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Early View

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Early-life and health behaviour influences on lung function in early-adulthood

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Author Contributions:

O.M. and J.H. conceived and designed the study. J.S. and O.M. designed the statistical analyses. O.M. conducted the statistical analyses, presented results and drafted the manuscript. O.M., R.G., G.P.P., J.G.A., D.J., J.S. and J.H. contributed to the interpretation of the results and critically reviewed the manuscript.

Running title: Early-life influences on adult lung function (44 char.)

"This article has an online data supplement, which is accessible from this issue's table of content online at XXX"

‘TAKE HOME’ MESSAGE

Perinatal characteristics, e.g., birth weight, and childhood characteristics, e.g., lean mass, fat mass and asthma at primary school age had the most influences on lung function in early-adulthood.

Summary of the ‘Take home’ message character count: 203 (including spaces).

ABSTRACT

Rationale: Early-life exposures may influence lung function at different stages of the life course. However, relative importance of characteristics at different stages of infancy and childhood are unclear.

Objectives: To examine the associations and relative importance of early-life events on lung function at age 24-years.

Methods: We followed 7,545 children from the Avon Longitudinal Study of Parents and Children from birth to 24-years. Using previous knowledge, we classified an extensive list of putative risk factors for low lung function, covering sociodemographic, environmental, lifestyle and physiological characteristics, according to timing of exposure: 1) demographic, maternal & child; 2) perinatal; 3) postnatal; 4) early-childhood; 5) adolescence characteristics. Lung function measurements (FVC, FEV_1, FEV_1/FVC, and FEF_{25-75}) were standardised for sex, age, and height. The proportion of the remaining variance explained by each characteristic was calculated. The association and relative importance (**RI**) of each characteristic for each lung function measure was estimated using linear regression, adjusted for other characteristics in the same and previous categories.

Results: Lower maternal perinatal body mass index (BMI), lower birthweight, lower lean mass, and higher fat mass in childhood had the largest **RI** ($\mathbf{0.5\% - 7.7\%}$) for decreased FVC. Having no-siblings, lower birthweight, lower lean mass, and higher fat mass were associated with decreased FEV_1 (**RI**: $\mathbf{0.5\% - 4.6\%}$). Higher lean mass and childhood-asthma were associated with decreased FEV_1/FVC (**RI**: $\mathbf{0.6\% - 0.8\%}$).

Conclusions: Maternal perinatal BMI, birthweight, childhood lean and fat mass and early-onset asthma are the factors in infancy and childhood that have the greatest influence on early-adult lung function.

Abstract word count: 247

Keywords:

ALSPAC; Lung function in early-adulthood; Early-life influences; Relative importance.

INTRODUCTION

Lung development commences in early gestation and lung growth continues until early adulthood (20-25 years of age) when a physiological plateau in lung function is attained (1-3). Low maximally attained lung function is associated with higher risk and earlier onset of chronic obstructive pulmonary disease (COPD), higher susceptibility to cardiorespiratory morbidity and all-cause mortality in adulthood (4). Based on many experimental and epidemiological observations of immunological and pulmonary development, characteristics of early-life, including the prenatal period, appear likely to have a major influence on lung function in adult life (5-7). Understanding the role of early development, exposure to environmental and health behaviour characteristics in attained lung function in early-adulthood may provide insights into later development of lung function impairment, explain growth-related differences in their risks and identify targets for early intervention (8-12).

Numerous studies have investigated variables that might influence lung function growth and related respiratory diseases in childhood and adolescence. Identified variables include: prenatal stress (6); mode of delivery (13); maternal diet (14); history of child early feeding (14, 15); infancy peak weight velocity (16); exposure to pollutions (17-19) and allergens (20, 21) in early childhood; the role of respiratory viral infections (22), physical activity (23), body composition (24), and pubertal growth (25-27). Most studies focused on one or few characteristics, but variations in lung function are likely due to simultaneous effects of several characteristics (2, 28). Few studies have investigated the simultaneous association of several characteristics with lung function in childhood and adolescence (29-31). But none to our

knowledge has neither combined sociodemographic, environmental, lifestyle and physiological characteristics risk factors measured at different stages of early life-course nor investigated their simultaneous associations with lung function in early-adulthood, around attainment of the physiological plateau in lung function.

We analysed data from a large population based British birth cohort to investigate associations of a wide range of characteristics covering the span from early-life events through adolescence with lung function in early-adult life, around expected peak lung function attainment. Our aims were to examine numerous characteristics (Figure 1) to identify those independently associated with lung function in early-adulthood, to assess proportions of explained variations in lung function parameters attributed to each characteristic, and hence to derive characteristics' relative importance for early-adult lung function.

METHODS

Study design, setting and population

We studied participants in the Avon Longitudinal Study of Parents and Children (ALSPAC), a British population-based birth cohort. The study protocol was presented previously (32-34), and a detailed description is provided in the online data supplement. Briefly, 14,541 pregnant women resident in Avon, UK, with expected delivery dates between April 1 1991, and December 31 1992, were recruited, and their 14,062 live-born children were monitored prospectively. The 7,545 participants who have lung function measured at least once at ages 8,

15 and 24 years were included in this study. A flow chart of the study participants is demonstrated in Figure 2. Additional details are in the online data supplement.

Lung function

Spirometry was performed according to ATS/ERS criteria (35, 36) by trained fieldworkers in a research clinic at ages 8, 15 and 24 years. All flow-volume curves were inspected *post hoc* for quality assurance by JH. Lung function at ages 15 and 24 years were measured before and 15 minutes after receiving 400 µg of salbutamol (37, 38). The highest measurement of each lung function parameter, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow, midexpiratory phase (FEF_{25-75}), amongst the best three technically acceptable flow-volume curves was used for analyses. Standardised post-bronchodilator lung function scores (SD-scores adjusted for sex, age and height) at age 24 years were used as the outcomes. Our SD-scores were not adjusted for race as the majority (96.3%) of participants in our study population (N = 7,545) were from the same ethnic group (described as white).

Description of characteristics

We considered sociodemographic, environmental, lifestyle and physiological characteristics based on a review of the literature (1, 28, 39), including previous ALSPAC publications (10, 11, 23-25, 40). Figure 1 shows an overview of the investigated characteristics, and Table 1 provides details of their descriptions. There were 33 characteristics identified and clustered into five life-course stages: (1) demographic, maternal and child; (2) perinatal; (3) postnatal; (4) early-childhood; (5) adolescence characteristics. Additional details are in the online data supplement.

Statistical analysis

We compared the characteristics of the study population (N = 7,545) with those of the original cohort (singleton and one of each twin birth alive at age 1 year, N = 13,798). Participants in the study population with (N = 2,800) and without (N = 4,745) lung function measurements at age 24 years were also compared.

To increase power and minimise selection bias, multiple imputation (20 imputed datasets) by chained equations was performed to impute missing data of investigated characteristics and lung function outcomes at age 24-years (41). Imputation models included all predictor variables analysed as well as measures of lung function at ages 8 and 15 years. We compared the characteristics of the study population using observed and imputed datasets to assess the empirical distributions of the examined characteristics and the lung function outcomes before and after the imputation. To assess the robustness of our findings, we repeated our analyses using data from only the participants with measured (non-imputed) lung function at age 24 years.

We estimated associations with lung function at age 24 years according to temporal ordering of life-course stages, starting with demographic, maternal and child characteristics. Firstly, mutually adjusted associations of these characteristics with each lung function parameter at age 24 years were estimated using multivariable linear regression models fitted to each of the 20 imputed datasets, with results combined using Rubin's rules (42). We then estimated

mutually adjusted associations of perinatal characteristics (our second stage), additionally adjusting for potential confounding by the characteristics from the previous stage for which the P-value was ≤ 0.1. This process continued by estimating associations of characteristics for the next three stages, adjusting for potential confounding by characteristics with $P \leq 0.1$ from previous stages.

Relative importance derivation

For each stage, we calculated the increment in the explained variance (R^2) in lung function at age 24 years when all characteristics in the stage were added to a model including the retained characteristics (those with $P \leq 0.1$) from previous stages, if any. This has been referred to as "stage incremental R^2". Within each stage, we derived the increment in R^2 attributed to each characteristic ("characteristic incremental R^2") by adding the characteristics one by one to a model. A characteristic's contribution to a stage incremental R^2 depends on the order in which the characteristic is added to the model among other characteristics in the same stage. A characteristic appears to contribute more to a stage's incremental R^2 when it is added first due to correlations between characteristics in the same stage. Therefore, we derived incremental R^2 for each characteristic by averaging its contribution to the stage incremental R^2 over all its possible orderings among the set of characteristics in its stage.

The relative importance (RI) of a characteristic is defined as its incremental R^2 when all characteristics in the same stage as the considered characteristic were added to the model including the retained characteristics from previous stages. It is then an estimate of the

proportion of variance in lung function at age 24-years explained by the characteristic using our model setup. This derivation of RI implies that the sum of the RI values of all characteristics within a stage equals the incremental R^2 of this stage.

All analyses were conducted using the statistical software R, version 3.5.0 (43). RI was derived by using the Lindeman, Merenda, and Gold (LMG) method (44) from the `relaimpo' R package (45). Further details on the methods are provided in the online data supplement.

RESULTS

Among 7,545 participants with at least one spirometry measurement at ages 8, 15 or 24 years, 51% were female, 18.3% had a single mother, 57.5% had a mother with low educational level, 47.3% had maternal history of asthma or allergy, 3.4% had family financial difficulties, 53.7% had siblings, 5.4% were born pre-term, 10.5% born with caesarean section, 20.9% and 30.2% had maternal smoking and anxiety during pregnancy respectively, see Table S1. Spirometry measurements were taken for 88%, 51% and 37% of participants at ages 8, 15 and 24 years respectively, Figure 2. The summary statistics for investigated characteristics showed similar results for the original ALSPAC cohort and our study population, Table S4, for observed and imputed data, Table S1, and for participants with and without lung function measurements at age 24-years, Table S5. The summary statistics for lung function outcomes at age 24-years were similar in observed and imputed data, Table S2. The amount of missing data for each characteristic and lung function measurements in the study population is depicted in Figure S1.

SD-scores of lung function measurements at age 24 years, standardised for sex, age and height showed positive linear correlations with SD-scores of lung function measured earlier at ages 8 years (coefficients ranged between 0.50 – 0.51 across different lung function parameters) and 15 years (0.46 – 0.48), Table S3. This degree of correlations enabled imputing missing lung function data at age 24 years by including earlier measurements of lung function in the imputation models.

Associations with lung function in early-adulthood

Among demographic, maternal and child characteristics, parity was positively associated with higher FVC, 0.12 SD (95% confidence interval (CI): 0.05 to 0.20) and FEV_1, 0.16 SD (95% CI: 0.09 to 0.23), and family financial difficulties with low FEV_1, -0.25 SD (95% CI: -0.46 to -0.03). Association of parity with FVC and FEV_1 were slightly attenuated, 0.10 SD (95% CI: 0.03 to 0.17) and 0.14 SD (95% CI: 0.06 to 0.21) respectively, when additionally adjusted for birthweight. Among perinatal characteristics, higher birthweight was associated with higher FVC, 0.16 SD (95% CI: 0.08 to 0.23) and FEV_1, 0.15 SD (95% CI: 0.07 to 0.23) per kilogram, and higher perinatal body mass index (BMI) and maternal smoking during pregnancy with higher FVC, 0.02 SD (95% CI: 0.01 to 0.03) per kilogram/meter^2, and 0.18 SD (95% CI: 0.07 to 0.29) respectively. Higher maternal age at delivery was associated with higher FEV_1, 0.09 SD (95%CI: 0.03 to 0.15). Among early-childhood characteristics, higher lean mass (LM), and lower fat mass (FM) at age 9 years were associated with higher FVC, 0.18 SD (95% CI: 0.16 to 0.20) per kg of LM and -0.05 SD (95% CI: -0.07 to -0.03) per kg/2 of FM, and FEV_1, 0.14 SD (95% CI: 0.12 to 0.16) and -0.05 SD (95% CI: -0.06 to -0.03) respectively. Among adolescence characteristics, smoking at age 14

years was associated with higher FVC, 0.13 SD (95% CI: 0.03 to 0.23), with no evidence of an association with FEV_1 0.09 SD (95% CI: -0.01 to 0.18), Figure 4, Table 2 and Table 3.

Among demographic, maternal and child characteristics, lower maternal education was associated with lower FEV_1/FVC, -0.08 SD (95% CI: -0.14 to -0.02) and FEF_{25-75}, -0.07 SD (95% CI: -0.13 to -0.01), and family financial difficulties and parity with lower and higher FEF_{25-75}, -0.24 SD (95% CI: -0.42 to -0.06) and 0.11 SD (95% CI: 0.03 to 0.18) respectively. Among perinatal characteristics, pre-term delivery was associated with lower FEV_1/FVC, -0.25 SD (95% CI: -0.41 to -0.08) and FEF_{25-75}, -0.23 SD (95% CI: -0.43 to -0.02), and higher maternal perinatal BMI and maternal smoking during pregnancy with lower FEV_1/FVC, -0.02 SD (95% CI: -0.03 to -0.01) and -0.17 SD (95% CI: -0.27 to -0.07) respectively. Among early-childhood characteristics, higher LM was associated with lower FEV_1/FVC, -0.05 SD (95% CI: -0.08 to -0.03), but higher FEF_{25-75}, 0.04 SD (95% CI: 0.01 to 0.06), and asthma at age 7.5 years with lower FEV_1/FVC, -0.22 SD (95% CI: -0.34 to -0.09), and FEF_{25-75}, -0.24 SD (95% CI: -0.34 to -0.14), Figure 4, Table 4 and Table 5.

There was little evidence for associations between postnatal characteristics and lung function outcomes, and for associations between adolescence characteristics and FEV_1/FVC or FEF_{25-75}.

Relative importance of factors in lung function models

After adjusting for sex, age and height, the proportions of remaining variance in lung function parameters explained by studied characteristics (R^2 of SD-score models) were 10.8%, 6.7%, 3.5% and 2.4% for FVC, FEV_1, FEV_1/FVC and FEF_{25-75}, respectively.

