53.6% (5513/10294)	P<0.0001
Low birth weight (≤2500 gr)	5.7% (790/13867)	4.3% (194/4503)	6.4% (596/9364)	P<0.0001
Environmental characteristics				
Breastfeeding 1st year	75.7% (8573/11332)	84.4% (3655/4331)	70.2% (4918/7001)	P<0.0001
Maternal smoking 1st year	24.2% (2714/11219)	15.7% (676/4294)	29.4% (2038/6925)	P<0.0001
Paternal smoking 1st year	26.2% (2208/8434)	20.4% (694/3402)	30.1% (1514/5032)	P<0.0001
Presence of cat 1st year	32.7% (2525/7733)	34.9% (1073/3075)	31.2% (1452/4658)	0.0006
Presence of dog 1st year	25.1% (1747/6955)	22.9% (594/2596)	26.5% (1153/4359)	0.0009

Table S3. *Characteristics of latent class profiles of FEV1/FVC in three cohorts using children with data on 2 or 3 time points: model comparison of goodness-of-fit using Bayesian Information Criterion (BIC).*

BIC (FEV1/FVC)			
Cohort	**MAAS** (N=801)	**IOW** (N=809)	**ALSPAC** (N=4767)
Number of classes			
2	16417	12959	75239
3	16258	12843	74785
4	16203	12820	74692
5	16200	12820	74701
6	*	*	74720

Table S4. *Posterior probability of the class membership conditional on most likely class assignment for FEV1/FVC (Class 1: Below Average; Class 2: Average; Class 3: Persistently Low; Class 4: Above average)*

		MAAS Class Assignment				IOW Class Assignment				ALSPAC Class Assignment			
		1	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*
Class Membership	*1*	*0.87*	*0.13*	*0.00*	*0.00*	*0.81*	*0.16*	*0.03*	*0.00*	*0.70*	*0.19*	*0.03*	*0.00*
	2	*0.05*	*0.82*	*0.00*	*0.13*	*0.07*	*0.77*	*0.00*	*0.16*	*0.09*	*0.73*	*0.00*	*0.20*
	3	*0.09*	*0.00*	*0.91*	*0.00*	*0.19*	*0.00*	*0.81*	*0.00*	*0.15*	*0.00*	*0.81*	*0.00*
	4	*0.00*	*0.16*	*0.00*	*0.84*	*0.00*	*0.13*	*0.00*	*0.87*	*0.00*	*0.17*	*0.00*	*0.84*

Table S5. *Confusion matrix showing similarity in classification when using children with FEV1/FVC on 2 or 3 time points, and classification based on information from children with data at all 3 time points.*

	Class assignment model based on children with FEV1/FVC data at 2 or 3 time points (ARI=0.63)											
	MAAS (N=346 with data at 3 time points)				**IOW (N=401 with data at 3 time points)**				**ALSPAC (N=2033 with data at 3 timepoints)**			
Class assignment model based on children with on FEV1/FVC data observed at all 3 time points	Peristently High	Average	Below Average	Persistently Low	Peristently High	Average	Below Average	Persistently Low	Peristently High	Average	Below Average	Persistently Low
Persistently High	105 (78.4%)	0	0	0	163 (100%)	0	0	0	827 (100%)	185 (22.2%)	0	0
Average	29 (21.6%)	140 (90.3%)	0	0	0	179 (100%)	0	0	0	648 (77.8%)	102 (32.0 %)	0
Below Average	0	15 (9.7%)	43 (84.3%)	0 (0%)	0	0	48 (100%)	0	0	0	217 (68.0%)	21 (38.9%)
Persistently Low	0	0	8 (15.7%)	6 (100%)	0	0	0	11 (100%)	0	0	0	33 (61.1 %)

***Table S6**. Sex, demographic and environmental characteristics of FEV_1/FVC trajectories: multinomial logistic regression analysis weighted by class membership probabilities; reference class is Average*

