Early View

Original research article

Characterization of lung function trajectories and associated early life predictors in an Australian birth cohort study

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Title

Characterization of lung function trajectories and associated early life predictors in an Australian birth cohort study

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Take home message

Early-life risk factors may influence lung function trajectories over time. Nonetheless, identifying children who have a high risk of having low lung function trajectories should be prioritized to prevent deficits in later life.

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Abbreviations:

ATS, American Thoracic Society; BIC, Bayesian information criteria; FEV₁, Forced Expiratory Volume in 1 sec; FVC, Forced Vital Capacity; GBTM, Group-based trajectory modelling; GLI, Global Lung Function Initiative NO₂, Nitrogen dioxide, PM_{2.5}Abs, Pm_{2.5}Absorbance

ABSTRACT

Background: There is growing evidence that lung function in early life predicts later lung function. Adverse events over the lifespan might influence an individual's lung function trajectory, resulting in poor respiratory health. The aim of this study is to identify early-life risk factors and their impact on lung function trajectories to prevent long term lung impairments.

Methods: Our study included participants from the Raine Study – a prospective pregnancy cohort -with at least two spirometry measurements. Lung function trajectories from the six to 22- year follow-ups were characterized using finite mixture modelling. Multinomial logistic regression analyses were used to evaluate the association between early-life predictors and lung function trajectories.

Main results: A total of 1512 participants (768 males, 744 females), representing 53% of the whole cohort, were included in this analysis. Four lung function trajectories of FEV₁, FVC and FEV₁/FVC (z-scores) were identified. FEV₁ and FVC trajectories were categorized as: “very low”, “low”, “average”, and “above average”, respectively. Based on their shape, lung function trajectories of FEV₁/FVC were categorized as “very low”, “low-average”, “average-low”, and “average”. Asthma and maternal smoke were identified as risk factors for low lung function trajectories in this cohort, as well as early-life exposure to PM_{2.5}Absorbance.

Conclusions: Early-life risk factors may influence lung function trajectories over time. Nonetheless, identifying children who have a high risk of having low lung function trajectories should be prioritized to prevent deficits in later life.

Abstract word count: 233

Keywords: lung function trajectories, early-life, risk factors, spirometry, longitudinal studies.

Introduction

Chronic respiratory diseases are a leading cause of mortality worldwide, accounting for more than 10% of all the disability adjusted-life-years (DALYs) [1]. In the traditional lung growth model, lung development starts *in utero* and attains maximal lung function into early adulthood. This phase is followed by a slow decline with age [2]. An accumulating body of evidence suggest that chronic respiratory diseases have their roots in fetal and early postnatal life. The insults occurring during these vulnerable periods may have long-term consequences, influencing individual lung function over time [3-5].

Several population-based studies have explored the hypothesis that lung function varies over time along predictable trajectories [6-11]. For instance, Bui et al. [8] identified six lung function trajectories of FEV₁ (z-score) from seven to 53 years of age using the Tasmanian Longitudinal Health Study (TAHS). In the Manchester Asthma Study and Allergy Study (MAAS) and the Avon Longitudinal Study of Parents and Children (ALSPAC), Belgrave and colleagues identified three lung function trajectories in 1,051 individuals using specific airway resistance measurements from three to 11 years of age [6] and four lung function trajectories for FEV₁ using two population-

based birth cohorts [12] Two lung function trajectories of percent of maximal predicted FEV₁ were found using data from the Tucson Children's Respiratory Study [7]. In the CAMP Study, individuals with asthma were followed during young adulthood, and they identified four trajectories of prebronchodilator FEV₁ percent predicted values within the group [13]. Early-life factors that may diminish maximally attainable lung function included respiratory infections, preterm birth, allergies, childhood asthma, *in utero* smoke and environmental exposure [2]. Together with FEV₁, forced vital capacity (FVC) and their ratio (FEV₁/FVC) provide information on general respiratory health. There is the need to investigate lung function over the lifespan further and identify groups at higher risk of lung disease and modifiable exposures.

Identifying the complex multifactorial determinants of abnormal lung function requires longitudinal data with a long follow-up over periods of lung growth. Our aim was to characterize lung function trajectories of FEV₁, FVC and (FEV₁/FVC) over a 16-year period from childhood to young adulthood, and to investigate early-life factors associated with these trajectories. We hypothesized that early life risk factors would be associated with low lung function trajectories in our cohort.

Methods

Study population

The Raine Study is a large prospective cohort of 2900 pregnant women recruited from King Edward Memorial Hospital in Perth, Western Australia between 1989 and 1991 [14]. Clinical and demographic data were collected during pregnancy and offspring assessed before birth and at 1, 2, 3, 5, 8, 10, 14, 17, 18, 20, 22, 27 and 28 years of age Detailed population recruitment information is presented elsewhere [15]. Children who had attended at least two or three visits with spirometry measurements within the six-, 14- or 22- year follow-ups were included (Supplementary Figure 1). At each year of follow up, participants completed a respiratory questionnaire adapted from the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire for school children [16]. This study was approved by the University of Western Australia Human Research Ethics approval committee (RA/4/1/2100). Each Raine follow-up used in this study received separate research ethics approval.

Outcome variables

Lung function was assessed at six, 14, and 22 years of age by spirometry according to the American Thoracic Society guidelines in place at each time point [17,18]. FEV₁ and FVC were measured from three forced expiratory curves with an acceptable start and end of test. The largest FEV₁ and the largest FVC were recorded after examining the data from all acceptable curves. FEV₁/FVC was calculated as the ratio of forced expiratory volume in the first one-second to the forced vital capacity. Reference values were derived from the Global Lung Function Initiative (GLI) reference equations [19] that has been validated in an Australasian population [20]. We calculated the z-scores for FEV₁, FVC, and FEV₁/FVC in participants that successfully completed and had acceptable and repeatable spirometry measurements, using the GLI Tool Software developed by the GLI Task Force Group (ERS).

Covariates

Asthma

Current asthma was defined if the children a) had wheezed in the past 12 months; b) “The child had taken asthma medications in the past 12 months” and c) “The child had received a doctor-diagnosis of asthma ever?”.

Atopy

Atopy was defined as positive at age six if the participants produced specific immunoglobulins (IgE) antibodies level >0.35 ug/mL in response to exposure to any of the following allergens: peanuts or food mix (food allergy); rye grass pollen, house dust mite, mould or cat fur (aeroallergens).

Wheeze, Eczema and Hay fever

Wheeze was defined as a positive response to “Has your child wheezed in the last 12 months?”. Eczema was defined as a positive response to “Child has eczema?” and a self-reported doctor diagnosis ever. Hay fever was defined as a positive response to “Child has hay fever?” and a self-reported doctor diagnosis.

Respiratory tract infections

Lower and upper respiratory tract infections during the first year of life were defined based on parental report through questionnaire. We defined the diseases using International Classification of Disease (ICD)-9 codes. Specifically, low respiratory tract infections were defined if the child had pneumonia, bronchitis, or tuberculosis, while upper respiratory tract infections were defined if the child had acute upper respiratory infections or chronic or allergic rhinitis.