Figure 3 presents the relative importance of characteristics clustered by stage of life-course for each spirometric parameter. Perinatal and early-childhood characteristics had the largest contributions to variations of all lung function parameters, compared with other stages. For FVC,

maternal perinatal BMI, birthweight, LM, and FM at age 9 years had RI of 0.6%, 0.5%, 7.7% and 0.6% respectively. For FEV_1, parity ($\mathrm{RI} = 0.5\%$), birthweight ($\mathrm{RI} = 0.5\%$), LM ($\mathrm{RI} = 4.6\%$) and FM ($\mathrm{RI} = 0.5\%$) were the most important influences. For FEV_1/FVC, maternal perinatal BMI ($\mathrm{RI} = 0.5\%$), maternal smoking during pregnancy ($\mathrm{RI} = 0.5\%$), LM ($\mathrm{RI} = 0.8\%$) and asthma at age 7.5 years ($\mathrm{RI} = 0.6\%$) had the greatest relative importance among studied characteristics. Asthma had the most important influence ($\mathrm{RI} = 0.7\%$), on FEF_{25-75}, see Tables 3-6.

Similar results for the associations and relative importance with lung function were obtained when restricting our analyses to only participants with measured (non-imputed) lung function at age 24-years, Figures S2 and S3, and Tables S6 – S9.

DISCUSSION

Main findings

This large population-based birth cohort study investigated the associations of sociodemographic, environmental, lifestyle and physiological characteristics from prenatal to adolescence with lung function at age 24 years (around its physiological maximum) and derived the relative importance of each of these characteristics. With information on many exposures, our study showed that influences of perinatal and early-childhood characteristics were relatively larger than that of demographic, postnatal and adolescence characteristics. However, all influences were modest that is the most influential characteristic, childhood lean mass, explained not more than 7.7% of the variation in lung function at age 24 years. Our study highlighted the relative importance of maternal perinatal BMI, birthweight, body composition in childhood, childhood asthma, socio-economic status (as captured by self-reported financial difficulties and lower maternal education) and birth order on four major lung function parameters (FVC, FEV_1, FEV_1/FVC and FEF_{25-75}). Although exposure to air pollution (source-specific particulate matter with diameter ≤10μm) during early childhood was associated with reduced lung volumes, we showed that it had much less influence on maximally attained levels of FVC and FEV_1 compared to other characteristics such as birthweight and childhood body composition.

Findings in the context of the literature

Our findings are in-line with the well-established evidence suggesting general primary roles of early-life exposures on adult lung function (12, 17, 28). It had been shown that increased

childhood BMI was associated with higher lung volume and airflow limitation in adolescents aged 15 years (30, 46). By partitioning BMI into LM and FM, our study showed that higher LM and lower FM at age 9 years (both of which are likely to track throughout childhood) were associated with higher FVC and FEV_1. These associations are described in another report from this study population looking at lung function at age 15 years (24). Importantly our analysis suggests that of all the studied characteristics, LM has the largest influence on both FVC and FEV_1. Moreover,

we found that higher LM at age 9 years was associated with lower FEV_1/FVC at age 24 years, which is likely to be attributed to a higher influence of LM on FVC than on FEV_1. A similar finding, with a wider confidence interval, has been reported in a previous study (24) with FEV_1/FVC at age 15 years. Our present study provides more evidence for such association.

Previous studies provided strong and consistent evidence of an association of lower birthweight with adult restrictive lung function impairment, with weaker evidence for airflow obstruction (47). Our study supports this with larger relative importance for FVC, compared with FEV_1/FVC (which was barely influenced by birthweight).

As might have been anticipated having asthma by the age of 7 had greater influence on FEV_1/FVC and midexpiratory flows than on lung volumes. Similar associations were reported with lung function in adolescence (10, 48).

Poverty has been shown to be associated with lower lung function in adolescence (49). Our study supports this, showing that children raised in families reporting family financial difficulties and with maternal lower education had lower lung function in early-adulthood. This association played a bigger role in FEV_1 reduction and airflow limitation than in FVC reduction.

Some of our findings are more difficult to interpret and explain. For example, having siblings was associated with increased lung function. Similar findings were previously reported for lung function in childhood (50, 51) with no adequate explanation of the mechanism of the association. Increased number of siblings has previously been shown to be inversely associated with asthma and hay fever at age 7 years, but this association did not persist after adjustment to the household size (52). Our results for crude associations showed no association of having siblings with lung function in early-adulthood, but this association appeared when the model was adjusted for the other demographic characteristics including overcrowded household. Since second-borns tend to have higher birthweights compared with first-borns (53), the association between parity and lung function might be due to differences in birthweight (weight at birth was positively associated with higher lung function). In a secondary analysis, we adjusted this association for birthweight and the results were only slightly attenuated. However, this secondary analysis might be liable to a collider bias induced by unmeasured common risk factors of birthweight and lung function (54).

Collider bias, residual confounding effects, or a combination of both might also be a plausible explanation for the association between maternal smoking during pregnancy and higher FVC.

We found clear evidence of detrimental effects of maternal smoking during pregnancy on FEV_1/FVC suggesting possible dysanapsis of lung growth, a physiological incongruence between the growth of the lung parenchyma and the caliber of the airways (55). The association of smoking at age 14 years with increased FVC could be due to a selection bias, e.g., adolescents with larger lung volume might be more likely to initiate smoking. Since smokers were defined as those who have ever smoked at least one cigarette, this result doesn't account for the amount of smoking. Studying sub-categories of smoking might reveal more on the association between smoking in adolescence and lung function in early-adulthood.

Higher maternal perinatal BMI was associated with reduced FEV_1/FVC, but with increased FVC suggesting that children of thinner mothers tended to have worse lung volumes. This may be a consequence of poor maternal perinatal nutrition and/or of poor childhood-feeding for children of thinner mothers (56).

Early-life exposure to higher air pollution (source-specific particulate matter with diameter ≤10μm) is believed to impact on developing lungs (57). Our findings suggested less importance of the early-life exposure to air pollution compared with other childhood characteristics such as LM and FM.

Implications of our study

There has long been an interest in the relationship of persistent low lung function from early-life with chronic pulmonary disease in later life but the importance of modifiable early-life

characteristics on lung function has been unclear. Our study addressed roles of early-life characteristics, provided evidence for their association, and quantified their relative importance on lung function in early-adulthood, around timing of its physiological maximum. This is relevant for better understanding of lung function growth and factors likely to contribute to lower maximal lung function attainment. Our study suggests that the association of early-life risk factors, e.g. birthweight and childhood asthma, with impaired lung function in late adulthood (5, 8, 12) is likely related to their association with maximally attained lung function, and not solely due to their impacts on lung function decline (9).

As various characteristics may influence, to a different extent, different lung function parameters, our assessment for relative importance of these characteristics can be beneficial in identifying the major determinants of restrictive and obstructive lung patterns. Our findings, together with earlier work showing evidence of lung function tracking throughout the life-course, can help prioritise public health policies directed to children that target risk factors of low lung function in later life.

Strengths and limitations

This study offers insights into the roles and relative importance of many early-life events on lung function at age 24 years, with all these characteristics simultaneously investigated. Since many of these characteristics are clustered (58), studies investigating only a subset of them are liable to risk of confounding. Our study used a wide range of characteristics with measurements covering prenatal stage through to early adulthood, with a single large (N=7,545) population-

based birth cohort study (ALSPAC) and therefore provides a more comprehensive analysis across the life course. Inevitably some data were missing, but we have used state of the art multiple imputation approaches to impute missing data, thus ensuring we are able to use all the information available increasing power and minimizing bias related to selective loss to follow-up. We repeated our analyses using only participants with measured (non-imputed) lung function (N=2,800). The results confirmed our findings obtained using the imputation approaches.

We used post-bronchodilator lung function parameters because they represent better the maximal lung function attained than their corresponding pre-bronchodilator values. The latter are not optimal when the study sample includes asthmatics, as lung function measurement may be affected by reversible airway limitation.

Despite adjustments for a wide range of relevant characteristics, this study – like all observational studies – is still liable to residual confounding by unmeasured characteristics such as diet and physical activity that were only available for a small number of participants in our cohort. Furthermore, mutual adjustments of characteristics in the life-course stage might induce collider bias via such unmeasured confounders, although we believe that our extensive adjustments for potential confounding minimised effects of such a bias. There is some evidence that men may reach maximal lung function later than females and we cannot rule out that this could have a small effect on our findings. Identification of the pathways through which characteristics affect lung function was beyond our remit. Our study adjusted only for events

that are potential confounders, i.e., that occur earlier or at time of exposure. However, mediation is a possible mechanism whereby earlier characteristics may influence lung function through factors that occur later, e.g. childhood characteristics might be mediators of perinatal characteristics.

Conclusions

Beside well-known variables included in lung function equations (sex and height), our study provides evidence for associations of perinatal and childhood characteristics, and quantifies their relative importance, with early-adult lung function. Birthweight, having siblings, LM and FM at age 9 years were the most important influences on early-adult FVC and FEV_1. Maternal perinatal BMI, smoking during pregnancy, pre-term delivery, impaired childhood respiratory health and increased LM at age 9 years were associated with lower FEV_1/FVC at age 24 years, with the largest detrimental effect from childhood asthma and LM. Childhood asthma, low LM and pre-term delivery played the largest roles in low FEF_{25-75}.

Our findings highlight the importance of early-life characteristics in lung function and suggest public health polices targeting modifiable risk factors in childhood may improve maximally attained lung function and minimise poor respiratory health in later life.

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REFERENCES

1. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet (London, England)* 2015; 385: 899-909.

2. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *The Lancet Respiratory medicine* 2013; 1: 728-742.

3. Vasquez MM, Zhou MH, Hu CC, Martinez FD, Guerra S. Low Lung Function in Young Adult Life Is Associated with Early Mortality. *Am J Resp Crit Care* 2017; 195: 1399-1401.

4. Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *The Lancet Respiratory medicine* 2017; 5: 935-945.

5. Apostol GG, Jacobs DR, Jr., Tsai AW, Crow RS, Williams OD, Townsend MC, Beckett WS. Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults study. *Am J Respir Crit Care Med* 2002; 166: 166-172.

6. Wright RJ. Perinatal stress and early life programming of lung structure and function. *Biol Psychol* 2010; 84: 46-56.

7. Litonjua AA, Gold DR. Early-Life Exposures and Later Lung Function. Add Pollutants to the Mix. *Am J Respir Crit Care Med* 2016; 193: 110-111.

8. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proceedings of the American Thoracic Society* 2009; 6: 272-277.

9. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, de Marco R, Norback D, Raherison C, Villani S, Wjst M, Svanes K, Anto JM. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010; 65: 14-20.

10. Granell R, Sterne JA, Henderson J. Associations of different phenotypes of wheezing illness in early childhood with environmental variables implicated in the aetiology of asthma. *PloS one* 2012; 7: e48359.

11. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souef PN, Simpson A, Henderson AJ, Custovic A. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *The Lancet Respiratory medicine* 2018.

12. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, Bowatte G, Gurrin L, Johns DP, Thompson BR, Hamilton GS, Frith PA, James AL, Thomas PS, Jarvis D, Svanes C,

Russell M, Morrison SC, Feather I, Allen KJ, Wood-Baker R, Hopper J, Giles GG, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *The Lancet Respiratory medicine* 2018.

13. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2008; 38: 629-633.

14. Willers SM, Wijga AH, Brunekreef B, Kerkhof M, Gerritsen J, Hoekstra MO, de Jongste JC, Smit HA. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Respir Crit Care Med* 2008; 178: 124-131.

15. Elliott L, Henderson J, Northstone K, Chiu GY, Dunson D, London SJ. Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). *The Journal of allergy and clinical immunology* 2008; 122: 49-54, 54.e41-43.

16. Claudia F, Thiering E, von Berg A, Berdel D, Hoffmann B, Koletzko S, Bauer CP, Koletzko B, Heinrich J, Schulz H. Peak weight velocity in infancy is negatively associated with lung function in adolescence. *Pediatric pulmonology* 2016; 51: 147-156.

17. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001; 163: 429-436.

18. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, Oldenwening M, Smit HA, Brunekreef B. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010; 181: 596-603.

19. Schultz ES, Hallberg J, Bellander T, Bergstrom A, Bottai M, Chiesa F, Gustafsson PM, Gruzieva O, Thunqvist P, Pershagen G, Melen E. Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence. *Am J Respir Crit Care Med* 2016; 193: 171-177.

20. Torrent M, Sunyer J, Garcia R, Harris J, Iturriaga MV, Puig C, Vall O, Anto JM, Newman Taylor AJ, Cullinan P. Early-life allergen exposure and atopy, asthma, and wheeze up to 6 years of age. *Am J Respir Crit Care Med* 2007; 176: 446-453.

21. Kerkhof M, Wijga AH, Brunekreef B, Smit HA, de Jongste JC, Aalberse RC, Hoekstra MO, Gerritsen J, Postma DS. Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy* 2009; 64: 1202-1208.

22. Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent

development of persistent asthma. *The Journal of allergy and clinical immunology* 2007; 119: 1105-1110.

23. Roda C, Mahmoud O, Peralta GP, Fuertes E, Granell R, Serra I, Henderson J, Jarvis D, Garcia-Aymerich J. Physical-activity trajectories during childhood and lung function at 15 years: findings from the ALSPAC cohort. *International Journal of Epidemiology* 2019.

24. Peralta GP, Fuertes E, Granell R, Mahmoud O, Roda C, Serra I, Jarvis D, Henderson J, Garcia-Aymerich J. Childhood Body Composition Trajectories and Adolescent Lung Function: Findings from the ALSPAC Study. *Am J Respir Crit Care Med* 2019.

25. Mahmoud O, Granell R, Tilling K, Minelli C, Garcia-Aymerich J, Holloway JW, Custovic A, Jarvis D, Sterne J, Henderson J. Association of Height Growth in Puberty with Lung Function: A Longitudinal Study. *Am J Respir Crit Care Med* 2018.

26. Minelli C, van der Plaat DA, Leynaert B, Granell R, Amaral AFS, Pereira M, Mahmoud O, Potts J, Sheehan NA, Bowden J, Thompson J, Jarvis D, Davey Smith G, Henderson J. Age at puberty and risk of asthma: A Mendelian randomisation study. *PLoS Med* 2018; 15: e1002634.