	Relative Risk Ratio (95%CI)								
	MAAS (Average n=379; 47.3%)			**IOW (Average n=368; 45.5%)**			**ALSPAC (Average n=1816; 38.1%)**		
	Above average (n=309; 38.6%)	**Below average (n=100; 12.5%)**	**Persistently low (n=13; 1.6%)**	**Above average (n=320; 39.6%)**	**Below average (n=97; 12.0%)**	**Persistently low (n=24; 3.0%)**	**Above average (n=2355; 49.4%)**	**Below average (n=516; 10.8%)**	**Persistently low (n=80; 1.7%)**
Male	0.54 (0.4, 0.74)	1.66 (1.04, 2.64)	9.35 (1.2, 72.65)	0.71 (0.52, 0.96)	1.60 (1.02, 2.53)	1.80 (0.77, 4.21)	0.64 (0.57, 0.73)	1.59 (1.31, 1.92)	2.10 (1.32, 3.33)
p value	<0.001	0.034	0.033	0.027	0.041	0.18	3.26E-12	1.87E-06	0.0016
Preterm (<37 weeks gestation)	NA	NA	NA	NA	NA	NA	0.73 (0.54, 0.98)	1.11 (0.74,1.67)	1.53 (0.67, 3.48)
p value							0.04	0.62	0.31
Low birth weight (<2500 g)	0.68 (0.28, 1.63)	0.53 (0.12, 2.37)	NA	1.49 (0.65, 3.46)	2.34 (0.83, 6.61)	1.51 (0.19, 12.3)	0.89 (0.65, 1.23)	1.40 (0.91, 2.15)	2.30 (1.05, 5.06)
p value	0.39	0.41	0.99	0.35	0.11	0.70	0.49	0.12	0.038
Maternal smoking (pregnancy or 1st year)	1.06 (0.67, 1.68)	1.13 (0.58, 2.19)	1.37 (0.29, 6.39)	1.02 (0.69, 1.5)	1.34 (0.79, 2.3)	2.16 (0.89, 5.26)	0.89 (0.74, 1.06)	1.30 (1.01, 1.67)	1.60 (0.93, 2.76)
p value	0.81	0.72	0.69	0.93	0.28	0.089	0.20	0.043	0.09
Paternal smoking (1st year)	0.74 (0.53, 1.04)	0.74 (0.45, 1.21)	0.98 (0.29, 3.27)	NA	NA	NA	1.00 (0.83, 1.20)	1.15 (0.88, 1.51)	1.50 (0.86,2.64)
p value	0.08	0.23	0.97				0.99	0.31	0.16
Paternal history asthma	1.06 (0.67, 1.68)	2.02 (1.14, 3.59)	0.63 (0.08, 4.98)	1.34 (0.8, 2.24)	1.71 (0.86, 3.43)	2.21 (0.71, 6.9)	0.87 (0.70, 1.08)	1.08 (0.78, 1.49)	1.01 (0.49, 2.09)
p value	0.81	0.017	0.66	0.27	0.13	0.17	0.22	0.64	0.99
Maternal history asthma	1.09 (0.75, 1.59)	1.11 (0.65, 1.92)	0.76 (0.17, 3.51)	0.93 (0.56, 1.54)	1.51 (0.78, 2.93)	1.27 (0.36, 4.45)	0.90 (0.74, 1.10)	1.14 (0.86, 1.53)	1.88 (1.07, 3.30)
p value	0.64	0.70	0.73	0.77	0.22	0.71	0.29	0.37	0.027
Cat ownership (pregnancy or year 1)	1.02 (0.7, 1.47)	0.81 (0.45, 1.45)	0.31 (0.04, 2.45)	0.92 (0.67, 1.27)	1.3 (0.82, 2.06)	2.38 (1.04, 5.48)	0.97 (0.85, 1.10)	1.05 (0.86, 1.28)	1.45 (0.93, 2.27)
p value	0.93	0.48	0.27	0.61	0.27	0.041	0.63	0.65	0.10
Dog ownership (pregnancy)	1.17 (0.76, 1.79)	1.66 (0.93, 2.94)	0.52 (0.07, 4.12)	0.74 (0.53, 1.03)	0.54 (0.31, 0.92)	0.54 (0.20, 1.49)	0.95 (0.83, 1.08)	1.02 (0.83, 1.24)	0.92 (0.58, 1.46)
p value	0.47	0.085	0.54	0.071	0.024	0.24	0.43	0.88	0.72

Table S6 continue

	Relative Risk Ratio (95%CI)								
	MAAS (Average n=379; 47.3%)			**IOW (Average n=368; 45.5%)**			**ALSPAC (Average n=1816; 38.1%)**		
	Above average (n=309; 38.6%)	**Below average (n=100; 12.5%)**	**Persistently low (n=13; 1.6%)**	**Above average (n=320; 39.6%)**	**Below average (n=97; 12.0%)**	**Persistently low (n=24; 3.0%)**	**Above average (n=2355; 49.4%)**	**Below average (n=516; 10.8%)**	**Persistently low (n=80; 1.7%)**
BMI (kg/m2, age 5)	0.96 (0.87, 1.07)	1.23 (1.09, 1.4)	0.99 (0.68, 1.44)	0.91 (0.81, 1.03)	1.03 (0.87, 1.23)	1.07 (0.79, 1.44)	NA	NA	NA
p value	0.47	0.001	0.95	0.13	0.71	0.66			
BMI (kg/m2, age 7-8)	0.95 (0.89, 1.02)	1.09 (1.01, 1.19)	1.02 (0.81, 1.28)	0.96 (0.91, 1.01)	1.02 (0.94, 1.09)	0.96 (0.83, 1.12)	0.92 (0.89, 0.95)	1.02 (0.98, 1.07)	1.08 (0.98, 1.19)
p value	0.03	0.16	0.89	0.14	0.68	0.60	1.11E-06	0.32	0.11