Early life exposure to air pollution

Geocodes of residential addresses were used to assign individual early-life air pollution exposures for all the participants. The address history was received from parents at each year of follow-up. Annual mean concentrations for nitrogen dioxide (NO₂) (µg/mg) and PM_{2.5}Absorbance (proxy for elemental carbon) (10⁻⁵m⁻¹) were assigned for each participant's individual geocoded current residential history. Exposure estimates were derived from Land Use Regression (LUR) models previously developed and validated for the Perth metropolitan area [21,22]. The estimates were extrapolated to the years of follow-up using air monitoring data obtained from the WA Department of Water and Environmental Regulation.

Familial characteristics

Maternal smoke was defined as: *In utero* smoking if the mother had smoked only during pregnancy; Smoking at age six if the mother smoked in the six years of follow up, but not in pregnancy; Smoking from pregnancy to age six if the mother smoked during pregnancy and was still smoking at the six-year follow-up. Preterm birth was defined as birth before 37 weeks of gestation. Socio-economic status (SES) when children were six was defined based on family income/year during pregnancy expressed in Australian dollars (\$AUD): a) less than 16000 b) between 16000 and 40000 c) more than 40000. Demographic variables were retrieved from the questionnaire completed by the parents when children were aged between three and five years. Parental asthma, eczema, wheeze, hay fever, smoking and maternal education were defined by parental self-report.

Statistical analysis

Lung function trajectories

Trajectories for FEV₁, FVC and FEV₁/FVC (z-scores) were modeled using group-based trajectory modelling, using “traj” plugin (STATA, version 16.0; StataCorp, College Station, TX) [23]. Sensitivity analyses were performed to assess the robustness of results to various assumptions regarding lung function trajectories membership. Traj analyzes longitudinal data using maximum likelihood estimation that account for missing data. Given the nature of FEV₁ and FVC values (z-scores), a censored normal model was fitted. Within the “traj” plugin, the optimal number and shape of lung function trajectories were determined based on the smallest absolute Bayesian Information Criterion (BIC) value and average posterior probabilities. An average posterior probability of >0.7 was considered as an indicator of good model fit [24]. We first started with a model consisting of one group with the highest polynomial order (cubic), the number of groups was then increased until the number that best fitted the data was identified [25]. Once the number of trajectories was identified, we reduced the polynomial orders until the highest order polynomial for each group was significant at the confidence level $\alpha(x)=0.05$. Participants were assigned to one of the groups based on their highest estimated group membership probabilities resulting in a distribution over classes. Trajectories for FEV₁, FVC and FEV₁/FVC were modelled separately.

Early-life predictors

The distribution of participants' characteristics by lung function trajectories were summarized using percentages, and Pearson's chi-squared tests were used to estimate differences between groups. We assessed the association of lung function trajectories with potential early-risk factors by multinomial logistic regression. Alpha was set at $p<0.05$.

Results

Participants with spirometry measurements at two or three time points were included for trajectory analysis (n=1512). The flow chart of participants in this study and their characteristics are shown in Figure 1 and Table 1. There was a higher proportion of childhood asthma or allergies in males, while low childbirth weight, wheezing and eczema in young adulthood were more prevalent in

females. Compared with those included, excluded participants had lower socio-economic status when they were six, fewer respiratory tract infections in the first year of life, less childhood and parental hay-fever, asthma, atopy, and more of them were born preterm or exposed to parental smoke (Supplementary Table 2).

Lung function trajectories

We identified four distinct lung function trajectories of FEV₁, FVC and FEV₁/FVC (Figures 2,3,4) that best fitted our data (Supplementary Table 3). FEV₁ and FVC trajectories were labelled respectively: “very low” (n= 51, 3.37% for FEV₁; n=61, 4.03% for FVC), “low” (n=746, 49.34% for FEV₁; n=855, 56.55% for FVC), “average” (n=611, 40.41% for FEV₁; n=457, 30.22% for FVC) and “above average” (n=104, 6.88% for FEV₁; n=139, 9.19% for FVC). Based on their shape, lung function trajectories of FEV₁/FVC were labelled as “very low” (n=131, 8.66%), “low-average” (n=198, 13.10%), “average” (n=654, 43.24%) “average-low (n=529, 34.99%)”. Most participants were in the low FEV₁ (49.3%) and FVC (56.5%) trajectories, and in the average trajectories of FEV₁/FVC (43.3%) (Supplementary Table 4).

Early-life predictors and lung function trajectories

The distribution of participants’ characteristics by lung function trajectories are shown in Supplementary Table 6. Adjusted associations between childhood, parental and environmental factors and lung function trajectories compared with the average trajectory (reference group) show that participants in the low trajectory of FEV₁ and in the very low and low-average trajectory of FVC were more likely to have childhood asthma when compared with the reference group (Table 3). Being in the average- low trajectory of FEV₁/FVC was associated to less likely have respiratory allergies alone or combined with food allergy during childhood. Participants in the very low trajectory of FEV₁/FVC were 2.47 times more likely to be exposed to both pre- and post-natal maternal smoke. . With respect to the average trajectory, being in the low trajectory of FEV₁ was associated with a higher risk of being exposed to PM_{2.5}Absorbance in early life, while being in the average-low trajectory of FEV₁/FVC was associated with a lower risk of being exposed to PM_{2.5}Absorbance and NO₂.

Discussion

Using data collected prospectively from the Raine Study, we characterized lung function trajectories from six to 22 years and identified four trajectories for FEV₁, FVC and FEV₁/FVC, respectively. Childhood asthma and maternal smoke were identified as risk factors for low lung function trajectories, as well as early-life exposure to air pollutants. To the best of our knowledge, this is the first study to characterize lung function trajectories for FEV₁, FVC and FEV₁/FVC in z-scores in the same cohort and consider the impact of early-life predictors.

At present, studies investigating lung function trajectories report a variety of outcomes, with FEV₁ being the most common [8, 12, 13]. Only one study explored FEV₁, FVC, and FEV₁/FVC trajectories from 10 to 26 years, separately for males and females [9], but this study reported raw values not adjusted for age. Similar to our study, trajectories of FEV₁/FVC showed a stable decline from puberty to young adulthood although the authors did not cover the early childhood period. The Tasmanian Longitudinal Health Study cohort however found six trajectories of FEV₁, of which two- the early below average, accelerated decline and early low, accelerate growth, normal decline- were newly identified compared with previous studies. This may be because the age of participants extended to middle age and were older than those in our cohort, thus, we did not detect lung function decline with age in early adulthood. These results together suggest that the number of trajectories highly differ according to the study population and the statistical method used to identify trajectories.

The results of our study confirmed our *a priori* hypothesis that poor lung function trajectories are associated with early-life factors. In our cohort, participants with asthma were more likely to belong to the low lung function trajectories. In our cohort, children at 6-years of age had lower GLI z-scores for FEV₁ and FVC. Nonetheless, the results continue to show that lung function tracks throughout time. Specifically, having asthma was associated with almost twofold risk of having a low lung function trajectory compared to an average trajectory for FEV₁. A similarly risk is associated with the very-low and low-average trajectories of FEV₁/FVC. This suggests that participants in the lowest trajectories have an increased risk of asthma diagnosis in childhood.