27. Gill D, Sheehan NA, Wielscher M, Shrine N, Amaral AFS, Thompson JR, Granell R, Leynaert B, Real FG, Hall IP, Tobin MD, Auvinen J, Ring SM, Jarvelin MR, Wain LV, Henderson J, Jarvis D, Minelli C. Age at menarche and lung function: a Mendelian randomization study. *European journal of epidemiology* 2017; 32: 701-710.

28. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. *European journal of epidemiology* 2014; 29: 871-885.

29. Trabelsi Y, Paries J, Harrabi I, Zbidi A, Tabka Z, Richalet JP, Buvry A. Factors affecting the development of lung function in Tunisian children. *American journal of human biology : the official journal of the Human Biology Council* 2008; 20: 716-725.

30. Luzak A, Fuertes E, Flexeder C, Standl M, von Berg A, Berdel D, Koletzko S, Heinrich J, Nowak D, Schulz H. Which early life events or current environmental and lifestyle factors influence lung function in adolescents? - results from the GINIplus & LISAplus studies. *Respiratory research* 2017; 18: 138.

31. Thacher JD, Schultz ES, Hallberg J, Hellberg U, Kull I, Thunqvist P, Pershagen G, Gustafsson PM, Melen E, Bergstrom A. Tobacco smoke exposure in early life and adolescence in relation to lung function. *Eur Respir J* 2018; 51.

32. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2013; 42: 111-127.

33. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 2013; 42: 97-110.

34. Northstone K, Lewcock M, Groom A, Boyd A, Macleod J, Timpson N, Wells N. The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019. *Wellcome open research* 2019; 4.

35. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107-1136.

36. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJ, Jones MH, Klug B, Lodrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJ, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, Tepper RS, Vilozni D, Wilson NM. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007; 175: 1304-1345.

37. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; 161: 309-329.

38. Pellegrino R, Decramer M, van Schayck CP, Dekhuijzen PN, Troosters T, van Herwaarden C, Olivieri D, Del Donno M, De Backer W, Lankhorst I, Ardia A. Quality control of spirometry: a lesson from the BRONCUS trial. *Eur Respir J* 2005; 26: 1104-1109.

39. Kouzouna A, Gilchrist FJ, Ball V, Kyriacou T, Henderson J, Pandyan AD, Lenney W. A systematic review of early life factors which adversely affect subsequent lung function. *Paediatr Respir Rev* 2016; 20: 67-75.

40. Granell R, Henderson AJ, Evans DM, Smith GD, Ness AR, Lewis S, Palmer TM, Sterne JA. Effects of BMI, fat mass, and lean mass on asthma in childhood: a Mendelian randomization study. *PLoS Med* 2014; 11: e1001669.

41. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011; 20: 40-49.

42. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996; 91: 473-489.

43. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.

44. Sawrey WL. Introduction to Bivariate and Multivariate-Analysis - Lindeman,Rh, Merenda,Pf, Gold,Rz. *Contemp Psychol* 1981; 26: 374-374.

45. Gromping U. Relative importance for linear regression in R: The package relaimpo. *J Stat Softw* 2006; 17.

46. Cibella F, Bruno A, Cuttitta G, Bucchieri S, Melis MR, De Cantis S, La Grutta S, Viegi G. An elevated body mass index increases lung volume but reduces airflow in Italian schoolchildren. *PloS one* 2015; 10: e0127154.

47. Saad NJ, Patel J, Burney P, Minelli C. Birth Weight and Lung Function in Adulthood: A Systematic Review and Meta-analysis. *Ann Am Thorac Soc* 2017; 14: 994-1004.

48. Granell R, Henderson AJ, Sterne JA. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: A population-based birth cohort. *The Journal of allergy and clinical immunology* 2016; 138: 1060-1070 e1011.

49. Hegewald MJ, Crapo RO. Socioeconomic status and lung function. *Chest* 2007; 132: 1608-1614.

50. Mattes J, Karmaus W, Storm van's Gravesande K, Moseler M, Forster J, Kuehr J. Pulmonary function in children of school age is related to the number of siblings in their family. *Pediatric pulmonology* 1999; 28: 414-417.

51. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *Journal of Epidemiology and Community Health* 2002; 56: 209-217.

52. Ponsonby A-L, Couper D, Dwyer T, Carmichael A. Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. *Archives of Disease in Childhood* 1998; 79: 328-333.

53. Bacci S, Bartolucci F, Chiavarini M, Minelli L, Pieroni L. Differences in birthweight outcomes: a longitudinal study based on siblings. *Int J Environ Res Public Health* 2014; 11: 6472-6484.

54. Stensrud MJ, Valberg M, Aalen OO. Can Collider Bias Explain Paradoxical Associations? *Epidemiology* 2017; 28: e39-e40.

55. Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, Cloutier MM, Canino G, Weiss ST, Litonjua AA, Celedon JC. Obesity and Airway Dysanapsis in Children with and without Asthma. *Am J Respir Crit Care Med* 2017; 195: 314-323.

56. Hanson C, Brigham E. Maternal nutrition and child respiratory outcomes: paradigms of lung health and disease. *Eur Respir J* 2020; 55.

57. Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet (London, England)* 2007; 369: 571-577.

58. Smith GD, Lawlor DA, Harbord R, Timpson N, Day I, Ebrahim S. Clustered environments and randomized genes: a fundamental distinction between conventional and genetic epidemiology. *PLoS Med* 2007; 4: e352.

59. Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol* 1988; 61 (Pt 3): 255-266.

TABLES

Table 1. Description of investigated factors grouped in five life-course stages.

Stage	Factor	Description	Assessment
Demographic, maternal and child characteristics	Overcrowding	positive if home has > 0.75 persons per room	questionnaires sent to mother during pregnancy or 3 to 12 months after delivery
	Gas cooking	yes or no (baseline)	
	Rented housing	yes or no (baseline)	
	Single mother	yes or no (baseline)	
	Low maternal education	positive if mother educated to school leaving certificate at 16 years (GCE level in UK) or lower	
	Maternal history of asthma or allergy	yes or no (baseline)	
	Family financial difficulties	positive if financial difficulties reported at all three assessment points	asked at 32 weeks in pregnancy, 8 and 21 months after delivery (questionnaire-based)
	Parity	positive if the child has >=1 sibling	at birth (questionnaire)
Perinatal characteristics	Maternal perinatal (early pregnancy) body mass index	continous, kilogram/meter^2.	measured at 12 weeks gestation
	Maternal age at delivery	dichotomised in ≤28 and > 28 years (median age served as the cut-off)	using delivery health care records
	Birthweight	continous, kilograms	
	Pre-term delivery	positive if gestation <37 weeks	
	Caesarean section	yes or no (baseline)	
	Maternal smoking during pregnancy	yes or no (baseline)	questionnaires sent at 32 weeks gestation
	Maternal anxiety during pregnancy*	yes or no (baseline)	
	Maternal gestational weight gain	continous, kilogram/week	mean of weight gain at 0-18 and 18-28 weeks in pregnancy
	Air pollution exposure during pregnancy	continous, micrograms/cubic metre	average of daily concentration of source especific particulate matter 10 micrometers or less in diameter (PM_{10})

Table 1 (continued)

Stage	Factor	Description	Assessment
Postnatal characteristics	Maternal smoking during first year of age	yes or no (baseline)	questionnaires sent from 3-15 months after birth
	Day care attendance during first year of age	yes or no (baseline)	
	Family pet ownership during first year of age	yes or no (baseline)	
	Maternal anxiety during first year of age*	yes or no (baseline)	
	Air pollution exposure during first year of age	continous, micrograms/cubic metre	average of daily concentration of source-specific particulate matter with diameter ≤10µm (PM_{10}) measured at age 6 and 12 months
	Breastfeeding during first 6 months	yes or no (baseline)	questionnaire-based, sent from 3-15 months after birth
	Early second-hand smoke exposure	yes or no (baseline)	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 years	positive if exposure to second-hand smoke at home reported at least in one questionnaire between age 1-8 years	annual questionnaires sent from age 1-6 and at 8 years
	Air pollution exposure during 1-7 years of age	continous, micrograms/cubic metre	cumulative concentration of source-specific particulate matter with diameter ≤10µm (PM_{10}) assessed annually during ages 1 to 7 years
	Child lean mass at 9 years	continous, kg, residual after adjustment for gender and height	measured at focus clinic and expressed as residuals from a linear regression of each on gender, height, and height squared. Residual fat mass was divided by 2 (see suppl. Methods)
	Child fat mass at 9 years	continous, kg/2, residual after adjustment for gender and height	
	Current asthma at age 7.5	yes or no (baseline)	questionnaire-based at age 7.5 years
	Allergic sensitization (Skin Prick Test) at age 7.5	positive if any of skin prick tests for grass, cat, or house dust mite reported positive result	measured using cut-off weal for positivety >=2 mm

Table 1 (continued)

Stage	Factor	Description	Assessment
Adolescence characteristics	Smoking status at 14 years	positive if smoked at least 1 cigarette	questionnaire-based at age 14 years
	Age at peak height velocity in puberty	continous, years	derived using mixed-effects models for repeated height measurements from age 5 to 20 years (25)
	Peak height velocity in puberty	continous, cm/year	

*Anxiety was measured using the validated self-report Crown Crisp Experiential Index which ranges from 0 (no anxious) to 16 (very anxious) (59). Maternal anxiety scores were not normally distributed and therefore were converted into 1st quartile [0 to 2], 2nd quartile [3-4], 3rd quartile [5-7] and 4th quartile [8-16]. Anxious mothers were defined as being in the 4th quartile.

†The peak height velocity is defined as the maximum of the first derivative of individual height growth trajectories, fitted using nonlinear mixed-effects models, from age 5-20 years, see (25).

Table 2. Adjusted association and relative importance of early-life characteristics with SD scores of FVC (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.060 (-0.145 to 0.024)	0.164	0.61	0.047	0.32
	Gas cooking	-0.015 (-0.086 to 0.056)	0.683		0.020	
	Rented housing	-0.010 (-0.159 to 0.138)	0.892		0.040	
	Single Mother	0.056 (-0.044 to 0.155)	0.277		0.033	
	Low maternal education	-0.020 (-0.081 to 0.041)	0.529		0.020	
	Maternal history of asthma or allergy	0.026 (-0.043 to 0.095)	0.460		0.033	
	Family financial difficulties	-0.141 (-0.395 to 0.112)	0.282		0.095	
	Parity (>= 1 siblings)	0.123 (0.050 to 0.196)	0.002		0.318	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.020 (0.009 to 0.032)	0.001	1.98	0.631	2.04
	Maternal age at delivery > 28 years (the median)	0.075 (0.003 to 0.147)	0.047		0.113	
	Birthweight (Kg)	0.157 (0.079 to 0.234)	2×10^{-4}		0.536	
	Pre-term delivery	0.161 (-0.036 to 0.357)	0.117		0.076	
	Caesarean section	0.010 (-0.117 to 0.137)	0.878		0.029	
	Maternal smoking during pregnancy	0.178 (0.068 to 0.288)	0.003		0.440	
	Maternal anxiety during pregnancy	-0.029 (-0.112 to 0.055)	0.505		0.032	
	Maternal gestational weight gain (Kg/week)	0.066 (-0.196 to 0.327)	0.624		0.036	
	Air pollution exposure during pregnancy (µg/m^3)	-0.009 (-0.020 to 0.003)	0.139		0.090	
Postnatal characteristics	Maternal smoking during first year of age	-0.100 (-0.258 to 0.059)	0.226	0.38	0.087	2.04
	Day care attendance during first year of age	0.107 (-0.026 to 0.241)	0.120		0.085	
	Family pet ownership during first year of age	-0.026 (-0.097 to 0.044)	0.467		0.026	
	Maternal anxiety during first year of age	0.040 (-0.050 to 0.131)	0.384		0.047	
	Air pollution during first year of age (µg/m^3)	-0.010 (-0.023 to 0.002)	0.118		0.077	
	Breastfeeding during first 6 months	0.042 (-0.054 to 0.138)	0.397		0.046	
	Early second-hand smoke exposure	0.016 (-0.058 to 0.089)	0.677		0.015	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.003 (-0.062 to 0.056)	0.921	8.58	0.008	10.48
	Air pollution during 1-7 years of age (µg/m^3)	-0.010 (-0.019 to -0.001)	0.034		0.172	
	Lean mass at age 9 years (SD-score)	0.180 (0.159 to 0.201)	1×10^{-16}		7.707	
	Fat mass at age 9 years (SD-score)	-0.051 (-0.073 to -0.028)	1×10^{-4}		0.556	
	Current asthma at 7.5 years	0.064 (-0.056 to 0.184)	0.304		0.104	
	Skin Prick Test at 7.5 years	0.015 (-0.083 to 0.113)	0.766		0.030	
Adoles.	Smoking status at 14 years	0.130 (0.031 to 0.228)	0.014	0.38	0.337	10.82
	Age at peak height velocity in puberty (years)	-0.003 (-0.028 to 0.022)	0.822		0.011	
	Peak height velocity in puberty (cm/year)	0.012 (-0.012 to 0.036)	0.319		0.033	