***Table S7**. Early-life characteristics of FEV_1/FVC trajectories: multinomial logistic regression analysis weighted by class membership probabilities; reference class is Average*

	Unadjusted Relative Risk Ratio (95%CI)								
	MAAS (Average n=379; 47.3%)			IOW (Average n=368; 45.5%)			ALSPAC (Average n=1816; 38.1%)		
	Above average (n=309; 38.6%)	Below average (n=100; 12.5%)	Persistently low (n=13 1.6%)	Above average (n=320; 39.6%)	Below average (n=97; 12.0%)	Persistently low (n=24; 3.0%)	Above average (n=2355; 49.4%)	Below average (n=516; 10.8%)	Persistently low (n=80; 1.7%)
WHEEZE AND ASTHMA									
Current wheeze (Age 4-5)	0.84 (0.57, 1.24)	2.61 (1.62, 4.21)	3.88 (1.22, 12.37)	0.97 (0.61, 1.54)	2.89 (1.66, 5.05)	3.6 (1.49, 8.72)	0.78 (0.64, 0.95)	2.04 (1.59, 2.61)	3.26 (2.01, 5.30)
p value	0.373	0	0.022	0.902	<0.001	0.005	0.013	p<0.001	p<0.001
Current wheeze (Age 7-8)*	0.74 (0.48, 1.15)	3.57 (2.19, 5.8)	2.26 (0.67, 7.56)	0.7 (0.47, 1.05)	2.61 (1.6, 4.24)	2.97 (1.27, 6.96)	0.63 (0.51, 0.78)	1.81 (1.41, 2.34)	3.95 (2.41, 6.47)
p value	0.182	<0.001	0.187	0.088	<0.001	0.012	p<0.001	p<0.001	p<0.001
Current Asthma (Age 4-5)	0.64 (0.42, 0.95)	2.36 (1.46, 3.81)	3.76 (1.18, 11.97)	0.82 (0.53, 1.3)	2.76 (1.61, 4.73)	3.31 (1.37, 7.98)	NA	NA	NA
p value	0.029	<0.001	0.025	0.403	<0.001	0.008	NA	NA	NA
Current Asthma (Age 7-8)*	0.75 (0.48, 1.15)	2.72 (1.65, 4.5)	3.25 (1.03, 10.26)	0.68 (0.45, 1.03)	2.64 (1.62, 4.3)	2.71 (1.13, 6.51)	0.71 (0.57, 0.87)	1.92 (1.47, 2.50)	3.62 (2.14, 6.11)
p value	0.187	0	0.045	0.068	<0.001	0.026	0.001	p<0.001	p<0.001
LRTI hospitalisation y age 3	0.48 (0.29, 0.8)	1.97 (1.11, 3.47)	3.41 (1.07, 10.82)	NA	NA	NA	NA	NA	NA
p value	0.005	0.02	0.037	NA	NA	NA	NA	NA	NA
Asthma/wheeze hospitalisation by age 3	0.42 (0.18, 0.96)	3.47 (1.73, 6.97)	4.36 (1.12, 17.01)	NA	NA	NA	NA	NA	NA
p value	0.039	<0.001	0.034	NA	NA	NA	NA	NA	NA
Ever RSV positive	0.8 (0.28, 2.26)	3.41 (1.23, 9.44)	6.73 (1.3, 34.88)	NA	NA	NA	NA	NA	NA
p value	0.668	0.018	0.023	NA	NA	NA	NA	NA	NA

Table S7 continue

	MAAS (Average n=379; 47.3%)			IOW (Average n=368; 45.5%)			ALSPAC (Average n=1816; 38.1%)		
	Above average (n=309; 38.6%)	**Below average (n=100; 12.5%)**	**Persistently low (n=13 1.6%)**	**Above average (n=320; 39.6%)**	**Below average (n=97; 12.0%)**	**Persistently low (n=24; 3.0%)**	**Above average (n=2355; 49.4%)**	**Below average (n=516; 10.8%)**	**Persistently low (n=80; 1.7%)**
ALLERGIC SENSITIZATION									
Sensitisation (SPT) (Age 4-5)	0.61 (0.42, 0.87)	1.23 (1.09, 1.4)	0.99 (0.68, 1.44)	0.75 (0.47, 1.2)	1.97 (1.11, 3.5)	3.84 (1.44, 10.21)	NA	NA	NA
p value	0.007	0.001	0.946	0.235	0.02	0.007	NA	NA	NA
Sensitisation (SPT) (Age 7-8)	0.6 (0.43, 0.84)	1.09 (1.01, 1.19)	1.02 (0.81, 1.28)	0.87 (0.61, 1.25)	1.72 (1.06, 2.79)	1.8 (0.76, 4.31)	0.93 (0.78, 1.10)	1.49 (1.17, 1.90)	2.41 (1.44, 4.03)
p value	0.003	0.055	0.082	0.46	0.027	0.184	0.39	1.18E-03	7.64E-04