Compared with the average trajectory, participants in the very low trajectory of FEV₁/FVC were threefold as likely to be exposed to maternal smoking during gestation or up to the age of six. The association was not seen if mothers only smoked in pregnancy or when the child was six years old. Although there was a lack of association with FEV₁ it is likely that maternal smoking increases airway obstruction risk, as defined by a low FEV₁/FVC trajectory. Previously reported associations between maternal smoke and low lung function trajectories support our findings [8,26], except for the Isle of Wight birth cohort, where exposure to *in utero* smoke was not a risk factor for low lung function trajectories [9].

Our findings suggest that early-life exposure to PM_{2.5}Absorbance was associated with the low FEV₁ trajectory. Inhalation of particles in early life might affect the airway epithelium, worsening the children's lung function and trajectory. These results have not been previously described. Only few studies reported information on the longitudinal effects of childhood exposure [27], despite a wide range of studies demonstrating the link cross-sectional associations between adverse effects of air pollution on lung function in children. Perth is an area with low concentrations of air pollutants. However, Dirgawati et al. [28] reported an association between PM_{2.5}Absorbance and an increased risk of all-cause mortality, hypothesizing that concentrations lower than those recommended by the World Health Organization might affect respiratory health. It is possible that PM_{2.5}Absorbance, defined as a surrogate for black carbon, may act on the respiratory system leading to early alterations in airway size or impaired gas exchange and lung function. Children are particularly vulnerable to the effects of air pollution, as respiratory airways development occurs during *in utero* and continues until six to eight years of age when the lungs reach full functionality [29]. Cohort participants were born between 1989 and 1990, years in which the air monitoring networks for the Perth area were not initiated. Thus, we defined early-life air pollution exposure at the first available time, when children were aged between three and four years, being unable to include periods in which most of the lung development occur. Previous studies reported adverse association between lung function and early life exposure to NO₂ [30,31,32], while no association was seen in our study. It may be possible that the strongest effects of NO₂ on lungs occur during *intrauterine* life and early postnatal period that were not included in our study.

Our low-average trajectory of FEV_1/FVC was associated with low childbirth weight, while the average-low trajectory of FEV_1/FVC was associated with childhood respiratory allergies alone or combined with food allergies. According to other studies [33,34], our results suggest that a food allergy response can lead to clinical symptoms, including airway inflammation that might decrease lung function over time. However, it is still unclear if having food allergies in childhood is an independent risk factor for decreasing lung function despite asthma status. Further, males were more likely to belong to the very low lung function trajectories of FVC. Socio-economic status, respiratory infections, preterm birth, paternal eczema and parental hay fever were not associated with the lung function trajectories of FEV_1 , FVC or FEV_1/FVC . While FEV_1 gives an indication of airway caliber, FVC is indicative of lung capacity. Previous research showed a lack of association between children's respiratory health and socio-economic status [35], while others supported the hypothesis that low education level can be a disadvantage factor for respiratory outcomes in children, such as the diagnosis of asthma [36] with different effects depending on race and ethnicity [37]. Respiratory infections in our study were also recorded based on parental recall which is not ideal in the absence of molecular detection. A potential explanation for the Average-Low trajectory is a limitation of spirometry. Spirometry is reliable and acceptable when performed at pre-school age although children might have difficulty exhaling completely. As such, the forced vital capacity measured at six years in our population sample may be underestimated, potentially leading to an artificially high FEV_1/FVC ratio because they did achieve a full FEV_1 , but a suboptimal FVC. We also observed a Low-Average trajectory in our cohort. The GLI have previously reported that predicted values of FEV_1/FVC fell from three to ten years of age in healthy children, but increased up to 16 years followed by a linear decline into adulthood [38]. Changes in FEV_1/FVC ratio in childhood and adolescence are not completely unexpected since this is a period of lung growth. The participants in this trajectory may have had an adolescent growth spurt prior to 14 years, leading to the observed catch-up growth.

Further limitations of our study are that in our study we had a high dropout rate and respiratory symptoms were more prevalent in included participants. This implies that children under study were more like to attend more visits for lung function testing. Although we investigated many risk factors, inclusion of pregnancy complications or chronic diseases among parents or children were not included in our analysis as there were small numbers and the results would not be meaningful.

Lastly, when we investigated the association between lung function trajectories and early-life exposure to air pollution, we back-extrapolated air pollution data for nineteen years of follow-up. Although LUR models have been shown to be stable over a period of 35 years [39,40], we might overestimate the results as some, but not all, areas in Perth may have undergone re-development or expansion and air pollution level may have varied over time, leading to prediction error from our models. Another limitation is that ideally, we would have liked to back-extrapolate the LUR models to the pregnancy timepoints. However, modelling historic air pollution exposure depends on the availability of monitored concentrations that were not available during the antenatal period and the first three years of life. Nonetheless, our study adds a unique contribution to the literature on long-term pollution at relatively low exposure levels in early life and lung function. The availability of detailed demographics and clinical information of children and their parents available for developmental periods enabled us to establish lung function trajectories over sixteen years from early life to young adulthood. The study is also strengthened by adopting a finite mixture model identifying lung function trajectories that were not based on any *a priori* hypothesis.

In conclusion, we found discrete trajectories in our study population from childhood to young adulthood with low lung function trajectories characterized by asthma, maternal smoke, low birthweight and early-life exposure to air pollution. Our findings reinforce the hypothesis that there are groups in the population that follow similar respiratory paths and that events occurring in the first years of life have a role in influencing lung function trajectories. These may be partly established before six years of age. Special attention should be given to participants belonging to the very low trajectory of FEV₁ who might be potentially at higher risk. This study's practical relevance is the opportunity to identify those children who have a higher risk to be in the low trajectories and, consequently, prevent deficits in later life, allowing individuals to maximize their lung function potential throughout life fully.

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Contributorship statement: FS, REF and GLH conceived and designed the study. DB and JH provided support on the air pollution data gathering, GIS analysis and back-extrapolation analysis. FS performed the statistical analysis. FS, REF and GLH interpreted the results. FS drafted the first draft of the manuscript. All the authors contributed to the interpretation of the results and critically reviewed and approved the final version of the manuscript.

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TABLES

Table 1. Childhood and parenthood characteristics in Raine Study participants with two or more spirometry measurements according to sex.

Participant demographics (n=1512)			
Variable	Male	Female	P-value
Sex, %	768 (50.79)	744 (49.21)	
Socio-economic status* (income in AUD\$)			0.713
≤16.000	67 (9.45)	70 (10.14)	
16000-40000	316 (44.57)	293 (42.46)	
≥40000	326 (45.98)	327 (47.39)	
Maternal education			0.416
Low	145 (18.88)	159 (21.37)	
Medium	217 (28.26)	200 (26.88)	
High	345 (44.92)	338 (45.43)	
Preterm (<37 gestational age),	45 (6.09)	56 (7.94)	0.167
Childbirth weight			<0.001
Low	45 (5.86)	77 (10.35)	
Normal	723 (94.14)	667 (89.65)	
Respiratory infections, %			0.879
URTI only	245 (35.61)	244 (36.31)	
LRTI or both	182 (26.45)	182 (27.08)	
Current asthma at age 6, %	133 (17.32)	99 (13.31)	0.030
Current asthma at age 14, %	78 (10.16)	69 (9.27)	0.563
Current asthma at age 22, %	40 (5.21)	63 (8.47)	0.012
Current wheeze at age 6, %	172 (23.40)	142 (20.03)	0.120
Current wheeze at age 14, %	98 (13.78)	94 (13.49)	0.871
Current wheeze at age 22, %	84 (17.54)	118 (22.96)	0.034
Current eczema at age 6, %	166 (22.90)	174 (24.96)	0.361
Current eczema at age 14, %	127 (17.81)	147 (21.06)	0.123
Current eczema at age 22, %	45 (9.53)	82 (16.43)	<0.001
Current hay fever at age 6, %	51 (6.64)	53 (7.12)	0.711