Abbreviations: Adoles. = adolescence characteristics; FVC = forced vital capacity; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables (with P-value ≤ 0.10) from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table 3. Adjusted association and relative importance of early-life characteristics with SD scores of FEV_1 (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.079 (-0.173 to 0.015)	0.107	1.21	0.104	0.89
	Gas cooking	-0.021 (-0.091 to 0.048)	0.552		0.022	
	Rented housing	-0.075 (-0.236 to 0.085)	0.366		0.134	
	Single Mother	0.067 (-0.036 to 0.169)	0.208		0.039	
	Low maternal education	-0.067 (-0.133 to -0.001)	0.050		0.141	
	Maternal history of asthma or allergy	0.017 (-0.054 to 0.088)	0.641		0.027	
	Family financial difficulties	-0.246 (-0.459 to -0.033)	0.029		0.220	
	Parity (>= 1 siblings)	0.161 (0.089 to 0.233)	5×10^{-5}		0.524	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.006 (-0.004 to 0.015)	0.263	1.06	0.086	1.59
	Maternal age at delivery > 28 years (the median)	0.086 (0.026 to 0.147)	0.006		0.170	
	Birthweight (Kg)	0.147 (0.066 to 0.229)	0.001		0.529	
	Pre-term delivery	0.011 (-0.184 to 0.206)	0.909		0.075	
	Caesarean section	-0.025 (-0.148 to 0.097)	0.689		0.027	
	Maternal smoking during pregnancy	0.066 (-0.048 to 0.180)	0.266		0.074	
	Maternal anxiety during pregnancy	-0.021 (-0.112 to 0.071)	0.657		0.038	
	Maternal gestational weight gain (Kg/week)	-0.076 (-0.329 to 0.177)	0.558		0.025	
	Air pollution exposure during pregnancy ($\mu g/m^3$)	-0.005 (-0.015 to 0.006)	0.372		0.035	
Postnatal characteristics	Maternal smoking during first year of age	-0.013 (-0.114 to 0.087)	0.793	0.27	0.025	1.59
	Day care attendance during first year of age	0.080 (-0.067 to 0.228)	0.289		0.057	
	Family pet ownership during first year of age	-0.002 (-0.075 to 0.071)	0.966		0.013	
	Maternal anxiety during first year of age	0.062 (-0.018 to 0.141)	0.134		0.076	
	Air pollution during first year of age ($\mu g/m^3$)	-0.008 (-0.020 to 0.005)	0.231		0.048	
	Breastfeeding during first 6 months	-0.018 (-0.125 to 0.088)	0.737		0.032	
	Early second-hand smoke exposure	0.009 (-0.068 to 0.085)	0.826		0.019	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	0.002 (-0.057 to 0.061)	0.948	5.26	0.011	6.63
	Air pollution during 1-7 years of age ($\mu g/m^3$)	-0.007 (-0.016 to 0.003)	0.167		0.096	
	Lean mass at age 9 years (SD-score)	0.140 (0.117 to 0.163)	3×10^{-15}		4.579	
	Fat mass at age 9 years (SD-score)	-0.045 (-0.063 to -0.026)	3×10^{-5}		0.465	
	Current asthma at 7.5 years	-0.072 (-0.171 to 0.026)	0.158		0.072	
	Skin Prick Test at 7.5 years	0.027 (-0.076 to 0.130)	0.612		0.032	
Adoles.	Smoking status at 14 years	0.088 (-0.002 to 0.178)	0.063	0.19	0.162	6.79
	Age at peak height velocity in puberty (years)	0.009 (-0.019 to 0.037)	0.542		0.019	
	Peak height velocity in puberty (cm/year)	-0.001 (-0.026 to 0.024)	0.921		0.012	

Abbreviations: Adoles. = adolescence characteristics; FEV_1 = forced expiratory volume in one second; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables (with P-value ≤ 0.10) from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table 4. Adjusted association and relative importance of early-life characteristics with SD scores of FEV_1/FVC (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.033 (-0.146 to 0.081)	0.574	0.79	0.067	0.45
	Gas cooking	-0.013 (-0.091 to 0.064)	0.736		0.025	
	Rented housing	-0.107 (-0.233 to 0.020)	0.106		0.194	
	Single Mother	0.019 (-0.084 to 0.123)	0.715		0.036	
	Low maternal education	-0.079 (-0.142 to -0.015)	0.017		0.184	
	Maternal history of asthma or allergy	-0.011 (-0.079 to 0.057)	0.751		0.018	
	Family financial difficulties	-0.194 (-0.386 to -0.002)	0.052		0.155	
	Parity (>= 1 siblings)	0.069 (-0.003 to 0.142)	0.067		0.106	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	-0.021 (-0.032 to -0.010)	0.001	1.66	0.543	1.85
	Maternal age at delivery > 28 years (the median)	0.027 (-0.047 to 0.101)	0.480		0.049	
	Birthweight (Kg)	-0.001 (-0.086 to 0.084)	0.980		0.046	
	Pre-term delivery	-0.247 (-0.413 to -0.082)	0.005		0.291	
	Caesarean section	-0.064 (-0.183 to 0.055)	0.298		0.089	
	Maternal smoking during pregnancy	-0.173 (-0.273 to -0.072)	0.002		0.495	
	Maternal anxiety during pregnancy	0.003 (-0.095 to 0.100)	0.953		0.039	
	Maternal gestational weight gain (Kg/week)	-0.229 (-0.476 to 0.019)	0.075		0.075	
	Air pollution exposure during pregnancy (µg/m^3)	0.004 (-0.007 to 0.016)	0.441		0.035	
Postnatal characteristics	Maternal smoking during first year of age	-0.073 (-0.251 to 0.105)	0.428	0.31	0.067	1.85
	Day care attendance during first year of age	-0.030 (-0.171 to 0.110)	0.672		0.022	
	Family pet ownership during first year of age	0.012 (-0.054 to 0.079)	0.714		0.012	
	Maternal anxiety during first year of age	0.021 (-0.049 to 0.091)	0.554		0.015	
	Air pollution during first year of age (µg/m^3)	0.001 (-0.014 to 0.016)	0.923		0.023	
	Breastfeeding during first 6 months	-0.077 (-0.208 to 0.054)	0.259		0.123	
	Early second-hand smoke exposure	-0.036 (-0.126 to 0.054)	0.433		0.047	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.036 (-0.109 to 0.037)	0.337	1.67	0.046	3.33
	Air pollution during 1-7 years of age (µg/m^3)	0.003 (-0.007 to 0.012)	0.559		0.031	
	Lean mass at age 9 years (SD-score)	-0.054 (-0.076 to -0.033)	6×10^{-6}		0.843	
	Fat mass at age 9 years (SD-score)	0.001 (-0.019 to 0.021)	0.925		0.071	
	Current asthma at 7.5 years	-0.217 (-0.342 to -0.092)	0.002		0.636	
	Skin Prick Test at 7.5 years	0.035 (-0.069 to 0.139)	0.510		0.038	
Adoles.	Smoking status at 14 years	-0.062 (-0.152 to 0.028)	0.182	0.21	0.100	3.44
	Age at peak height velocity in puberty (years)	0.021 (-0.003 to 0.045)	0.096		0.064	
	Peak height velocity in puberty (cm/year)	-0.018 (-0.039 to 0.003)	0.099		0.048	

Abbreviations: Adoles. = adolescence characteristics; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity ; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table 5. Adjusted association and relative importance of early-life characteristics with SD scores of FEF_{25-75} (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.029 (-0.143 to 0.085)	0.625	0.84	0.050	0.61
	Gas cooking	-0.021 (-0.098 to 0.056)	0.599		0.029	
	Rented housing	-0.069 (-0.190 to 0.052)	0.271		0.102	
	Single Mother	0.014 (-0.093 to 0.120)	0.802		0.034	
	Low maternal education	-0.073 (-0.134 to -0.012)	0.020		0.152	
	Maternal history of asthma or allergy	0.003 (-0.065 to 0.071)	0.939		0.016	
	Family financial difficulties	-0.238 (-0.420 to -0.057)	0.012		0.204	
	Parity (>= 1 siblings)	0.108 (0.034 to 0.181)	0.006		0.254	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	-0.001 (-0.011 to 0.009)	0.859	1.03	0.019	1.07
	Maternal age at delivery > 28 years (the median)	0.066 (-0.003 to 0.135)	0.064		0.130	
	Birthweight (Kg)	0.053 (-0.025 to 0.131)	0.187		0.175	
	Pre-term delivery	-0.227 (-0.429 to -0.024)	0.034		0.333	
	Caesarean section	-0.075 (-0.190 to 0.039)	0.202		0.081	
	Maternal smoking during pregnancy	-0.090 (-0.203 to 0.023)	0.129		0.190	
	Maternal anxiety during pregnancy	0.026 (-0.065 to 0.117)	0.579		0.036	
	Maternal gestational weight gain (Kg/week)	-0.170 (-0.417 to 0.077)	0.183		0.055	
	Air pollution exposure during pregnancy ($\mu g/m^3$)	0.000 (-0.011 to 0.010)	0.977		0.013	
Postnatal characteristics	Maternal smoking during first year of age	-0.146 (-0.316 to 0.025)	0.103	0.40	0.164	1.07
	Day care attendance during first year of age	0.063 (-0.067 to 0.194)	0.344		0.036	
	Family pet ownership during first year of age	0.030 (-0.041 to 0.100)	0.412		0.029	
	Maternal anxiety during first year of age	0.029 (-0.041 to 0.099)	0.422		0.020	
	Air pollution during first year of age ($\mu g/m^3$)	-0.002 (-0.016 to 0.011)	0.726		0.020	
	Breastfeeding during first 6 months	-0.065 (-0.187 to 0.056)	0.300		0.094	
	Early second-hand smoke exposure	-0.024 (-0.112 to 0.063)	0.587		0.036	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.063 (-0.134 to 0.008)	0.088	1.21	0.095	2.17
	Air pollution during 1-7 years of age ($\mu g/m^3$)	-0.001 (-0.010 to 0.008)	0.807		0.019	
	Lean mass at age 9 years (SD-score)	0.035 (0.012 to 0.058)	0.004		0.309	
	Fat mass at age 9 years (SD-score)	-0.006 (-0.024 to 0.013)	0.566		0.033	
	Current asthma at 7.5 years	-0.239 (-0.339 to -0.139)	2×10^{-5}		0.695	
	Skin Prick Test at 7.5 years	0.064 (-0.045 to 0.173)	0.257		0.059	
Adoles	Smoking status at 14 years	-0.031 (-0.120 to 0.058)	0.495	0.09	0.042	2.17
	Age at peak height velocity in puberty (years)	0.014 (-0.011 to 0.038)	0.279		0.031	
	Peak height velocity in puberty (cm/year)	-0.010 (-0.032 to 0.011)	0.351		0.021	

Abbreviations: Adoles. = adolescence characteristics; FEF_{25-75} = forced expiratory flow, midexpiratory phase; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables (with P-value ≤ 0.10) from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

FIGURES

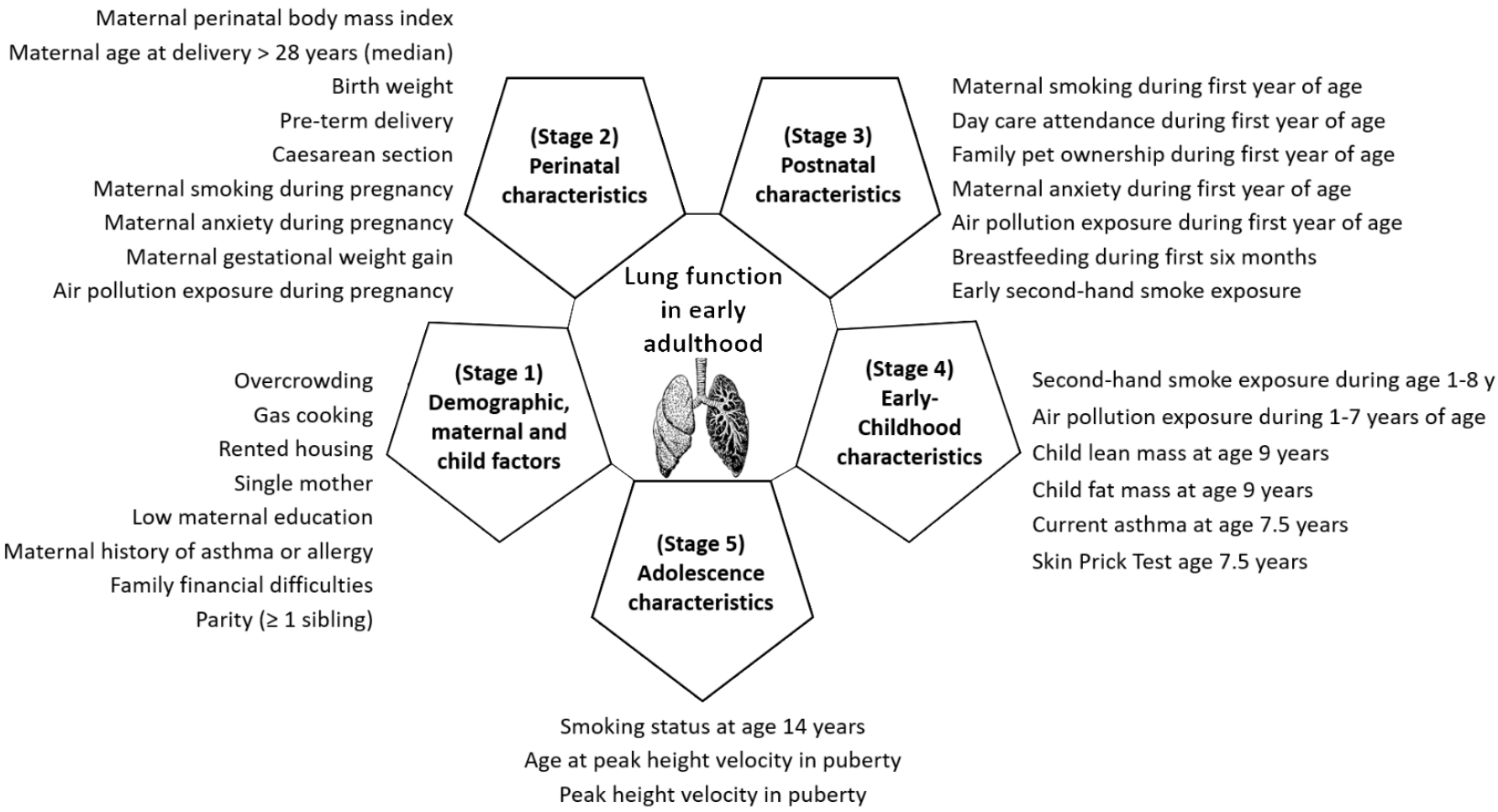

Figure 1. Characteristics examined for association and relative importance with lung function at age 24 years (Detailed description presented in Table 1).