* Year 10 for IOW; RSV Respiratory syncytial virus; SPT Skin Prick Test

Table S8. *Comparison of FEV_1/FVC trajectories and spell-based partition-around-medoids (PAM)phenotypes [23] (N and column %) using most likely class assignment*

WHEEZE PHENOTYPES-PAM joint	Peristently High	Average	Below Average	Peristently Low	Total	Peristently High	Average	Below Average	Peristently Low	Total
			MAAS					IOW		
Never wheeze	180	185	30	2	397	198	195	33	6	432
	58.3	48.8	30	15.4	49.6	61.9	53	34	25	53.4
Early-transient wheeze	73	94	20	4	191	45	50	15	3	113
	23.6	24.8	20	30.8	23.9	14.1	13.6	15.5	12.5	14
Intermittent wheeze	22	32	15	2	71	16	22	5	3	46
	7.1	8.4	15	15.4	8.9	5	6	5.2	12.5	5.7
Late onset wheeze	15	24	10	0	49	40	75	21	5	141
	4.9	6.3	10	0	6.1	12.5	20.4	21.7	20.8	17.4
Persistent wheeze	19	44	25	5	93	21	26	23	7	77
	6.2	11.6	25	38.5	11.6	6.6	7.1	23.7	29.2	9.5
Total	309	379	100	13	801	320	368	97	24	809
	100	100	100	100	100	100	100	100	100	100
Chi-square test p<0.001						Chi-square test p<0.001				

Table S8 continue

WHEEZE PHENOTYPES-PAM joint	Peristently High	Average	Below Average	Peristently Low	Total
			ALSPAC		
Never wheeze	370 23.52	310 25.9	96 26.82	16 27.59	792 24.86
Early-transient wheeze	72 4.58	75 6.27	41 11.45	9 15.52	197 6.18
Intermittent wheeze	78 4.96	71 5.93	25 6.98	7 12.07	181 5.68
Late onset wheeze	971 61.73	646 53.97	138 38.55	11 18.97	1766 55.43
Persistent wheeze	82 5.21	95 7.94	58 16.2	15 25.86	250 7.85
Total	1573 100	1197 100	358 100	58 100	3186 100

Chi-square test p<0.001

Table S9. *Associations between FEV1/FVC trajectories (8 to 24 years) and blood pressure at 20 years in 476-492 individuals in MAAS. Lung function trajectories treated as a) multinomial with Average as the reference class, and b) as continuous: 1. Above average (38.6%); 2. Average (47.3%); 3. Below average (12.5%); and 4. Persistently low (1.6%). Linear regression crude and adjusted analyses weighted by class membership probabilities.*

a) Lung function trajectories included as multinomial predictor with Average as the reference class

	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	Mean difference p-value	95% CI	Mean difference p-value	95% CI
Crude N=492				
Above Average	-2.55 0.034	[-4.89,-0.20]	0.22 0.780	[-1.35,1.80]
Average	0 [ref]		0 [ref]	
Below Average	1.08 0.526	[-2.26,4.42]	0.64 0.574	[-1.60,2.88]
Persistently Low	5.05 0.209	[-2.83,12.94]	2.69 0.317	[-2.59,7.97]
ADJUSTED by gender, BMI at 8 years and maternal smoking N=476				
Above Average	-1.43 0.199	[-3.62,0.75]	0.22 0.788	[-1.39,1.83]
Average	0 [ref]		0 [ref]	
Below Average	-1.54 0.345	[-4.75,1.66]	0.68 0.575	[-1.69,3.04]
Persistently Low	1.05 0.788	[-6.63,8.74]	1.8 0.532	[-3.86,7.47]
Male	10.62 <0.001	[8.55,12.69]	0.06 0.943	[-1.47,1.58]
BMI (age 8)	0.39 0.094	[-0.07,0.84]	0.09 0.613	[-0.25,0.42]
Maternal smoking (recruitment)	0.29 0.874	[-3.24,3.81]	1.25 0.345	[-1.35,3.85]