Current hay fever at age 14, %	156 (21.88)	135 (19.37)	0.244
Current hay fever at age 22, %	73 (15.37)	104 (20.47)	0.037
Atopy at age 6%, %			<0.001
Food Allergy only	17 (2.21)	15 (2.02)	
Aeroallergens only or both	205 (26.69)	127 (17.07)	
Maternal smoking			0.287
Only in pregnancy	31 (4.41)	35 (5.21)	
Only at age 6	52 (7.41)	54 (8.04)	
Both in pregnancy and at age 6	130 (18.49)	147 (21.88)	
Paternal smoking	256 (33.33)	253 (34.01)	0.669
Parental asthma, %			0.268
Mother only	111 (16.82)	104 (16.48)	
Father only	53 (8.03)	71 (11.25)	
Both	18 (2.73)	18 (2.85)	
Parental eczema, %			0.445
Mother only	117 (17.67)	106 (16.80)	
Father only	42 (6.34)	55 (8.72)	
Both	21 (3.17)	19 (3.01)	
Parental hay fever, %			0.481
Mother only	231 (30.08)	210 (28.23)	
Father only	123 (16.02)	116 (15.59)	
Both	97 (12.63)	114 (15.32)	
Parental wheeze, %	313 (43.05)	313 (44.78)	0.512

SES=socio economic status was defined by the family incomes, expressed in Australian dollars (\$AUD), LRTI= low respiratory tract infections in the first year of life, URTI= upper respiratory tract infections in the first year of life. Significance of differences was evaluated by X^2 test.*

Table 2. Association expressed as Risk Relative Ratio between childhood, parental factors, air pollution exposure and FEV₁, FVC and FEV₁/FVC lung function trajectories in Raine participants with two or more spirometry.

	FEV ₁ (n=1512)			FVC (n=1512)			FEV ₁ /FVC (n=1512)		
	RRR (95% CI)-			RRR (95% CI)-			RRR (95% CI)-		
	<i>Average (Reference category) (n=611)</i>			<i>Average (Reference category) (n=457)</i>			<i>Average (Reference category) (n=654)</i>		
Variable	Very low (n=51)	Low (n=746)	Above average (n=104)	Very low (n=61)	Low (n=855)	Above average (n=139)	Very Low (n=131)	Low-average (n=198)	Average-low (n=529)
Females	0.61 (0.34- 1.10)	1.03 (0.84-1.29)	0.88 (0.58- 1.33)	0.67 (0.39- 1.15)	1.04 (0.83- 1.31)	0.88 (0.60-1.29)	0.83 (0.57- 1.22)	1.17 (0.85-1.61)	0.80 (0.63- 1.01)
SES									
16000-40000	2.24 (0.66-7.61)	0.97 (0.65- 1.43)	1.33 (0.60- 2.98)	2.13 (0.62- 7.35)	0.84 (0.54- 1.29)	0.67 (0.35-1.28)	1.05 (0.52- 2.13)	0.60 (0.33-1.07)	0.77 (0.51- 1.18)
≥40000	1.09 (0.66- 7.61)	1.06 (0.72- 1.55)	1.11 (0.50- 2.51)	1.43 (0.41- 5.01)	0.82 (0.53- 1.25)	0.62 (0.33-1.19)	0.91 (0.45- 1.85)	0.95 (0.54-1.67)	0.74 (0.48- 1.21)
Preterm	1.04 (0.31- 3.51)	1.30 (0.84- 2.01)	0.97 (0.30- 2.37)	1.51 (0.60- 3.79)	1.03 (0.38- 1.62)	0.85 (0.38-1.90)	0.94 (0.38- 2.30)	2.03 (1.11-3.71)	1.92 (1.19- 3.08)
Childbirth weight	1.59 (0.80- 3.17)	0.80 (0.59-1.08)	0.63 (0.29- 1.37)	1.66 (0.74- 3.76)	0.95 (0.63- 1.44)	0.67 (0.31-1.48)	0.97 (0.44- 2.13)	1.77 (1.02-3.08)	1.63 (0.90- 2.50)
Respiratory Infections									
URTI only	0.41 (0.18- 3.56)	0.82 (0.64- 1.06)	1.25 (0.76- 2.04)	0.55 (0.28- 1.99)	1.02 (0.78- 1.34)	1.30 (0.84-2.02)	0.82 (0.52- 1.29)	1.07 (0.74-1.56)	0.93 (0.71- 1.22)
LRTI or both	1.49 (0.75- 2.93)	1.06 (0.79- 1.43)	1.30 (0.72- 2.34)	1.02 (0.52- 1.99)	1.08 (0.79- 1.48)	1.04 (0.61-1.77)	0.99 (0.60- 1.63)	1.04 (0.67-1.62)	1.00 (0.73- 1.38)

Asthma at age 6	2.07 (0.90- 4.74)	1.68 (1.20- 2.36)	0.89 (0.42-1.90)	0.97 (0.44- 2.16)	1.02 (0.72- 1.44)	0.93 (0.51-1.67)	3.31 (2.01-5.47)	1.98 (1.21-3.24)	1.57 (1.08-2.28)
Atopy (IgE) at age 6									
Food Allergy (only)	1.20 (1.15- 9.75)	1.16 (0.52- 2.56)	1.20 (0.26- 2.57)	-	1.41 (0.59- 3.41)	1.42 (0.36-6.64)	-	2.35 (0.82-6.77)	1.90 (0.81- 4.46)
Aeroallergens only or both	0.46 (0.17- 1.24)	0.96 (0.72-.1.27)	1.37 (0.81- 2.31)	0.94 (0.46- 2.92)	0.95 (0.59- 3.41)	1.23 (0.76-1.97)	0.74 (0.45- 1.22)	0.77 (0.50-1.19)	0.70 (0.51- 0.95)
Maternal Smoke									
Smoke in pregnancy only	1.07 (0.24- 4.83)	0.72 (0.40- 1.32)	1.75 (0.75- 4.06)	1.38 (0.38- 5.01)	0.69 (0.37- 1.30)	1.57 (0.70-3.56)	2.22 (0.90- 5.50)	1.25 (0.51-3.02)	1.38 (0.74- 2.58)
Smoke at 6 only	0.34 (0.04-2.70)	1.07 (0.70- 1.62)	0.35 (0.11- 1.18)	1.61 (0.57- 4.56)	1.42 (0.88- 2.31)	0.45 (0.15-1.33)	1.05 (0.47- 2.34)	0.92 (0.47-1.79)	0.90 (0.56- 1.43)
Both	1.40 (0.66- 2.96)	1.12 (0.83- 1.51)	0.57 (0.29- 1.13)	1.23 (0.61- 2.47)	0.73 (0.53- 1.14)	0.69 (0.37-1.30)	2.47 (1.52- 2.50)	1.35 (0.85-2.14)	0.77 (0.55-1.09)
Parental Asthma									
Mother Asthma only	1.29 (0.52- 3.20)	1.02 (0.70- 1.49)	0.67 (0.31- 1.47)	1.94 (0.79- 4.80)	0.91 (0.60- 1.35)	0.62 (0.32-1.21)	0.92 (0.48- 1.75)	0.88 (0.49-1.57)	0.74 (0.50- 1.10)
Father Asthma only	1.04 (0.31- 3.47)	1.14 (0.73- 1.80)	0.34 (0.10- 1.19)	1.99 (0.67- 5.91)	1.13 (0.69- 1.84)	0.61 (0.25-1.45)	0.99 (0.46- 2.11)	0.84 (0.41-1.71)	1.49 (0.91- 2.45)
Both	-	1.82 (0.80- 4.12)	0.56 (0.07- 4.73)	2.41 (0.43- 3.49)	1.19 (0.50- 2.80)	0.27 (0.03-2.28)	0.99 (0.25- 3.93)	1.27 (0.37-4.35)	1.76 (0.73- 4.26)