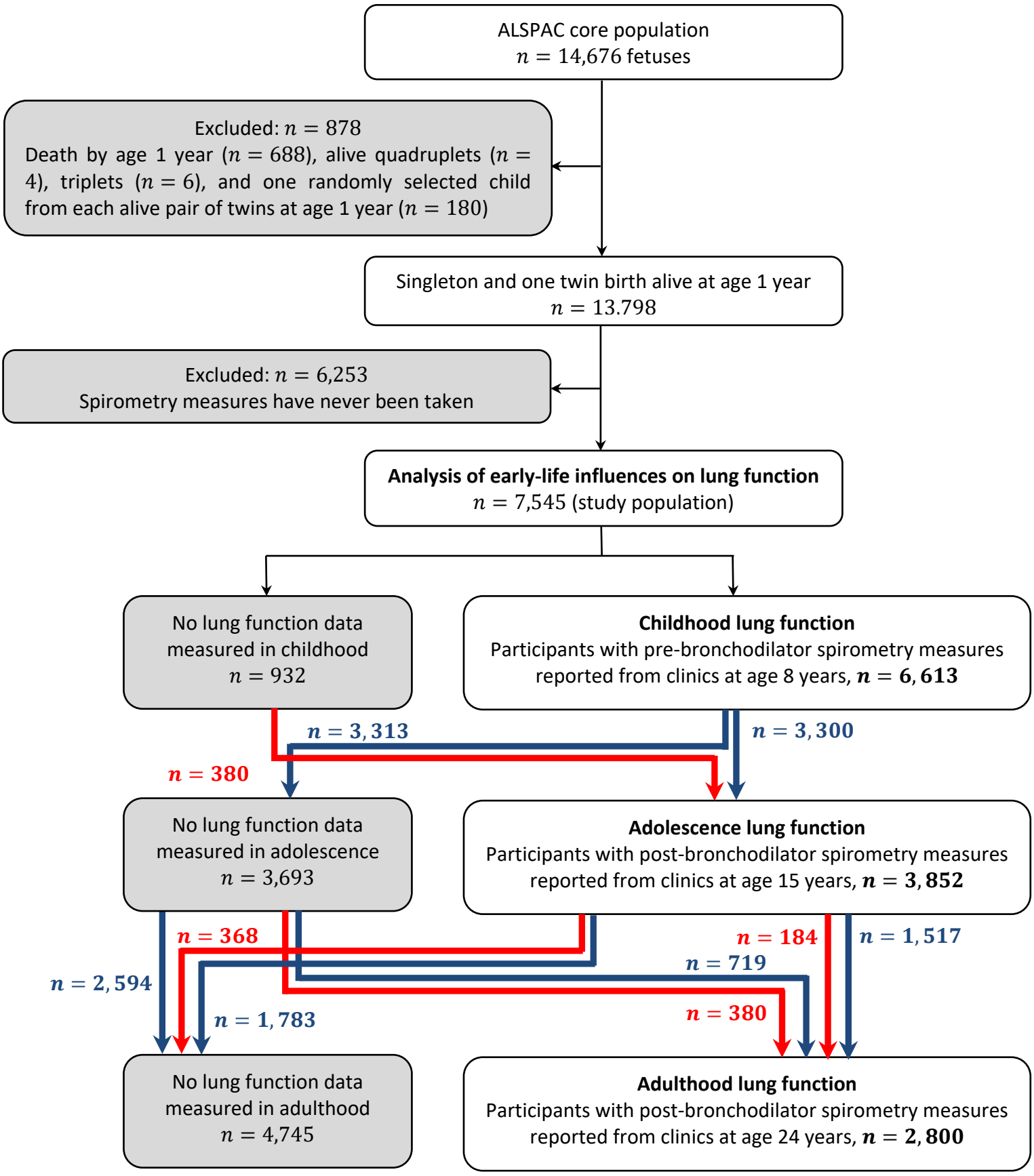

Figure 2. Flow chart of study participants. The blue and red arrows refer to different follow-up paths for spirometry clinics at ages 8, 15 and 24 years. For example, the blue arrow from 'Childhood' to 'Adolescence' lung function boxes represents participants ($n = 3{,}300$) whose lung function was measured at both clinics, of those $n = 1{,}517$ participants had given their lung function measurements in adulthood but $n = 1{,}783$ had not (the two blue arrows coming out from the box of 'Adolescence lung function'). ALSPAC = Avon Longitudinal Study of Parents and Children.

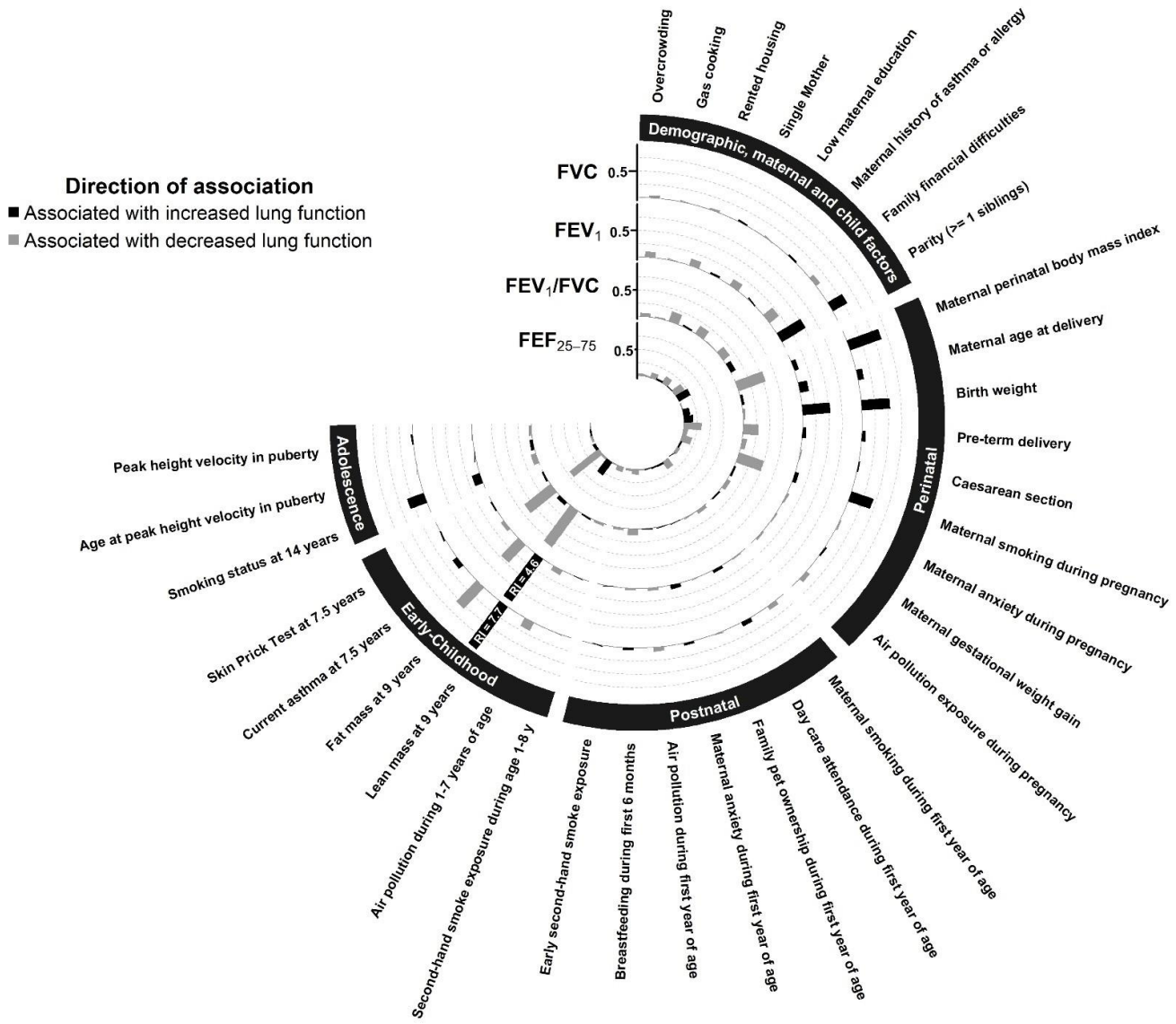

Figure 3. Circular plot of characteristics' relative importance (RI), on lung function parameters at age 24 years. Associations with higher and lower lung function were highlighted in black and grey colours respectively. Bars' height represented levels of RI, expressed in %, except for characteristics whose RI $> 1\%$, where exact RI values are displayed on their corresponding bars.

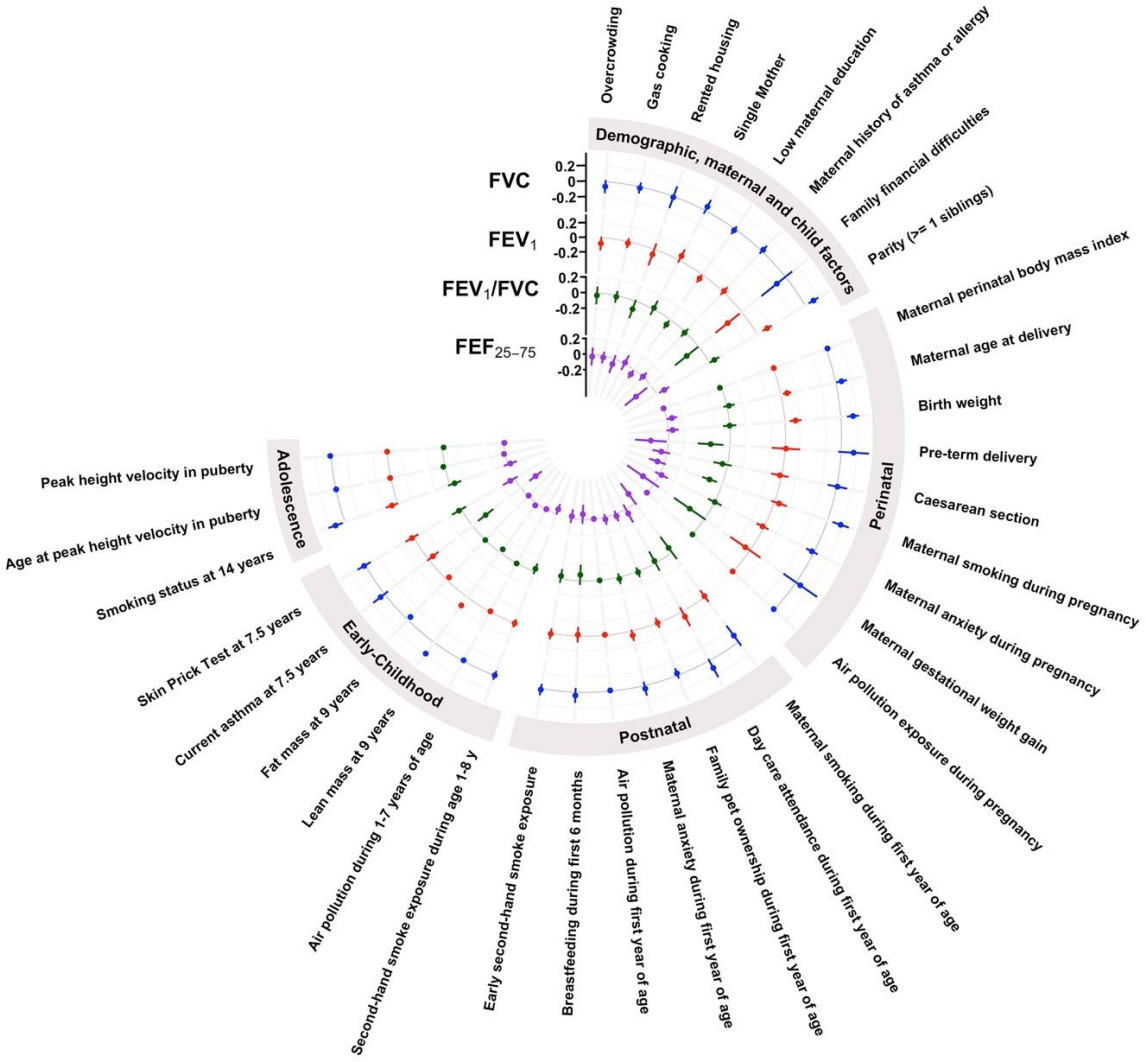

Figure 4. Circular plot of characteristics' association (point estimates and 95% confidence intervals) with lung function parameters at age 24 years for our study population (N=7,545). The raw data used for generating this plot are reported in Table 2 - Table 5

Early-life and health behaviour influences on lung function in early-adulthood

Online Data Supplement

METHODS

Participants and data collection

ALSPAC initially recruited 14,541 pregnant women resident in Avon, UK with expected delivery dates between April 1, 1991 and December 31. This initial number of pregnancies, known as core sample, included the mothers enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a 'Children in Focus' research clinic by 19th July 1999. These initial pregnancies had a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at age one-year. When the oldest children were approximately seven years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, there are extra data available when considering variables collected from the age of seven years onwards. The number of new pregnancies, not in the core sample, known as phases II and III enrolments, is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper (1). Therefore, the total sample size for which the ALSPAC data collected after the age of seven years is therefore 15,247 pregnancies, resulting in 15,458 fetuses with 14,775 live births and 14,701 alive children at one-year of age.

We restricted our study (N = 7,545) to the core sample participants who have lung function measured at least once, after excluding quadruplets, triplets and one random child of each twin births. The study was approved by the ALSPAC Ethics and Law Committee and 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.

Data were collected from several sources: self-administered questionnaires sent to mothers at approximately annual intervals from 6 to 198 months (16½ years); annual physical examinations carried out during research clinics from age 7 to 13 years and at 15, 17 and 24 years. Study data were collected and managed using REDCap electronic data capture tools(2, 3) hosted at University of Bristol. The ALSPAC study website contains details of all data through a fully searchable data dictionary that is available on the following Web page:

http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/

Investigated characteristics

Factors were categorized according to their nature and timing: (1) demographic, maternal and child characteristics that do not change over time and/or were measured before birth, e.g. gas cooking, maternal asthma or allergy, family financial difficulties; (2) perinatal characteristics, e.g. birthweight, maternal smoking during pregnancy; (3) postnatal characteristics, e.g. maternal smoking during first year of age, air pollution exposure during first year of age; (4) early-childhood, e.g. exposure to second-hand smoking during age 1-8 years, air pollution exposure during age 1-7 years; lean and fat mass at age 9 years, current

asthma at age 7.5 years (5) adolescence characteristics, e.g. smoking status at age 14 years, pubertal age. Figure 1 shows an overview of investigated characteristics and a detailed description is provided in Table 1.