Table S9 continue

b) Lung function trajectories included as continuous predictor

	Systolic (mmHg)		Diastolic (mmHg)	
	Mean p-value	95% CI	Mean p-value	95% CI
CRUDE N=492				
FEV1/FVC (per-class)	2.05	[0.63,3.47]	0.15	[-0.80,1.11]
	0.005		0.754	
ADJUSTED by gender, BMI at 8 years and maternal smoking N=476				
	0.34	[-1.07,1.74]	0.08	[-0.96,1.11]
FEV1/FVC (per-class)	0.638		0.887	
Male	10.57	[8.50,12.64]	0.14	[-1.38,1.67]
	<0.001		0.853	
BMI (age 8)	0.37	[-0.08,0.83]	0.096	[-0.24,0.43]
	0.107		0.570	
Maternal smoking (recruitment)	0.40	[-3.12,3.92]	1.25	[-1.35,3.84]
	0.824		0.346	

Note: 'per-class increase' is equivalent to 'with decreasing lung function'

Granell R, *et al. Thorax* 2024;0:1–8. doi: 10.1136/thorax-2023-220485

Table S10. *Associations between FEV1/FVC trajectories 8 to 24 years and Cardiovascular Outcomes at 24 years in ALSPAC. Linear regression crude and adjusted analyses weighted by class membership probabilities.*

FEV1/FVC trajectories 8 to 24 years		Left Ventricular mass indexed to height 2.7 (g/m^2.7)	Left atrium diameter indexed to height (cm/m)	Left Ventricle Posterior Wall Diastolic Thickness Average (cm)	Left Ventricle Posterior Wall Systolic Thickness Average (cm)	Relative Wall Thickness†
	N (%)			Mean Difference (95%CI) p-value		
	CRUDE N=1,660					
Above Average	862 (52.0)	-1.413 (-2.103, -0.724) <0.001	-3.113 (-4.662, -1.564) <0.001	-0.029 (-0.043, -0.016) <0.001	-0.031 (-0.049, -0.012) 0.001	-0.006 (-0.012, 0.001) 0.09
Average	595 (35.8)	0 [ref]	0 [ref]	0 [ref]	0 [ref]	0 [ref]
Below Average	182 (11.0)	0.486 (-0.609, 1.582) 0.384	2.393 (-0.068, 4.855) 0.057	0.017 (-0.004, 0.038) 0.118	0.037 (0.008, 0.066) 0.014	0.001 (-0.009, 0.011) 0.81
Persistent Low	22 (1.3)	1.891 (-0.904, 4.686) 0.185	5.659 (-0.619, 11.937) 0.077	0.027 (-0.028, 0.081) 0.341	0.060 (-0.014, 0.134) 0.11	-0.005 (-0.030, 0.021) 0.71
	ADJUSTED by gender, maternal lower education level* and child's BMI at 7 years N=1,460					
Above Average	753 (51.6)	-0.791 (-1.491, -0.091) 0.027	-1.475 (-2.971, 0.020) 0.053	-0.014 (-0.028, -0.001) 0.039	-0.010 (-0.028, 0.009) 0.296	-0.002 (-0.009, 0.004) 0.47
Average	522 (35.7)	0 [ref]	0 [ref]	0 [ref]	0 [ref]	0 [ref]
Below Average	166 (11.4)	0.254 (-0.836, 1.344) 0.648	1.094 (-1.236, 3.423) 0.357	0.009 (-0.012, 0.030) 0.409	0.023 (-0.005, 0.051) 0.113	0.002 (-0.009, 0.012) 0.78
Persistent Low	20 (1.4)	0.692 (-2.088, 3.473) 0.625	1.334 (-4.606, 7.273) 0.66	-0.003 (-0.057, 0.050) 0.901	0.022 (-0.049, 0.094) 0.536	-0.006 (-0.033, 0.021) 0.65