Parental Hay fever									
Mother Hay fever	1.06 (0.59-1.92)	0.84 (0.62- 1.13)	1.06 (0.59- 1.92)	0.97 (0.45- 2.07)	0.79 (0.46- 1.37)	1.06 (0.62-1.81)	0.59 (0.34- 1.03)	0.89 (0.57-1.37)	0.96 (0.70- 1.32)
Father Hay fever	0.56 (0.21- 1.49)	0.73 (0.52- 1.02)	1.04 (0.54- 2.03)	0.82 (0.47- 1.43)	0.97 (0.43- 2.23)	1.04 (0.57-1.88)	1.27 (0.72- 2.23)	1.17 (0.71-1.92)	1.26 (0.87- 1.32)
Both	0.49 (0.17- 1.43)	0.72 (0.50- 1.04)	1.38 (0.70- 2.71)	0.82 (0.31- 2.17)	0.76 (0.51- 1.12)	1.60 (0.87-2.95)	0.76 (0.40- 1.45)	0.99 (0.58-1.68)	0.99 (0.67- 1.46)
Parental Eczema									
Mother Eczema only	0.41 (0.12- 1.40)	1.06 (0.78- 1.46)	0.73 (0.37- 1.45)	0.81 (0.46- 1.41)	0.88 (0.40- 1.94)	0.75 (0.54-1.04)	1.35 (0.79- 2.31)	0.72 (0.44-1.18)	0.97 (0.69- 1.37)
Father Eczema only	1.59 (0.52- 4.88)	1.47 (0.92- 2.36)	0.98 (0.36- 2.62)	0.71 (0.28- 1.80)	1.66 (0.63- 4.39)	1.10 (0.67-1.80)	2.38 (1.20- 4.72)	0.88 (0.42-1.83)	1.26 (0.76- 2.08)
Both	0.41 (0.12- 1.40)	1.06 (0.78- 1.46)	0.73 (0.37- 1.45)	0.81 (0.46- 1.41)	0.88 (0.40- 1.94)	0.75 (0.54-1.04)	1.35 (0.79- 2.31)	0.72 (0.44-1.18)	0.97 (0.69- 1.37)
PM_{2.5Abs}	0.29 (0.09- 1.06)	1.63 (1.06-2.51)	1.09 (0.57- 2.08)	0.74 (0.29- 1.88)	0.99 (0.54- 1.81)	0.97 (0.65-1.44)	0.62 (0.33- 1.17)	0.58 (0.33- 1.01)	0.52 (0.35- 0.79)
NO₂	0.78 (0.66- 1.10)	0.95 (0.90- 1.01)	1.04 (0.93-1.17)	0.91 (0.79- 1.06)	1.04 (0.94- 1.15)	1.02 (0.95-1.08)	0.96 (0.86- 1.06)	0.94 (0.86-1.02)	0.90 (0.84- 0.96)

*Note. *Relative Risk Ratios (95% confidence intervals) and significance differences from the average trajectory were derived from a multinomial logistic regression. **Bold values indicate a significant association at $\alpha = 0.05$. ***For asthma, model was adjusted for maternal smoking, parental asthma, sex and socio-economic status. For atopy, model was adjusted for childhood asthma, parental asthma, parental hayfever, parental wheezing, sex and socio-economic status. For respiratory tract infections, model was adjusted for maternal smoking, sex and socio-economic status. For maternal smoke, model was adjusted for childhood asthma, maternal asthma, and socio-economic status. For parental asthma, model was adjusted for parental hay fever, parental eczema, parental wheezing, sex and socio-economic status. For parental hayfever, model was adjusted for parental asthma, parental wheezing, sex and socio-economic status. For parental eczema, model was adjusted for parental asthma, parental hayfever, sex, and socio-economic status. For PM_{2.5Abs} and NO₂, model was adjusted for childhood asthma,*

*childhood hayfever, parental eczema, parental wheezing, sex and socio-economic status. ****SES=socio economic status, LRTI= low respiratory tract infections in the first year of life, URTI= upper respiratory tract infections in the first year of life. *****The average trajectory of FEV₁, FEV₁/FVC and FVC were used as reference category. *****-: Low number of participants in the category*

FIGURE CAPTIONS

Figure 1. Flow chart of participants in this study from the Raine Study

The Raine Study participants attending at least two visit that included the spirometry measurement within the 6, 14 or 22 years of follow-up were included in this study (n=1512)

Figure 2. Lung function trajectories (FEV₁) from six to 22 years of follow up in the Raine participants with two or more spirometry measurements

N. of subjects contributing data= 1512. The dashed lines represent the 95% confidence intervals.

Figure 3. Lung function trajectories (FVC) from six to 22 years of follow up in the Raine participants two one or more spirometry measurements

N. of subjects contributing data= 1512. The dashed lines represent the 95% confidence intervals.

Figure 4. Lung function trajectories (FEV₁/FVC) from six to 22 years of follow up in the Raine participants two or more spirometry measurements

N. of subjects contributing data= 1512. The dashed lines represent the 95% confidence intervals.

FIGURES

Figure 1. Flow chart of participants in this study from the Raine Study

Figure 2. Lung function trajectories (FEV₁) from six to 22 years of follow up in the Raine participants with two or more spirometry measurements

Note The 95% confidence intervals are represented by dashed lines*

Figure 3. Lung function trajectories (FVC) from six to 22 years of follow up in the Raine participants two one or more spirometry measurements

Note The 95% confidence intervals are represented by dashed lines*

Figure 4. Lung function trajectories (FEV₁/FVC) from six to 22 years of follow up in the Raine participants two or more spirometry measurements

Note The 95% confidence intervals are represented by dashed lines*

SUPPLEMENTARY

Title

Characterization of lung function trajectories and associated early life predictors in
in an Australian birth cohort study

Authors

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Appendix S1. Additional methods and results

Statistical analysis

Early life predictors

Associations between early life predictors and lung function trajectories were first evaluated by unadjusted multinomial linear and logistic regression. Childhood, parental and environmental predictors associated with lung function trajectories with $p < 0.1$ were retained for entry into full models. The final models were carried out separately for FEV₁, FVC and FEV₁/FVC z-scores, and were adjusted for sex, socio-economic status, preterm birth, childhood asthma, childhood respiratory infections, childhood atopy, maternal smoking, parental asthma, parental hay fever, parental eczema, and early life exposure to NO₂ and PM_{2.5}Absorbance.