Lean mass and fat mass residuals

To adjust for differences in fat mass between females and males, and to adjust for height, the measures of fat mass and lean mass included in the analyses were calculated as the residuals from a linear regression of each on gender, height, and height squared. The standard deviation of fat mass residuals was 4.35 kg, approximately double that of lean mass (1.71 kg) residuals. We divided the fat mass residuals by two in subsequent analyses, so that regression coefficients for fat mass, and lean mass that were of similar size reflected associations of similar strength (4).

Statistical analysis

Dealing with missing data:

To assess whether missing values of lung function at age 24 years (outcomes) can plausibly be imputed using information from earlier lung function measurements, linear correlation coefficients between SD-scores of lung function measured at different ages were examined (Table 2). A layout of missing data of investigated characteristics and lung function outcomes at ages 8, 15 and 24 years was depicted in Figure S1.

Among the study population ($N = 7{,}545$), there were small amounts of missing data for all stages of factors (Figure S1). This varied from none, e.g. for pre-term delivery and maternal age at delivery, to 38%, for smoking status at age 14 years. The skin prick test (SPT) was

performed for only a selected random sub-sample. Therefore, the amount of its missing data was relatively high, 27%.

To increase power and minimize selection bias, multiple imputation by chained equations was performed to impute missing data among our study population (5). In our imputation models, we included all lung function measures at ages 8, 15 and 24 years, exposures, potential confounders, and additional variables that might be predictive of missingness or of the missing values themselves. These included all characteristics of interest as presented in Table 1, smoking status at ages 16, 18, 20, 22 and 23 years, current asthma at ages 9, 11, 13, 14 and 15, immunoglobulin-E blood test and maternal ever caesarean section delivery. We generated 20 imputed datasets using 10 cycles of regression switching (5). These datasets were then used for the main analyses. Since estimates of associations given by the regression models are derived to be normally distributed, we aggregated the findings across the imputed datasets using the Rubin's rules (6) and obtained 95% confidence intervals for characteristics' association by using the pooled means and pooled standard errors of estimated coefficients. The Rubin's rules produced average of individual coefficients and total average of between-imputation and within-imputation variances as the combined estimates of size of associations and their variances respectively.

Relative importance (RI) of influences on each lung function outcome were assessed using the Lindeman, Merenda, and Gold (LMG) method (7). The LMG analyses the explained variance, R^2, of a considered model and estimates the incremental R^2, defined as partial contribution to the total R^2, attributed to the characteristic of interest. The incremental R^2

for each characteristic might be influenced by the order in which its variable was entered in a model, particularly when correlations among variables exist, i.e. it is larger when the variable entered first and lower when entered last. The LMG derives RI for each characteristic using its incremental R^2 by averaging over all possible orderings among the set of characteristics in the same stage as the characteristic of interest. Thus, the relative importance of factors included in a model are normalized to sum up to its R^2. The procedures for calculating RI were implemented using the `relaimpo' R package (8).

RESULTS:

Table S1 reports characteristics of the study population using the observed and multiple imputed datasets. The summary statistics for most characteristics were similar in imputed and observed data due to their large proportions of observed data ($\geq 90\%$) and the large size of study population ($N = 7{,}545$). For characteristics with lower proportions of observed data, including smoking status at age 14 years (62%), current asthma at age 7.5 years (73%), skin prick test at age 7.5 years (73%), air pollution during 1-7 years of age (81%) and second-hand smoke exposure during age 1-8 years, the differences in summary statistics between observed and imputed data were small, -0.6%, -2.3%, -0.01%, $0.06\ \mu g/m^3$, 1.7% respectively. Lung function, age and height distributions at 24 years clinic were similar in observed and imputed data, see Table S2. The medians and interquartile ranges (IQRs) of height and age were identical in both observed and imputed datasets.

We have reported the crude associations of the investigated characteristics with lung function measurements, only adjusted by sex, age and height, in Tables S10 – S13.

REFERENCES

1. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2013; 42: 111-127.
2. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377-381.
3. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN, Consortium RE. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95: 103208.
4. Granell R, Henderson AJ, Evans DM, Smith GD, Ness AR, Lewis S, Palmer TM, Sterne JA. Effects of BMI, fat mass, and lean mass on asthma in childhood: a Mendelian randomization study. *PLoS Med* 2014; 11: e1001669.
5. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011; 20: 40-49.
6. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996; 91: 473-489.
7. Sawrey WL. Introduction to Bivariate and Multivariate-Analysis - Lindeman,Rh, Merenda,Pf, Gold,Rz. *Contemp Psychol* 1981; 26: 374-374.
8. Gromping U. Relative importance for linear regression in R: The package relaimpo. *J Stat Softw* 2006; 17.

TABLES

***Table S1**. Characteristics of study population using the observed and imputed datasets.*

Stage	Factor	Observed data		Imputed data (N = 7545)
		N	% or Median	% or Median
Demographic, maternal and child characteristics	Overcrowding	7214	20.57	20.8
	Gas cooking	7222	53.96	53.95
	Rented housing	7020	14.09	14.98
	Single Mother	7356	18.28	18.54
	Low maternal education*	7225	57.49	57.99
	Maternal history of asthma or allergy	7110	47.33	47.27
	Family financial difficulties	7423	3.37	3.43
	Parity (>= 1 siblings)	7250	53.7	53.65
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2) †	6747	22.18	22.27
	Maternal age at delivery > 28 years (the median)	7528	53.21	53.21
	Birthweight (Kg) †	7437	3.44	3.44
	Pre-term delivery	7528	5.37	5.38
	Caesarean section	7357	10.51	10.5
	Maternal smoking during pregnancy	7146	20.86	21.05
	Maternal anxiety during pregnancy	6593	30.15	30.42
	Maternal gestational weight gain (Kg/week) †	6906	0.43	0.42
	Air pollution exposure during pregnancy (µg/m^3) †	6983	32.72	32.7
Postnatal characteristics	Maternal smoking during first year of age	6929	18.82	20.05
	Day care attendance during first year of age	6879	6.72	6.63
	Family pet ownership during first year of age	6938	69.07	69.27
	Maternal anxiety during first year of age	6893	21.44	21.93
	Air pollution during first year of age (µg/m^3) †	6932	31.38	31.38
	Breastfeeding during first 6 months	6978	81.76	81.23
	Early second-hand smoke exposure	7031	33.15	34.25
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	6333	62.92	61.14
	Air pollution during 1-7 years of age (µg/m^3) †	6140	73.14	73.07
	Lean mass at age 9 years (kg) †	5707	-0.12	-0.1
	Fat mass at age 9 years (kg/2) †	5707	-0.47	-0.37
	Current asthma at 7.5 years	5533	14.19	16.52
	Skin Prick Test at 7.5 years	5522	21.06	21.09
Adoles.	Smoking status at 14 years	4679	24.96	25.68
	Age at peak height velocity in puberty (years) †	7240	12.48	12.48
	Peak height velocity in puberty (cm/year) †	7240	8.88	8.89

Abbreviations: Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

†Continuous variables where medians were calculated.

***Table S2**. Summary statistics of lung function outcomes at age 24 years for the study population using the observed and imputed datasets.*

Variable	Observed data		Imputed data (N = 7545)
	N	Median (IQR)	Median (IQR)
Age (years)	3391	24.4 (23.9 to 25.1)	24.5 (23.9 to 25.1)
Height at lung function clinic (metres)	3371	1.7 (1.6 to 1.8)	1.7 (1.6 to 1.8)
Forced vital capacity, FVC (L)	2800	4.3 (3.7 to 5.2)	4.6 (3.9 to 5.5)
Forced expiratory volume in one second, FEV_1 (L)	2800	3.7 (3.2 to 4.4)	3.9 (3.3 to 4.6)
FEV_1/FVC (%)	2800	85.9 (82.0 to 89.5)	85.4 (81.0 to 89.4)
Forced expiratory flow, midexpiratory phase (L/s)	2800	4.1 (3.4 to 4.8)	4.2 (3.5 to 5.0)

Abbreviations: IQR= interquartile range ; L=litre ; s=second

Table S3. Pairwise linear correlation coefficients between SD scores (adjusted for sex, age and height) of lung function measurements at different timepoints.

	FVC		FEV_1		FEF_{25-75}	
	15 years	**24 years**	**15 years**	**24 years**	**15 years**	**24 years**
8 years	0.399	0.504	0.372	0.508	0.424	0.513
15 years		0.475		0.455		0.484

Table S4. Comparisons of the characteristics of study population with the original ALSPAC population.

Stage	Factor	Study population (N = 7,545)		Original ALSPAC population (N= 13,798)	
		N	% or Median	N	% or Median
Demographic, maternal and child characteristics	Overcrowding	7214	20.57	12645	27.01
	Gas cooking	7222	53.96	12731	52.63
	Rented housing	7020	14.09	12202	22.68
	Single Mother	7356	18.28	12980	24.38
	Low maternal education*	7225	57.49	12261	64.62
	Maternal history of asthma or allergy	7110	47.33	12047	45.56
	Family financial difficulties	7423	3.37	12807	5.36
	Parity (>= 1 siblings)	7250	53.7	12765	55.22
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2) †	6747	22.18	11374	22.18
	Maternal age at delivery > 28 years (the median)	7528	53.21	13798	45.14
	Birthweight (Kg) †	7437	3.44	13622	3.42
	Pre-term delivery	7528	5.37	13798	5.55
	Caesarean section	7357	10.51	8116	17.58
	Maternal smoking during pregnancy	7146	20.86	12171	29.52
	Maternal anxiety during pregnancy	6593	30.15	11120	34.07
	Maternal gestational weight gain (Kg/week) †	6906	0.43	12438	0.42
	Air pollution exposure during pregnancy (µg/m^3) †	6983	32.72	12638	32.67
Postnatal characteristics	Maternal smoking during first year of age	6929	18.82	11073	24.2
	Day care attendance during first year of age	6879	6.72	10825	6
	Family pet ownership during first year of age	6938	69.07	10941	69.42
	Maternal anxiety during first year of age	6893	21.44	11023	22.42
	Air pollution during first year of age (µg/m^3) †	6932	31.38	12493	31.36
	Breastfeeding during first 6 months	6978	81.76	11196	75.8
	Early second-hand smoke exposure	7031	33.15	11328	38.06
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	6333	62.92	9804	72.23
	Air pollution during 1-7 years of age (µg/m^3) †	6140	73.14	10896	73.12
	Lean mass at age 9 years (kg) †	5707	-0.12	6339	-0.11
	Fat mass at age 9 years (kg/2) †	5707	-0.47	6339	-0.46
	Current asthma at 7.5 years	5533	14.19	7218	14.13
	Skin Prick Test at 7.5 years	5522	21.06	6438	20.69
Adoles.	Smoking status at 14 years	4679	24.96	5586	25.67
	Age at peak height velocity in puberty (years) †	7240	12.48	9032	12.5
	Peak height velocity in puberty (cm/year) †	7240	8.88	9032	8.91

Considered ALSPAC population = Singleton and one twin birth alive at age 1 year of the Avon Longitudinal Study of Parents and Children.

Abbreviations: Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

†Continuous variables where medians were calculated.

Table S5. Comparisons of the characteristics of participants in the study population with and without the lung function measurements at age 24 years.

Stage	Factor	With Lung function measurements at age 24 years (N= 2,800)		Without lung function measurements at age 24 years (N= 4,745)	
		N	% or Median	N	% or Median
Demographic, maternal and child characteristics	Overcrowding	2692	17.27	4522	22.53
	Gas cooking	2690	54.68	4532	53.53
	Rented housing	2624	10.02	4396	16.52
	Single Mother	2745	15.63	4611	19.87
	Low maternal education*	2711	50.02	4514	61.98
	Maternal history of asthma or allergy	2660	49.32	4450	46.13
	Family financial difficulties	2759	2.79	4664	3.71
	Parity (>= 1 siblings)	2710	53.1	4540	54.05
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2) †	2543	21.97	4204	22.36
	Maternal age at delivery > 28 years (the median)	2794	58.2	4734	50.27
	Birthweight (Kg) †	2758	3.43	4679	3.45
	Pre-term delivery	2794	5.05	4734	5.56
	Caesarean section	2740	10.88	4617	10.29
	Maternal smoking during pregnancy	2666	16.69	4480	23.35
	Maternal anxiety during pregnancy	2465	28.72	4128	31.01
	Maternal gestational weight gain (Kg/week) †	2558	0.43	4348	0.42
	Air pollution exposure during pregnancy (µg/m^3) †	2591	32.76	4392	32.7
Postnatal characteristics	Maternal smoking during first year of age	2599	15.04	4330	21.09
	Day care attendance during first year of age	2585	7.58	4294	6.19
	Family pet ownership during first year of age	2605	68.25	4333	69.56
	Maternal anxiety during first year of age	2587	20.6	4306	21.95
	Air pollution during first year of age (µg/m^3) †	2561	31.41	4371	31.35
	Breastfeeding during first 6 months	2625	85.56	4353	79.46
	Early second-hand smoke exposure	2637	28.97	4394	35.66
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	2378	55.38	3955	67.46
	Air pollution during 1-7 years of age (µg/m^3) †	2219	73.09	3921	73.16
	Lean mass at age 9 years (kg) †	2132	-0.14	3575	-0.11
	Fat mass at age 9 years (kg/2) †	2132	-0.5	3575	-0.46
	Current asthma at 7.5 years	2119	13.17	3414	14.82
	Skin Prick Test at 7.5 years	2068	20.94	3454	21.13
Adoles.	Smoking status at 14 years	2128	23.03	2551	26.58
	Age at peak height velocity in puberty (years) †	2693	12.24	4547	12.69
	Peak height velocity in puberty (cm/year) †	2693	8.6	4547	9.06

Abbreviations: Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

†Continuous variables where medians were calculated.