Table S10 continue

FEV1/FVC trajectories 8 to 24 years		Pulse presure (mmHg)		Right carotid intima-media thickness-Mean (mm)	Left carotid intima-media thickness-Mean (mm)	Average carotid intima-media thickness-Mean (mm)
	N (%)	Mean Difference (95% CI) p-value	N (%)		Mean Difference (95% CI) p-value	
	CRUDE N=3,201		**CRUDE N=1,710**			**CRUDE N=1,651**
Persistent High	1591 (49.7)	-1.086 (-1.759, -0.413) 0.002	863 (50.5)	-0.005 (-0.011, 0.001) 0.079	-0.003 (-0.009, 0.003) 0.275	-0.004 (-0.009, 0.001) 0.112
Average	1191 (37.2)	0 [ref]	634 (37.0)	0 [ref]	0 [ref]	0 [ref]
Below Average	374 (11.7)	1.225 (0.184, 2.267) 0.021	190 (11.1)	0.006 (-0.004, 0.016) 0.217	0.006 (-0.003, 0.015) 0.206	0.006 (-0.002, 0.014) 0.126
Persistent Low	47 (1.5)	1.958 (-0.666, 4.581) 0.144	24 (1.4)	0.015 (-0.009, 0.039) 0.213	0.009 (-0.015, 0.033) 0.46	0.015 (-0.006, 0.035) 0.156
	ADJUSTED by gender, maternal lower education level* and child's BMI at 7 years					
	N=2,759		**N=1,502**			**N=1,452**
Persistent High	1364 (49.4)	0.022 (-0.592, 0.636) 0.944	754 (50.1)	-0.003 (-0.009, 0.004) 0.386	-0.002 (-0.008, 0.005) 0.642	-0.002 (-0.007, 0.003) 0.45
Average	1032 (37.4)	0 [ref]	556 (37.0)	0 [ref]	0 [ref]	0 [ref]
Below Average	321 (11.6)	0.219 (-0.728, 1.165) 0.651	172 (11.4)	0.003 (-0.007, 0.013) 0.511	0.003 (-0.006, 0.013) 0.488	0.004 (-0.005, 0.012) 0.398
Persistent Low	43 (1.6)	-0.681 (-2.992, 1.630) 0.563	22 (1.4)	0.012 (-0.013, 0.037) 0.337	-0.003 (-0.028, 0.023) 0.846	0.008 (-0.014, 0.029) 0.491

ǂ 2 × Left Ventricle Posterior Wall Diastolic Thickness Average)/ LV internal diameter diastolic

* Educated to the General Certificate of Education level (school-leaving certificate) or lower.

Table S11. *Associations between FEV1/FVC trajectories 8 to 24 years and Blood Measures at 24 years in ALSPAC. Linear regression crude and adjusted analyses weighted by class membership probabilities.*

FEV1/FVC trajectories 8 to 24 years		Average seated systolic blood pressure (mmHg)	Average seated diastolic blood pressure (mmHg)	Heart rate (bpm)
	N (%)	Mean Difference (95%CI) p-value	Mean Difference (95%CI) p-value	Mean Difference (95%CI) p-value
		Crude N=3,201		
Above Average	1591 (49.7)	-1.812 (-2.666, -0.959) <0.001	-0.726 (-1.320, -0.133) 0.017	0.648 (-0.117, 1.413) 0.097
Average	1191 (37.2)	0 [ref]	0 [ref]	0 [ref]
Below Average	374 (11.7)	1.150 (-0.171, 2.471) 0.088	-0.075 (-0.995, 0.844) 0.872	-0.892 (-2.076, 0.291) 0.14
Persistent Low	47 (1.5)	2.021 (-1.306, 5.348) 0.234	0.063 (-2.252, 2.378) 0.957	-2.142 (-5.123, 0.839) 0.159
ADJUSTED by gender, maternal lower education level* and child's BMI at 7 years N=2,759				
Above Average	1364 (49.4)	-0.283 (-1.088, 0.521) 0.49	-0.305 (-0.943, 0.332) 0.348	0.368 (-0.443, 1.178) 0.374
Average	1032 (37.4)	0 [ref]	0 [ref]	0 [ref]
Below Average	321 (11.6)	-0.025 (-1.264, 1.214) 0.968	-0.244 (-1.226, 0.739) 0.627	-0.525 (-1.773, 0.723) 0.41
Persistent Low	43 (1.6)	-1.276 (-4.302, 1.750) 0.408	-0.595 (-2.994, 1.804) 0.627	-1.869 (-4.918, 1.179) 0.229

* Educated to the General Certificate of Education level (school-leaving certificate) or lower.

Table S12. *Associations between FEV1/FVC trajectories 8 to 24 years and Fasting Lipids at 24 years in ALSPAC. Linear regression crude and adjusted analyses weighted by class membership probabilities.*