Results of air pollution exposure in participants

Descriptive summary statistics for early-life exposure to PM_{2.5}Absorbance and NO₂ in the participants are shown in Supplementary Table 1.

Results of Lung function trajectories

We also assessed the overlap of participants in both FEV₁ and FVC lung function trajectories where participants in the lowest trajectories of FEV₁ were not necessary in the lowest trajectories of FVC (Supplementary Table 5).

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Supplementary Table 1 A, B. Descriptive summary of PM_{2.5}Absorbance and NO₂ during early-life in the Raine participants

	Mean	Std Dev	Min	Max
Pm_{2.5} Absorbance (10 ⁻⁵ m ⁻¹)	0.94	± 0.37	0.02	2.99
NO₂ (µg/m ³)	5.15	± 2.08	0.06	12.19

Supplementary Table 2. Childhood and parenthood characteristics in included and excluded Raine Study participants

Participant demographics			
Variable	Included (n=1512)	Excluded (n=1356)	P- value
Female sex, %	744 (49.21)	670 (49.41)	0.913
Missing values	0 (0.0)	0 (0.0)	
Ethnic origin, %			0.797
Caucasian	1321 (87.37)	533 (39.31)	
Other	116 (7.67)	49 (3.61)	
Missing values	75 (4.96)	774 (57.08)	
Socio-economic status, %**			<0.001
≤16.000	137 (9.06)	95 (7.01)	
16000-40000	609 (40.28)	359 (26.47)	
≥40000	653 (43.19)	252 (18.58)	
Missing values	113 (7.47)	650 (47.94)	
Maternal education, %			<0.001
Low	304 (20.11)	211 (15.56)	
Medium	417 (27.58)	277 (20.43)	
High	683 (45.17)	765 (56.42)	
Missing values	108 (7.14)	103 (7.60)	
Respiratory infections, %			<0.001
URTI only	503 (33.27)	346 (25.52)	

LRTI or both	333 (33.27)	227 (16.74)	
Missing values	0 (0.0)	(0.0)	
Preterm (<37 gestational age), %	101 (6.68)	117 (8.63)	0.046
Missing values	68 (4.50)	66 (4.87)	
Birthweight			0.218
Low	122 (8.25)	127 (9.37)	
Missing values	34 (22.49)	46 (33.92)	
Current asthma at age 6, %	235 (15.54)	114 (8.41)	<0.001
Missing values	0 (0.0)	(0.0)	
Current asthma at age 14, %	147 (9.72)	49 (3.61)	<0.001
Missing values	0 (0.0)	(0.0)	
Current asthma at age 22, %	103 (6.81)	18 (1.33)	<0.001
Missing values	0 (0.0)	0 (0.0)	
Current wheeze at age 6, %	314 (20.77)	168 (12.39)	0.610
Missing values	68 (4.50)	616 (45.43)	
Current wheeze at age 14, %	192 (12.70)	61 (4.50)	0.296
Missing values	104 (6.88)	968 (71.39)	
Current wheeze at age 22, %	202 (13.36)	28 (2.06)	0.582
Missing values	519 (34.33)	1204 (88.79)	
Current eczema at age 6, %	340 (22.49)	155 (11.43)	0.131
Missing values	90 (5.95)	619 (45.65)	
Current eczema at age 14, %	274 (18.12)	64 (4.72)	0.192
Missing values	101 (6.68)	968 (71.39)	
Current eczema at age 22, %	127 (8.40)	24 (1.77)	0.314

Missing values	541 (35.78)	1207 (89.01)	
Current hay fever at age 6, %	104 (6.88)	50 (3.69)	<0.001
Missing values	0 (0.0)	0 (0.0)	
Current hay fever at age 14, %	291 (19.25)	66 (4.87)	0.113
Missing values	102 (6.75)	968 (71.39)	
Current hay fever at age 22, %	177 (11.71)	26 (1.92)	0.814
Missing values	102 (34.99)	968 (88.86)	
Atopy at age 6, %			<0.001
Food Allergy only	32 (2.12)	9 (0.66)	
Aeroallergens only or both	332 (21.96)	78 (5.75)	
Missing values	0 (0.0)	0 (0.0)	
Current FEV₁ at age 6, (z-scores), %	-0.85 (0.98)	-0.89 (0.99)	0.261
Missing values	139 (9.01)	986 (72.71)	
Current FEV₁ at age 14, (z-scores), %	-0.46 (1.04)	-0.63 (1.07)	0.024
Missing values	120 (7.94)	1202 (88.64)	
Current FEV₁ at age 22, (z-scores), %	-0.11 (0.99)	-0.29 (1.07)	0.071
Missing values	522 (34.52)	1286 (94.84)	
Current FVC at age 6, (z-scores), %	-1.08 (1.05)	-1.04 (1.31)	0.753
Missing values	139 (9.19)	987 (72.79)	
Current FVC at age 14, (z-scores), %	-0.79 (1.06)	-0.87 (1.01)	0.181
Missing values	120 (7.93)	1202 (88.64)	
Current FVC at age 22, (z-scores), %	0.08 (0.93)	-0.02 (0.82)	0.189
Missing values	523 (34.59)	1288 (94.99)	
Current FEV₁/FVC at age 6, (z-scores), %	0.71 (1.18)	0.66 (1.26)	0.263

Missing values	141 (9.33)	987 (72.79)	
Current FEV₁/FVC at age 14, (z-scores), %	0.71 (1.19)	0.52 (1.32)	0.030
Missing values	120 (7.94)	1202 (88.64)	
Current FEV₁/FVC at age 22, (z-scores), %	-0.34 (0.92)	-0.50 (1.03)	0.078
Missing values	523 (34.59)	1288 (94.99)	
Current FEV₁ at age 6, (liters), %	1.09 (0.47-1.47)	1.08 (0.57 -1.98)	
Current FEV₁ at age 14, (liters), %	3.07 (1.07- 5.05)	2.95 (1.75- 5.01)	
Current FEV₁ at age 22, (liters), %	4.01 (1.97- 6.41)	3.93 (2.18- 6.49)	
Current FVC at age 6, (liters), %	1.16 (0.51- 2.07)	1.17 (0.65- 2.76)	
Current FVC at age 14, (liters), %	3.38 (1.15- 5.8)	3.29 (2.04- 5.62)	
Current FVC at age 22, (liters), %	4.82 (2.62- 8.42)	4.79 (2.73- 7.95)	
Current FEV₁/FVC at age 6, (liters), %	0.94 (0.34- 1.00)	0.94 (0.33- 1.00)	
Current FEV₁/FVC at age 14, (liters), %	0.91 (0.6- 1.00)	0.90 (0.63- 1.00)	
Current FEV₁/FVC at age 22, (liters), %	0.84 (0.45- 1.00)	0.82 (0.59- 0.99)	
Maternal smoking, %			0.003
Only in pregnancy	66 (4.37)	45 (3.32)	
Only at age 6	106 (7.01)	62 (4.57)	
Both in pregnancy and at age 6	277 (18.32)	183 (13.50)	
Missing values	137 (9.06)	646 (47.64)	
Paternal smoking, %	509 (33.66)	629 (46.39)	<0.001
Missing values	55 (3.64)	58 (4.28)	
Parental asthma, %			0.291
Mother only	215 (14.22)	88 (6.49)	
Father only	124 (8.20)	55 (4.06)	