Table S6. Adjusted association and relative importance of early-life characteristics with SD scores (adjusted for sex, age and height) of FVC measurements (non-imputed) at age 24 years (N=2800).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.084 (-0.191 to 0.023)	0.126	0.64	0.078	0.40
	Gas cooking	0.016 (-0.060 to 0.091)	0.683		0.011	
	Rented housing	-0.080 (-0.225 to 0.065)	0.280		0.073	
	Single Mother	0.077 (-0.035 to 0.189)	0.178		0.031	
	Low maternal education	-0.004 (-0.080 to 0.073)	0.921		0.004	
	Maternal history of asthma or allergy	0.029 (-0.047 to 0.106)	0.448		0.020	
	Family financial difficulties	-0.098 (-0.329 to 0.132)	0.404		0.028	
	Parity (>= 1 siblings)	0.139 (0.062 to 0.217)	4×10^{-4}		0.398	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.017 (0.006 to 0.028)	0.003	1.56	0.413	1.82
	Maternal age at delivery > 28 years (the median)	0.086 (0.008 to 0.164)	0.030		0.141	
	Birthweight (Kg)	0.163 (0.080 to 0.247)	1×10^{-4}		0.561	
	Pre-term delivery	0.144 (-0.046 to 0.334)	0.139		0.042	
	Caesarean section	0.019 (-0.103 to 0.141)	0.759		0.008	
	Maternal smoking during pregnancy	0.174 (0.070 to 0.277)	0.001		0.309	
	Maternal anxiety during pregnancy	-0.034 (-0.120 to 0.053)	0.449		0.015	
	Maternal gestational weight gain (Kg/week)	0.066 (-0.222 to 0.355)	0.653		0.025	
	Air pollution exposure during pregnancy (µg/m^3)	-0.007 (-0.019 to 0.005)	0.261		0.049	
Postnatal characteristics	Maternal smoking during first year of age	-0.096 (-0.263 to 0.071)	0.261	0.38	0.063	1.82
	Day care attendance during first year of age	0.107 (-0.039 to 0.252)	0.150		0.084	
	Family pet ownership during first year of age	-0.056 (-0.142 to 0.029)	0.197		0.073	
	Maternal anxiety during first year of age	0.001 (-0.092 to 0.095)	0.977		0.002	
	Air pollution during first year of age (µg/m^3)	-0.010 (-0.025 to 0.005)	0.200		0.059	
	Breastfeeding during first 6 months	0.085 (-0.027 to 0.196)	0.137		0.098	
	Early second-hand smoke exposure	-0.001 (-0.090 to 0.088)	0.978		0.005	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	0.018 (-0.065 to 0.101)	0.669	7.93	0.014	9.69
	Air pollution during 1-7 years of age (µg/m^3)	-0.008 (-0.018 to 0.002)	0.098		0.131	
	Lean mass at age 9 years (SD-score)	0.178 (0.153 to 0.203)	1×10^{-16}		7.115	
	Fat mass at age 9 years (SD-score)	-0.056 (-0.076 to -0.037)	1×10^{-8}		0.621	
	Current asthma at 7.5 years	0.005 (-0.109 to 0.120)	0.927		0.014	
	Skin Prick Test at 7.5 years	0.047 (-0.067 to 0.161)	0.418		0.035	
Adoles.	Smoking status at 14 years	0.124 (0.032 to 0.216)	0.009	0.29	0.256	9.95
	Age at peak height velocity in puberty (years)	0.014 (-0.018 to 0.047)	0.387		0.021	
	Peak height velocity in puberty (cm/year)	0.007 (-0.021 to 0.035)	0.612		0.012	

Abbreviations: Adoles. = adolescence characteristics; FVC = forced vital capacity; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables (with P-value ≤ 0.10) from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table S7. Adjusted association and relative importance of early-life characteristics with SD scores (adjusted for sex, age and height) of FEV_1 measurements (non-imputed) at age 24 years (N=2800).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.088 (-0.194 to 0.019)	0.108	1.10	0.102	0.70
	Gas cooking	0.027 (-0.049 to 0.102)	0.485		0.029	
	Rented housing	-0.105 (-0.250 to 0.040)	0.157		0.137	
	Single Mother	0.088 (-0.024 to 0.200)	0.122		0.036	
	Low maternal education	-0.050 (-0.126 to 0.027)	0.204		0.084	
	Maternal history of asthma or allergy	0.020 (-0.056 to 0.097)	0.605		0.011	
	Family financial difficulties	-0.222 (-0.452 to 0.008)	0.058		0.143	
	Parity (>= 1 siblings)	0.165 (0.088 to 0.242)	3×10^{-5}		0.556	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.004 (-0.007 to 0.016)	0.465	1.12	0.052	1.60
	Maternal age at delivery > 28 years (the median)	0.079 (0.001 to 0.156)	0.048		0.133	
	Birthweight (Kg)	0.186 (0.102 to 0.270)	1×10^{-5}		0.771	
	Pre-term delivery	0.041 (-0.149 to 0.232)	0.671		0.063	
	Caesarean section	-0.016 (-0.137 to 0.106)	0.799		0.006	
	Maternal smoking during pregnancy	0.084 (-0.020 to 0.188)	0.115		0.054	
	Maternal anxiety during pregnancy	-0.039 (-0.126 to 0.048)	0.382		0.027	
	Maternal gestational weight gain (Kg/week)	-0.047 (-0.337 to 0.242)	0.749		0.014	
	Air pollution exposure during pregnancy ($\mu g/m^3$)	-0.002 (-0.014 to 0.011)	0.801		0.004	
Postnatal characteristics	Maternal smoking during first year of age	-0.003 (-0.117 to 0.111)	0.957	0.11	0.003	1.60
	Day care attendance during first year of age	0.067 (-0.077 to 0.211)	0.360		0.034	
	Family pet ownership during first year of age	-0.013 (-0.097 to 0.071)	0.753		0.006	
	Maternal anxiety during first year of age	0.042 (-0.053 to 0.137)	0.389		0.031	
	Air pollution during first year of age ($\mu g/m^3$)	-0.005 (-0.020 to 0.009)	0.487		0.018	
	Breastfeeding during first 6 months	0.021 (-0.091 to 0.134)	0.709		0.010	
	Early second-hand smoke exposure	0.011 (-0.078 to 0.099)	0.811		0.003	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	0.045 (-0.037 to 0.127)	0.286	5.81	0.057	7.28
	Air pollution during 1-7 years of age ($\mu g/m^3$)	-0.005 (-0.015 to 0.005)	0.330		0.047	
	Lean mass at age 9 years (SD-score)	0.150 (0.124 to 0.176)	1×10^{-16}		4.983	
	Fat mass at age 9 years (SD-score)	-0.052 (-0.071 to -0.032)	2×10^{-7}		0.573	
	Current asthma at 7.5 years	-0.101 (-0.220 to 0.017)	0.096		0.121	
	Skin Prick Test at 7.5 years	0.035 (-0.083 to 0.152)	0.564		0.024	
Adoles.	Smoking status at 14 years	0.072 (-0.024 to 0.169)	0.141	0.13	0.092	7.28
	Age at peak height velocity in puberty (years)	0.018 (-0.015 to 0.050)	0.286		0.032	
	Peak height velocity in puberty (cm/year)	-0.006 (-0.034 to 0.022)	0.683		0.006	

Abbreviations: Adoles. = adolescence characteristics; FEV_1 = forced expiratory volume in one second; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables (with P-value ≤ 0.10) from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table S8. Adjusted association and relative importance of early-life characteristics with SD scores (adjusted for sex, age and height) of FEV_1/FVC measurements (non-imputed) at age 24 years (N=2800).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.017 (-0.125 to 0.091)	0.755	0.46	0.015	0.33
	Gas cooking	0.006 (-0.071 to 0.083)	0.883		0.005	
	Rented housing	-0.047 (-0.187 to 0.092)	0.504		0.046	
	Single Mother	0.007 (-0.105 to 0.118)	0.908		0.008	
	Low maternal education	-0.080 (-0.157 to -0.004)	0.040		0.173	
	Maternal history of asthma or allergy	-0.018 (-0.094 to 0.058)	0.642		0.008	
	Family financial difficulties	-0.228 (-0.460 to 0.003)	0.053		0.159	
	Parity (>= 1 siblings)	0.047 (-0.030 to 0.124)	0.232		0.046	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	-0.019 (-0.030 to -0.008)	0.001	1.23	0.396	1.31
	Maternal age at delivery > 28 years (the median)	-0.006 (-0.085 to 0.072)	0.875		0.001	
	Birthweight (Kg)	0.026 (-0.057 to 0.110)	0.538		0.056	
	Pre-term delivery	-0.220 (-0.411 to -0.029)	0.024		0.238	
	Caesarean section	-0.077 (-0.199 to 0.044)	0.210		0.090	
	Maternal smoking during pregnancy	-0.161 (-0.269 to -0.053)	0.003		0.340	
	Maternal anxiety during pregnancy	-0.007 (-0.097 to 0.083)	0.879		0.015	
	Maternal gestational weight gain (Kg/week)	-0.182 (-0.470 to 0.106)	0.215		0.032	
	Air pollution exposure during pregnancy (µg/m^3)	0.007 (-0.005 to 0.020)	0.248		0.057	
Postnatal characteristics	Maternal smoking during first year of age	-0.056 (-0.228 to 0.116)	0.523	0.22	0.020	1.31
	Day care attendance during first year of age	-0.059 (-0.204 to 0.087)	0.429		0.025	
	Family pet ownership during first year of age	0.042 (-0.041 to 0.125)	0.318		0.039	
	Maternal anxiety during first year of age	0.060 (-0.037 to 0.156)	0.225		0.058	
	Air pollution during first year of age (µg/m^3)	0.002 (-0.013 to 0.017)	0.803		0.003	
	Breastfeeding during first 6 months	-0.076 (-0.189 to 0.037)	0.189		0.071	
	Early second-hand smoke exposure	-0.004 (-0.094 to 0.086)	0.934		0.002	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.004 (-0.090 to 0.083)	0.930	1.34	0.006	2.55
	Air pollution during 1-7 years of age (µg/m^3)	0.004 (-0.006 to 0.014)	0.437		0.028	
	Lean mass at age 9 years (SD-score)	-0.052 (-0.078 to -0.025)	1×10^{-4}		0.707	
	Fat mass at age 9 years (SD-score)	0.001 (-0.021 to 0.023)	0.939		0.041	
	Current asthma at 7.5 years	-0.199 (-0.325 to -0.072)	0.003		0.536	
	Skin Prick Test at 7.5 years	0.007 (-0.101 to 0.114)	0.904		0.026	
Adoles.	Smoking status at 14 years	-0.087 (-0.194 to 0.019)	0.109	0.22	0.151	2.55
	Age at peak height velocity in puberty (years)	0.013 (-0.020 to 0.045)	0.453		0.024	
	Peak height velocity in puberty (cm/year)	-0.018 (-0.047 to 0.010)	0.210		0.049	

Abbreviations: Adoles. = adolescence characteristics; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity ; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table S9. Adjusted association and relative importance of early-life characteristics with SD scores (adjusted for sex, age and height) of FEF_{25-75} measurements (non-imputed) at age 24 years (N=2800).

Stage	Factor	Adjusted* difference in SD scores of FVC (95% CI)	P-value	Inc. R^2 (%)	RI(%)	Retained R^2
Demographic, maternal and child characteristics	Overcrowding	-0.016 (-0.124 to 0.093)	0.775	0.59	0.009	0.41
	Gas cooking	0.020 (-0.056 to 0.097)	0.607		0.016	
	Rented housing	-0.048 (-0.190 to 0.094)	0.508		0.042	
	Single Mother	0.031 (-0.081 to 0.143)	0.589		0.007	
	Low maternal education	-0.059 (-0.137 to 0.018)	0.131		0.099	
	Maternal history of asthma or allergy	-0.006 (-0.083 to 0.071)	0.879		0.003	
	Family financial difficulties	-0.267 (-0.497 to -0.037)	0.023		0.199	
	Parity (>= 1 siblings)	0.099 (0.022 to 0.176)	0.012		0.212	
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.000 (-0.012 to 0.011)	0.959	0.87	0.004	1.02
	Maternal age at delivery > 28 years (the median)	0.038 (-0.040 to 0.116)	0.342		0.039	
	Birthweight (Kg)	0.089 (0.005 to 0.173)	0.039		0.309	
	Pre-term delivery	-0.206 (-0.397 to -0.015)	0.034		0.296	
	Caesarean section	-0.073 (-0.194 to 0.048)	0.239		0.065	
	Maternal smoking during pregnancy	-0.081 (-0.186 to 0.024)	0.132		0.105	
	Maternal anxiety during pregnancy	0.014 (-0.074 to 0.103)	0.749		0.006	
	Maternal gestational weight gain (Kg/week)	-0.139 (-0.428 to 0.150)	0.347		0.021	
	Air pollution exposure during pregnancy (µg/m^3)	0.005 (-0.008 to 0.017)	0.441		0.027	
Postnatal characteristics	Maternal smoking during first year of age	-0.136 (-0.304 to 0.032)	0.112	0.25	0.099	1.02
	Day care attendance during first year of age	0.038 (-0.107 to 0.183)	0.606		0.012	
	Family pet ownership during first year of age	0.051 (-0.032 to 0.134)	0.231		0.054	
	Maternal anxiety during first year of age	0.052 (-0.046 to 0.151)	0.298		0.046	
	Air pollution during first year of age (µg/m^3)	0.001 (-0.014 to 0.016)	0.900		0.002	
	Breastfeeding during first 6 months	-0.051 (-0.163 to 0.061)	0.373		0.034	
	Early second-hand smoke exposure	-0.004 (-0.093 to 0.085)	0.930		0.002	
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.020 (-0.107 to 0.067)	0.650	1.30	0.014	2.24
	Air pollution during 1-7 years of age (µg/m^3)	0.002 (-0.008 to 0.012)	0.690		0.007	
	Lean mass at age 9 years (SD-score)	0.047 (0.020 to 0.073)	0.001		0.509	
	Fat mass at age 9 years (SD-score)	-0.008 (-0.029 to 0.013)	0.448		0.024	
	Current asthma at 7.5 years	-0.243 (-0.362 to -0.124)	8×10^{-5}		0.716	
	Skin Prick Test at 7.5 years	0.053 (-0.051 to 0.158)	0.319		0.029	
Adoles	Smoking status at 14 years	-0.047 (-0.151 to 0.057)	0.381	0.09	0.051	2.24
	Age at peak height velocity in puberty (years)	0.013 (-0.020 to 0.046)	0.437		0.024	
	Peak height velocity in puberty (cm/year)	-0.009 (-0.037 to 0.019)	0.535		0.012	

Abbreviations: Adoles. = adolescence characteristics; FEF_{25-75} = forced expiratory flow, midexpiratory phase; Inc. R^2 = incremental R^2 for variables in the corresponding stage; RI = relative importance (proportion of explained variation in lung function attributed to each variable – averaging over all its possible orderings among characteristics in same stage); Retained R^2 = Total R^2 for retained variables (with P-value ≤ 0.10) from previous stages and corresponding stage, Kg = kilogram; m = metre; µg = microgram; cm = centimetre

* Adjusted for all variables in same stage in addition to characteristics from previous stages that yield P-value ≤ 0.10.