FEV1/FVC trajectories 8 to 24 years		Glucose (mmol/L)	C-Reactive Protein (mg/L)	Triglycerides (mmol/L)	High-density lipoprotein (HDL) (mmol/L)	Low-density lipoprotein (LDL) (mmol/L)	Cholesterol (mmol/L)
	N (%)	Mean Difference (95%CI) of log-transformed outcome p-value			Mean Difference (95% CI) p-value		
	Crude N=2,617						
Above Average	1283 (49.0)	-0.007 (-0.016, 0.002)	-0.039 (-0.142, 0.064)	-0.035 (-0.071, 0.000)	0.054 (0.019, 0.089)	-0.028 (-0.091, 0.035)	0.007 (-0.062, 0.076)
		0.129	0.46	0.051	0.003	0.381	0.849
Average	974 (37.2)	0 [ref]	0 [ref]	0 [ref]	0 [ref]	0 [ref]	0 [ref]
Below Average	322 (12.3)	0.004 (-0.009, 0.018)	-0.139 (-0.296, 0.018)	0.021 (-0.032, 0.075)	0.009 (-0.044, 0.062)	-0.024 (-0.119, 0.071)	-0.000 (-0.105, 0.104)
		0.538	0.083	0.436	0.744	0.615	0.995
Persistent Low	40 (1.5)	-0.005 (-0.039, 0.029)	-0.048 (-0.437, 0.341)	0.121 (-0.015, 0.257)	-0.080 (-0.213, 0.053)	0.259 (0.020, 0.499)	0.231 (-0.033, 0.495)
		0.776	0.809	0.081	0.24	0.034	0.087
	ADJUSTED by gender, maternal lower education level* and child's BMI at 7 years N=2,269						
Above Average	1106 (48.7)	0.001 (-0.008, 0.010)	-0.044 (-0.153, 0.064)	-0.013 (-0.050, 0.025)	0.023 (-0.013, 0.059)	-0.011 (-0.079, 0.056)	0.004 (-0.070, 0.079)
		0.822	0.423	0.512	0.212	0.747	0.91
Average	847 (37.3)	0 [ref]	0 [ref]	0 [ref]	0 [ref]	0 [ref]	0 [ref]
Below Average	281 (12.4)	-0.003 (-0.016, 0.010)	-0.117 (-0.281, 0.046)	0.010 (-0.046, 0.067)	0.027 (-0.027, 0.081)	-0.046 (-0.148, 0.055)	-0.010 (-0.122, 0.101)
		0.678	0.159	0.719	0.335	0.369	0.856
Persistent Low	36 (1.6)	-0.016 (-0.048, 0.017)	0.030 (-0.368, 0.428)	0.088 (-0.051, 0.228)	-0.014 (-0.147, 0.120)	0.220 (-0.030, 0.471)	0.242 (-0.034, 0.518)
		0.352	0.883	0.215	0.84	0.085	0.086

* Educated to the General Certificate of Education level (school-leaving certificate) or lower

Table S13. *Associations between FEV_1/FVC trajectories (8 to 24 years) and markers of cardiovascular disease risk at 24 years in ALSPAC stratified by sex.*

		Per-FEV_1/FVC trajectory 8 to 24 years						
MALES ONLY	**N**	**Mean 95% CI**	**P-value**	**Adjusted†**	**P-value**	**N**	**Further Adjusted††**	**P-value**
Cardiovascular Outcomes at 24 years								
Left Ventricular Mass Indexed to Height 2.7 ($g/m^{2.7}$)	563	0.80 (0.08, 1.51)	0.029	0.52 (-0.16,1.20)	0.13	501	0.79 (0.08, 1.50)	0.030
Left Ventricle Posterior Wall Systolic Thickness Average (cm)	553	0.02 (0.00, 0.04)	0.021	0.02 (-0.00,0.04)	0.06	491	0.02 (-0.00, 0.04)	0.08
Carotid Femoral Pulse Wave Velocity (m/s)	662	-0.03 (-0.14, 0.08)	0.57	-0.03 (-0.14,0.08)	0.58	592	-0.02 (-0.14, 0.10)	0.69
Pulse Pressure (mmHg)	1097	-0.05 (-0.71, 0.60)	0.87	-0.08 (-0.73,0.58)	0.82	964	-0.13 (-0.83, 0.57)	0.71
Average Carotid Intima-Media Thickness-Mean (mm)	565	0.00 (-0.00, 0.01)	0.10	0.00 (-0.00, 0.01)	0.14	504	0.01 (-0.00, 0.01)	0.06
Blood Pressure Measures at 24 years								
Systolic (mmHg)	1097	-0.06 (-0.86, 0.74)	0.89	-0.16 (-0.96, 0.64)	0.69	964	-0.26 (-1.10, 0.59)	0.55
Diastolic (mmHg)	1097	-0.01 (-0.62, 0.61)	0.98	-0.09 (-0.70, 0.53)	0.78	964	-0.13 (-0.77, 0.52)	0.71
Fasting Lipids at 24 years								
Triglycerides (mmol/L, log)	964	0.03 (-0.01, 0.06)	0.14	0.03 (-0.01, 0.06)	0.16	855	0.02 (-0.01, 0.06)	0.21
HDL (mmol/L)	964	0.01 (-0.02, 0.04)	0.66	0.00 (-0.02, 0.03)	0.74	855	0.00 (-0.03, 0.03)	0.84