Both	36 (2.38)	23 (1.70)	
Missing values	221 (14.62)	726 (53.54)	
Parental eczema, %			0.701
Mother only	223 (14.75)	118 (8.70)	
Father only	97 (6.42)	44 (3.24)	
Both	40 (2.65)	15 (1.11)	
Missing values	219 (14.48)	717 (52.88)	
Parental hay fever, %			<0.001
Mother only	441 (29.17)	207 (15.27)	
Father only	239 (15.81)	122 (9.00)	
Both	21 (13.96)	77 (5.68)	
Missing values	0 (0.0)	0 (0.0)	
Parental wheeze, %	626 (43.90)	307 (41.60)	0.306
Missing values	86 (5.69)	618 (45.58)	

**Values are means (SD) or percentages (absolute numbers). Differences were tested by using the Student t test for continuous variables, and the X^2 test for categorical variables. **SES=socio economic status was defined by the family incomes, expressed in Australian dollars (\$AUD), LRTI= low respiratory tract infections in the first year of life, URTI= upper respiratory tract infections in the first year of life.*

Supplementary Table 3. Average posterior probabilities for each group within FEV₁, FVC, and FEV₁/FVC trajectories.

	FEV ₁				FVC				FEV ₁ /FVC			
	Trajectories				Trajectories				Trajectories			
	Very Low	Low	Average	Above Average	Very Low	Low	Average	Above Average	Very Low	Low-Average	Average	Average-Low
Average posterior probabilities	0.81	0.84	0.79	0.83	0.72	0.77	0.72	0.79	0.84	0.82	0.79	0.85

Supplementary Table 4. Distribution of forced expiratory flow in one second (FEV₁), forced vital capacity (FVC) and their ratio (FEV₁/FVC) in the lung function trajectories in the Raine Study participants with two or more spirometry measurements.

	FEV ₁ n (%)				FVC n (%)				FEV ₁ /FVC n (%)			
Trajectory	Very Low	Low	Average	Above Average	Very Low	Low	Average	Above Average	Very Low	Low-Average	Average	Average-Low
	51 (3.37)	746 (49.34)	611 (40.41)	104 (6.88)	61 (4.03)	855 (56.55)	457 (30.22)	139 (9.19)	131 (8.66)	198 (13.10)	654 (43.25)	529 (34.99)
Total	1512				1512				1512			

Note. *All values are given as frequencies with percentages in parentheses.

Supplementary Table 5. Individual distribution of FEV₁ and FVC lung function trajectories in the Raine Study participants with two or more spirometry measurements.

	FVC				
FEV ₁	Very low n (%)	Low n (%)	Average n (%)	Above Average n (%)	Total
Very low	26 (42.62)	23 (2.69)	1 (0.22)	1 (0.72)	51 (3.37)
Low	35 (57.38)	626 (73.22)	82 (17.94)	3 (2.16)	746 (49.34)
Average	0 (0.00)	206 (24.09)	343 (75.05)	62 (44.60)	611 (40.41)
Above average	0 (0.00)	0 (0.00)	31 (6.78)	73 (52.52)	104 (6.88)
Total	61	457	139	855	1,512

Note. *All values are given as frequencies with percentages in parentheses.

Supplementary Table 6. Childhood and parental characteristics in participants with two or more spirometry measurements within FEV₁, FVC and FEV₁/FVC lung function trajectory groups

	FEV ₁					FVC					FEV ₁ /FVC				
Variable	Very low n (%)	Low n (%)	Average n (%)	Above average n (%)	P-value	Very low n (%)	Low n (%)	Average n (%)	Above Average n (%)	P- value	Very low n (%)	Low- High n (%)	High- Low n (%)	Average n (%)	P- value
Female	19 (37.2)	375 (50.3)	302 (49.2)	48 (46.2)	0.302	24 (39.3)	431 (50.4)	225 (49.2)	64 (46.0)	0.331	61 (46.6)	109 (55.1)	240 (45.4)	334 (51.1)	0.069
SES															
≤16.000	3 (6.4)	69 (10.0)	57 (10.1)	8 (8.4)	0.211	3 (5.1)	81 (10.3)	36 (8.6)	17 (12.8)	0.454	11 (8.8)	20 (10.8)	54 (11.1)	52 (8.6)	0.078
16000-40000	29 (61.7)	288 (41.6)	246 (43.5)	46 (48.4)		32 (54.2)	340 (43.0)	180 (43.2)	57 (42.9)		60 (48.0)	62 (33.5)	217 (44.7)	270 (44.8)	
≥40000	15 (31.9)	335 (48.4)	262 (46.4)	41 (43.2)		24 (40.7)	369 (46.7)	201 (48.2)	59 (44.4)		54 (43.2)	103 (55.7)	215 (44.2)	281 (46.6)	
Maternal education					0.117					0.139					0.505
Low	8 (15.69)	143 (19.17)	124 (20.29)	29 (27.88)		14 (22.95)	164 (19.18)	91 (19.91)	35 (25.18)		23 (17.56)	50 (25.25)	97 (18.34)	134 (20.49)	
Medium	9 (17.65)	196 (26.27)	182 (29.79)	30 (28.85)		15 (24.59)	223 (26.08)	146 (31.95)	33 (23.74)		37 (28.24)	53 (26.77)	145 (27.41)	182 (27.83)	
High	30 (58.82)	355 (47.59)	262 (42.88)	36 (34.62)		31 (50.82)	406 (47.49)	186 (40.70)	60 (43.17)		63 (48.09)	78 (39.39)	244 (46.12)	298 (45.57)	
Current Asthma at age 6															
No	39 (76.47)														
	609 (81.64)	539 (88.22)	93 (89.42)	<0.001	48 (78.69)	726 (84.91)	386 (84.46)	120 (86.33)	0.566	93 (70.99)	166 (83.84)	439 (82.99)	582 (88.99)	<0.001	
Yes	12 (23.53)	137 (18.36)	72 (11.78)	11 (10.58)		13 (21.31)	129 (15.09)	71 (15.54)	19 (13.67)		38 (29.01)	32 (16.16)	90 (17.01)	72 (11.01)	
Current wheeze at age 6	14 (29.2)	173 (24.3)	109 (18.6)	18 (18.8)	0.042	16 (26.7)	182 (22.2)	86 (19.9)	30 (22.6)	0.599	42 (32.6)	42 (21.7)	116 (23.6)	114 (18.1)	0.002
Atopic status at age 6															
Never	39 (76.47)	568 (76.14)	468 (76.60)	73 (70.19)	0.872	46 (75.41)	657 (76.84)	348 (76.15)	97 (69.78)	0.496	101 (77.10)	150 (75.56)	406 (76.75)	491 (75.08)	
Food Allergy only	1 (1.96)	17 (2.28)	12 (1.96)	2 (1.92)		0 (0.0)	20 (2.34)	9 (1.97)	3 (2.16)		0 (0.0)	6 (3.03)	16 (3.02)	10 (1.53)	