Table S13 continue

	Per-FEV_1/FVC trajectory 8 to 24 years							
FEMALES ONLY	**N**	**Mean 95%CI**	**P-value**	**Adjusted†**	**P-value**	**N**	**Further Adjusted††**	**P-value**
Cardiovascular Outcomes at 24 years								
Left Ventricular Mass Indexed to Height 2.7 ($g/m^{2.7}$)	896	0.83 (0.24, 1.42)	0.006	0.61 (0.03,1.19)	0.038	785	0.59 (-0.02, 1.21)	0.06
Left Ventricle Posterior Wall Systolic Thickness Average (cm)	868	0.02 (0.00, 0.03)	0.043	0.01 (-0.00,0.03)	0.18	760	0.01 (-0.00, 0.03)	0.17
Carotid Femoral Pulse Wave Velocity (m/s)	1039	0.01 (-0.07, 0.10)	0.80	0.01 (-0.08,0.09)	0.91	906	-0.00 (-0.09, 0.09)	0.94
Pulse Pressure (mmHg)	1661	0.16 (-0.30, 0.62)	0.49	0.07 (-0.39,0.53)	0.77	1436	0.20 (-0.30, 0.70)	0.44
Average Carotid Intima-Media Thickness-Mean (mm)	885	0.00 (-0.00, 0.01)	0.35	0.00 (-0.00, 0.01)	0.48	772	0.00 (-0.00, 0.01)	0.39
Blood Pressure Measures at 24 years								
Systolic (mmHg)	1661	0.54 (-0.12, 1.20)	0.11	0.26 (-0.39, 0.91)	0.44	1436	0.46 (-0.26, 1.17)	0.21
Diastolic (mmHg)	1661	0.38 (-0.15, 0.91)	0.16	0.19 (-0.34, 0.71)	0.49	1436	0.26 (-0.32, 0.83)	0.39
Fasting Lipids at 24 years								
Triglycerides (mmol/L, log)	1304	0.01 (-0.02, 0.04)	0.37	0.01 (-0.02, 0.04)	0.64	1127	0.00 (-0.03, 0.04)	0.84
HDL (mmol/L)	1304	-0.02 (-0.06, 0.01)	0.18	-0.02 (-0.05, 0.02)	0.33	1127	-0.02 (-0.06, 0.02)	0.29

† Adjusted by maternal lower education level (educated to the General Certificate of Education level 'school-leaving certificate' or lower) and child's BMI at 7 year. †† Further Adjusted by low birth weight, maternal postnatal smoking and child tobacco smoke exposure at 8 years.

Table S14. *Associations between* ***predicted FEV_1/FVC trajectories*** *(8 to 24 years) and markers of cardiovascular disease risk at 24 years in ALSPAC*

	N	Mean 95%CI per-FEV_1/FVC trajectory 8 to 24 years CRUDE effect	P-value	N	Mean 95%CI **per-predicted** FEV_1/FVC trajectory 8 to 24 years CRUDE effect	P-value
Cardiovascular Outcomes at 24 years						
Left Ventricular Mass Indexed to Height 2.7 ($g/m^{2.7}$)	1460	1.14 (0.68, 1.60)	1.30×10^{-6}	1501	0.90 (0.43, 1.36)	1.5×10^{-4}
Left Ventricle Posterior Wall Systolic Thickness Average (cm)	1422	0.033 (0.020, 0.045)	2.0×10^{-7}	1464	0.02 (0.01, 0.03)	0.004
Carotid Femoral Pulse Wave Velocity (m/s)	1702	0.058 (-0.011, 0.13)	0.10	1746	-0.01 (-0.08, 0.06)	0.70
Pulse Pressure (mmHg)	2759	1.10 (0.65, 1.55)	1.82×10^{-6}	2819	0.02 (-0.44, 0.47)	0.94
Average Carotid Intima-Media Thickness-Mean (mm)	1451	0.005 (0.001, 0.008)	0.008	1487	0.00 (-0.00, 0.01)	0.074
Blood Pressure Measures at 24 years						
Systolic (mmHg)	2759	1.44 (0.87, 2.02)	8.4×10^{-7}	2819	0.18 (-0.40, 0.75)	0.55
Diastolic (mmHg)	2759	0.34 (-0.06, 0.74)	0.09	2819	0.16 (-0.24, 0.56)	0.43
Fasting Lipids at 24 years						
Triglycerides (mmol/L, log)	2269	0.032 (0.009, 0.056)	0.006	2311	0.02 (-0.01, 0.04)	0.16
HDL (mmol/L)	2269	-0.035 (-0.059, -0.012)	0.003	2311	-0.01 (-0.03, 0.01)	0.45

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