Aeroallergens only or both	11 (21.57)	161 (21.58)	131 (21.44)	29 (27.88)		15 (24.59)	178 (20.82)	100 (21.88)	39 (28.06)		30 (22.90)	42 (21.21)	107 (20.23)	153 (23.39)	
Maternal smoking															
Never	25 (62.5)	454 (67.2)	379 (66.8)	68 (73.9)	0.018	31 (58.5)	533 (68.7)	273 (65.3)	89 (69.5)	0.022	67 (54.9)	126 (69.6)	307 (64.9)	426 (71.1)	0.005
Smoking in pregnancy only	2 (5.0)	24 (3.6)	31 (5.5)	9 (9.8)		3 (5.7)	30 (3.9)	22 (5.3)	11 (8.6)		7 (5.7)	8 (4.4)	29 (6.1)	22 (3.7)	
Smoke at 6 only	0 (0.0)	56 (8.3)	47 (8.3)	3 (3.3)		5 (9.4)	72 (9.3)	25 (6.0)	4 (3.1)		8 (6.6)	12 (6.6)	34 (7.2)	52 (8.7)	
Both	13 (32.5)	142 (21.0)	110 (19.4)	12 (13.0)		14 (26.4)	141 (18.2)	98 (23.4)	24 (18.8)		40 (32.8)	35 (19.3)	103 (21.8)	99 (16.5)	
Paternal smoking					0.983					0.739					0.631
No	32 (62.75)	476 (63.81)	378 (61.87)	62 (59.62)		35 (57.38)	546 (63.86)	283 (61.93)	84 (60.43)		72 (54.96)	127 (64.14)	332 (62.76)	417 (63.76)	
Yes	17 (33.33)	243 (32.57)	211 (34.53)	38 (36.54)		25 (40.98)	278 (32.51)	155 (33.92)	51 (36.69)		52 (39.69)	65 (32.83)	178 (33.65)	214 (32.72)	
Respiratory infections															
Never	26 (51.0)	345 (46.3)	263 (43.0)	42 (40.4)	0.080	32 (52.5)	380 (44.4)	206 (45.1)	58 (41.7)	0.532	62 (47.4)	84 (42.4)	240 (45.4)	290 (44.3)	0.928
URTI only	9 (17.7)	233 (31.2)	221 (36.2)	40 (38.5)		14 (23.0)	283 (33.1)	152 (33.3)	54 (38.9)		39 (29.8)	69 (34.9)	170 (32.1)	225 (34.4)	
LRTI or both	16 (31.4)	168 (22.5)	127 (20.8)	22 (21.2)		15 (24.6)	192 (22.5)	99 (21.7)	27 (19.4)		30 (22.9)	45 (22.7)	119 (22.5)	139 (21.3)	
Preterm birth	3 (6.4)	56 (7.9)	36 (6.1)	6 (6.0)	0.649	6 (10.0)	57 (7.0)	30 (6.9)	8 (5.9)	0.776	6 (4.7)	18 (9.6)	46 (9.1)	31 (5.0)	0.015
Birthweight					0.132					0.369					0.058
Low	10 (13.89)	62 (7.49)	170 (9.18)	7 (5.98)		8 (13.11)	68 (7.95)	38 (8.32)	8 (5.76)		123 (93.86)	177 (89.39)	477 (90.17)	613 (93.73)	
Normal	62 (86.11)	766 (92.51)	1681 (90.82)	110 (94.02)		53 (86.89)	787 (92.05)	419 (91.68)	131 (94.24)		8 (6.11)	21 (10.61)	52 (9.83)	41 (6.27)	
Parental Asthma															
No	25 (64.1)	446 (69.9)	376 (71.4)	69 (79.3)	0.485	29 (58.0)	523 (71.6)	272 (70.1)	92 (74.8)	0.677	72 (65.5)	135 (76.3)	288 (65.2)	421 (74.9)	0.064
Mother only	10 (25.6)	104 (16.3)	90 (17.1)	11 (12.6)		13 (26.0)	115 (15.8)	67 (17.3)	20 (16.3)		21 (19.1)	25 (14.1)	88 (19.9)	81 (14.4)	
Father only	4 (10.3)	66 (10.3)	49 (9.3)	5 (5.8)		6 (12.0)	72 (9.9)	37 (9.5)	9 (7.3)		14 (12.7)	13 (7.3)	50 (11.3)	47 (8.4)	
Both	0 (0.00)	22 (3.5)	12 (2.3)	2 (2.3)		2 (7.3)	20 (2.7)	12 (3.1)	2 (1.6)		3 (2.7)	4 (2.3)	16 (3.6)	13 (2.3)	
Parental Eczema															
No	32 (80.0)	453 (71.3)	379 (71.6)	69 (77.5)	0.399	36 (69.2)	541 (73.9)	265 (68.3)	91 (75.2)	0.399	69 (63.9)	136 (76.4)	317 (72.1)	411 (72.5)	0.265
Mother only	3	113	96	11		9	115	79	20		23	24	74	102	

	(7.5)	(17.8)	(18.2)	(12.4)		(17.3)	(15.7)	(20.4)	(16.5)		(21.3)	(13.5)	(16.8)	(18.0)	
Father only	4 (10.0)	54 (8.5)	33 (6.2)	6 (6.7)		6 (11.5)	57 (7.8)	27 (7.0)	7 (5.8)		14 (13.0)	11 (6.2)	36 (8.2)	36 (6.4)	
Both	1 (2.5)	15 (2.4)	21 (4.0)	3 (3.4)		1 (1.9)	19 (2.6)	17 (4.4)	3 (2.5)		2 (1.9)	7 (3.9)	13 (3.0)	18 (3.2)	
Parental Hay Fever															
No	26 (51.0)	325 (43.6)	229 (37.5)	41 (39.4)	0.444	24 (39.3)	384 (44.9)	167 (36.5)	46 (33.1)	0.052	56 (42.8)	75 (37.9)	217 (41.0)	273 (41.7)	0.771
Mother only	14 (27.5)	214 (28.7)	185 (30.3)	28 (26.9)		19 (31.2)	242 (28.3)	138 (30.2)	42 (30.2)		32 (24.4)	60 (30.3)	150 (28.4)	199 (30.4)	
Father only	6 (11.8)	111 (14.9)	104 (17.0)	18 (17.3)		11 (18.0)	117 (13.7)	86 (18.8)	25 (18.0)		26 (19.9)	34 (17.2)	88 (16.6)	91 (13.9)	
Both	5 (9.8)	96 (12.9)	93 (15.2)	17 (16.35)		7 (11.5)	112 (13.1)	66 (14.4)	26 (18.7)		17 (13.0)	29 (14.7)	74 (14.0)	91 (13.9)	
Parental Wheeze	27 (57.4)	306 (43.6)	252 (43.5)	41 (42.3)	0.298	28 (48.3)	345 (42.8)	190 (44.6)	63 (46.7)	0.708	74 (59.2)	78 (40.4)	226 (46.2)	248 (40.1)	0.001

*Note. *All values are given as frequencies with percentages in parentheses. **Significance of differences was evaluated by chi-square test and are given in bold.*

****SES= socio economic status, LRTI= low respiratory tract infections in the first year of life, URTI= upper respiratory tract infections in the first year of life*

*****The average trajectory of FEV₁, FEV₁/FVC and FVC respectively were used as reference category.*