Table S10. Crude associations of early-life characteristics with SD scores of FVC (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Difference in SD scores of FVC (95% CI)	P-value
Demographic, maternal and child characteristics	Overcrowding	-0.034 (-0.114 to 0.046)	0.402
	Gas cooking	-0.009 (-0.077 to 0.060)	0.806
	Rented housing	-0.019 (-0.144 to 0.105)	0.762
	Single Mother	0.012 (-0.069 to 0.094)	0.769
	Low maternal education*	-0.024 (-0.083 to 0.034)	0.417
	Maternal history of asthma or allergy	0.027 (-0.041 to 0.095)	0.442
	Family financial difficulties	-0.127 (-0.377 to 0.123)	0.326
	Parity (>= 1 siblings)	0.102 (0.033 to 0.170)	0.005
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.023 (0.012 to 0.033)	0.000
	Maternal age at delivery > 28 years (the median)	0.073 (0.004 to 0.141)	0.043
	Birthweight (Kg)	0.146 (0.083 to 0.208)	0.000
	Pre-term delivery	-0.025 (-0.198 to 0.148)	0.778
	Caesarean section	0.020 (-0.103 to 0.142)	0.754
	Maternal smoking during pregnancy	0.136 (0.032 to 0.240)	0.015
	Maternal anxiety during pregnancy	-0.011 (-0.093 to 0.070)	0.786
	Maternal gestational weight gain (Kg/week)	0.040 (-0.199 to 0.280)	0.743
	Air pollution exposure during pregnancy (µg/m^3)	-0.009 (-0.021 to 0.002)	0.111
Postnatal characteristics	Maternal smoking during first year of age	0.065 (-0.038 to 0.168)	0.225
	Day care attendance during first year of age	0.074 (-0.058 to 0.206)	0.277
	Family pet ownership during first year of age	-0.025 (-0.092 to 0.041)	0.456
	Maternal anxiety during first year of age	0.049 (-0.041 to 0.139)	0.291
	Air pollution during first year of age (µg/m^3)	-0.010 (-0.022 to 0.003)	0.147
	Breastfeeding during first 6 months	0.002 (-0.095 to 0.099)	0.969
	Early second-hand smoke exposure	0.045 (-0.026 to 0.117)	0.220
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	0.050 (-0.011 to 0.111)	0.109
	Air pollution during 1-7 years of age (µg/m^3)	-0.011 (-0.020 to -0.002)	0.017
	Lean mass at age 9 years (kg) †	0.169 (0.151 to 0.188)	0.000
	Fat mass at age 9 years (kg/2) †	0.007 (-0.012 to 0.025)	0.475
	Current asthma at 7.5 years	0.092 (-0.029 to 0.214)	0.145
	Skin Prick Test at 7.5 years	0.008 (-0.089 to 0.105)	0.874
Adoles.	Smoking status at 14 years	0.163 (0.067 to 0.258)	0.002
	Age at peak height velocity in puberty (years)	-0.013 (-0.035 to 0.009)	0.248
	Peak height velocity in puberty (cm/year)	0.011 (-0.010 to 0.033)	0.290

Abbreviations: FVC = forced vital capacity; Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

Table S11. Crude associations of early-life characteristics with SD scores of FEV_1 (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Difference in SD scores of FEV_1 (95% CI)	P-value
Demographic, maternal and child characteristics	Overcrowding	-0.074 (-0.157 to 0.009)	0.084
	Gas cooking	-0.008 (-0.076 to 0.061)	0.828
	Rented housing	-0.103 (-0.235 to 0.029)	0.136
	Single Mother	-0.018 (-0.108 to 0.072)	0.695
	Low maternal education*	-0.081 (-0.147 to -0.016)	0.018
	Maternal history of asthma or allergy	0.021 (-0.050 to 0.092)	0.564
	Family financial difficulties	-0.252 (-0.461 to -0.042)	0.023
	Parity (>= 1 siblings)	0.130 (0.060 to 0.200)	0.001
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.009 (0.000 to 0.018)	0.068
	Maternal age at delivery > 28 years (the median)	0.111 (0.051 to 0.171)	0.000
	Birthweight (Kg)	0.162 (0.103 to 0.221)	0.000
	Pre-term delivery	-0.169 (-0.324 to -0.014)	0.037
	Caesarean section	-0.043 (-0.161 to 0.075)	0.479
	Maternal smoking during pregnancy	0.008 (-0.102 to 0.119)	0.881
	Maternal anxiety during pregnancy	-0.039 (-0.129 to 0.052)	0.408
	Maternal gestational weight gain (Kg/week)	-0.004 (-0.239 to 0.231)	0.971
	Air pollution exposure during pregnancy ($\mu g/m^3$)	-0.006 (-0.016 to 0.005)	0.299
Postnatal characteristics	Maternal smoking during first year of age	-0.055 (-0.157 to 0.048)	0.303
	Day care attendance during first year of age	0.075 (-0.072 to 0.223)	0.322
	Family pet ownership during first year of age	-0.031 (-0.098 to 0.037)	0.379
	Maternal anxiety during first year of age	0.047 (-0.033 to 0.126)	0.253
	Air pollution during first year of age ($\mu g/m^3$)	-0.009 (-0.021 to 0.004)	0.169
	Breastfeeding during first 6 months	-0.006 (-0.108 to 0.096)	0.907
	Early second-hand smoke exposure	-0.023 (-0.104 to 0.059)	0.588
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.025 (-0.089 to 0.040)	0.458
	Air pollution during 1-7 years of age ($\mu g/m^3$)	-0.009 (-0.019 to 0.001)	0.074
	Lean mass at age 9 years (kg) †	0.124 (0.105 to 0.144)	0.000
	Fat mass at age 9 years (kg/2) †	-0.009 (-0.025 to 0.007)	0.277
	Current asthma at 7.5 years	-0.064 (-0.162 to 0.033)	0.203
	Skin Prick Test at 7.5 years	-0.001 (-0.103 to 0.100)	0.977
Adoles.	Smoking status at 14 years	0.094 (0.008 to 0.181)	0.038
	Age at peak height velocity in puberty (years)	0.003 (-0.021 to 0.027)	0.800
	Peak height velocity in puberty (cm/year)	0.000 (-0.022 to 0.022)	0.998

Abbreviations: FEV_1 = forced expiratory volume in one second; Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

Table S12. Crude associations of early-life characteristics with SD scores of FEV_1/FVC (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Difference in SD scores of FEV_1/FVC (95% CI)	P-value
Demographic, maternal and child characteristics	Overcrowding	-0.068 (-0.164 to 0.029)	0.175
	Gas cooking	-0.001 (-0.078 to 0.076)	0.978
	Rented housing	-0.140 (-0.248 to -0.031)	0.015
	Single Mother	-0.052 (-0.153 to 0.049)	0.323
	Low maternal education*	-0.095 (-0.156 to -0.034)	0.003
	Maternal history of asthma or allergy	-0.006 (-0.075 to 0.064)	0.873
	Family financial difficulties	-0.226 (-0.408 to -0.044)	0.018
	Parity (>= 1 siblings)	0.051 (-0.019 to 0.121)	0.157
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	-0.020 (-0.030 to -0.010)	0.000
	Maternal age at delivery > 28 years (the median)	0.068 (-0.004 to 0.140)	0.069
	Birthweight (Kg)	0.037 (-0.031 to 0.106)	0.291
	Pre-term delivery	-0.250 (-0.404 to -0.096)	0.002
	Caesarean section	-0.104 (-0.222 to 0.014)	0.089
	Maternal smoking during pregnancy	-0.198 (-0.296 to -0.100)	0.000
	Maternal anxiety during pregnancy	-0.042 (-0.137 to 0.053)	0.397
	Maternal gestational weight gain (Kg/week)	-0.067 (-0.305 to 0.172)	0.587
	Air pollution exposure during pregnancy ($\mu g/m^3$)	0.005 (-0.006 to 0.016)	0.404
Postnatal characteristics	Maternal smoking during first year of age	-0.189 (-0.298 to -0.081)	0.002
	Day care attendance during first year of age	0.009 (-0.130 to 0.149)	0.897
	Family pet ownership during first year of age	-0.013 (-0.079 to 0.054)	0.703
	Maternal anxiety during first year of age	-0.005 (-0.077 to 0.066)	0.880
	Air pollution during first year of age ($\mu g/m^3$)	0.000 (-0.015 to 0.015)	0.973
	Breastfeeding during first 6 months	-0.007 (-0.127 to 0.114)	0.911
	Early second-hand smoke exposure	-0.106 (-0.183 to -0.029)	0.010
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.118 (-0.182 to -0.054)	0.001
	Air pollution during 1-7 years of age ($\mu g/m^3$)	0.002 (-0.007 to 0.012)	0.640
	Lean mass at age 9 years (kg) †	-0.063 (-0.084 to -0.042)	0.000
	Fat mass at age 9 years (kg/2) †	-0.027 (-0.046 to -0.008)	0.009
	Current asthma at 7.5 years	-0.238 (-0.349 to -0.127)	0.000
	Skin Prick Test at 7.5 years	-0.003 (-0.097 to 0.091)	0.952
Adoles.	Smoking status at 14 years	-0.101 (-0.188 to -0.014)	0.027
	Age at peak height velocity in puberty (years)	0.024 (0.002 to 0.046)	0.031
	Peak height velocity in puberty (cm/year)	-0.016 (-0.035 to 0.004)	0.115

Abbreviations: FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

Table S13. Crude associations of early-life characteristics with SD scores of FEF_{25-75} (scores adjusted for sex, age and height) at age 24 years (N=7545).

Stage	Factor	Difference in SD scores of FEF_{25-75} (95% CI)	P-value
Demographic, maternal and child characteristics	Overcrowding	-0.045 (-0.143 to 0.054)	0.378
	Gas cooking	-0.010 (-0.087 to 0.067)	0.802
	Rented housing	-0.102 (-0.201 to -0.003)	0.049
	Single Mother	-0.052 (-0.146 to 0.043)	0.290
	Low maternal education*	-0.084 (-0.143 to -0.026)	0.006
	Maternal history of asthma or allergy	0.007 (-0.061 to 0.076)	0.834
	Family financial difficulties	-0.252 (-0.424 to -0.079)	0.005
	Parity (>= 1 siblings)	0.090 (0.020 to 0.160)	0.014
Perinatal characteristics	Maternal perinatal body mass index (Kg/m^2)	0.001 (-0.009 to 0.011)	0.843
	Maternal age at delivery > 28 years (the median)	0.097 (0.031 to 0.163)	0.005
	Birthweight (Kg)	0.112 (0.056 to 0.168)	0.000
	Pre-term delivery	-0.302 (-0.470 to -0.135)	0.001
	Caesarean section	-0.102 (-0.215 to 0.012)	0.085
	Maternal smoking during pregnancy	-0.123 (-0.237 to -0.008)	0.044
	Maternal anxiety during pregnancy	-0.010 (-0.101 to 0.081)	0.825
	Maternal gestational weight gain (Kg/week)	-0.086 (-0.332 to 0.161)	0.499
	Air pollution exposure during pregnancy ($\mu g/m^3$)	-0.001 (-0.012 to 0.010)	0.858
Postnatal characteristics	Maternal smoking during first year of age	-0.160 (-0.271 to -0.048)	0.008
	Day care attendance during first year of age	0.068 (-0.060 to 0.195)	0.301
	Family pet ownership during first year of age	0.001 (-0.067 to 0.068)	0.982
	Maternal anxiety during first year of age	0.006 (-0.065 to 0.078)	0.866
	Air pollution during first year of age ($\mu g/m^3$)	-0.005 (-0.018 to 0.008)	0.434
	Breastfeeding during first 6 months	-0.035 (-0.152 to 0.081)	0.553
	Early second-hand smoke exposure	-0.069 (-0.151 to 0.013)	0.108
Early-Childhood characteristics	Second-hand smoke exposure during age 1-8 y	-0.103 (-0.171 to -0.035)	0.004
	Air pollution during 1-7 years of age ($\mu g/m^3$)	-0.003 (-0.013 to 0.006)	0.472
	Lean mass at age 9 years (kg) †	0.031 (0.010 to 0.052)	0.007
	Fat mass at age 9 years (kg/2) †	-0.002 (-0.020 to 0.016)	0.798
	Current asthma at 7.5 years	-0.229 (-0.317 to -0.142)	0.000
	Skin Prick Test at 7.5 years	0.003 (-0.099 to 0.105)	0.955
Adoles.	Smoking status at 14 years	-0.048 (-0.131 to 0.035)	0.262
	Age at peak height velocity in puberty (years)	0.007 (-0.015 to 0.029)	0.545
	Peak height velocity in puberty (cm/year)	-0.011 (-0.031 to 0.009)	0.293

Abbreviations: FEF_{25-75} = forced expiratory flow, midexpiratory phase; Adoles. = adolescence; Kg = kilogram; m = metre; µg = microgram; cm = centimetre.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower, see **Error! Reference source not found.**.

FIGURES

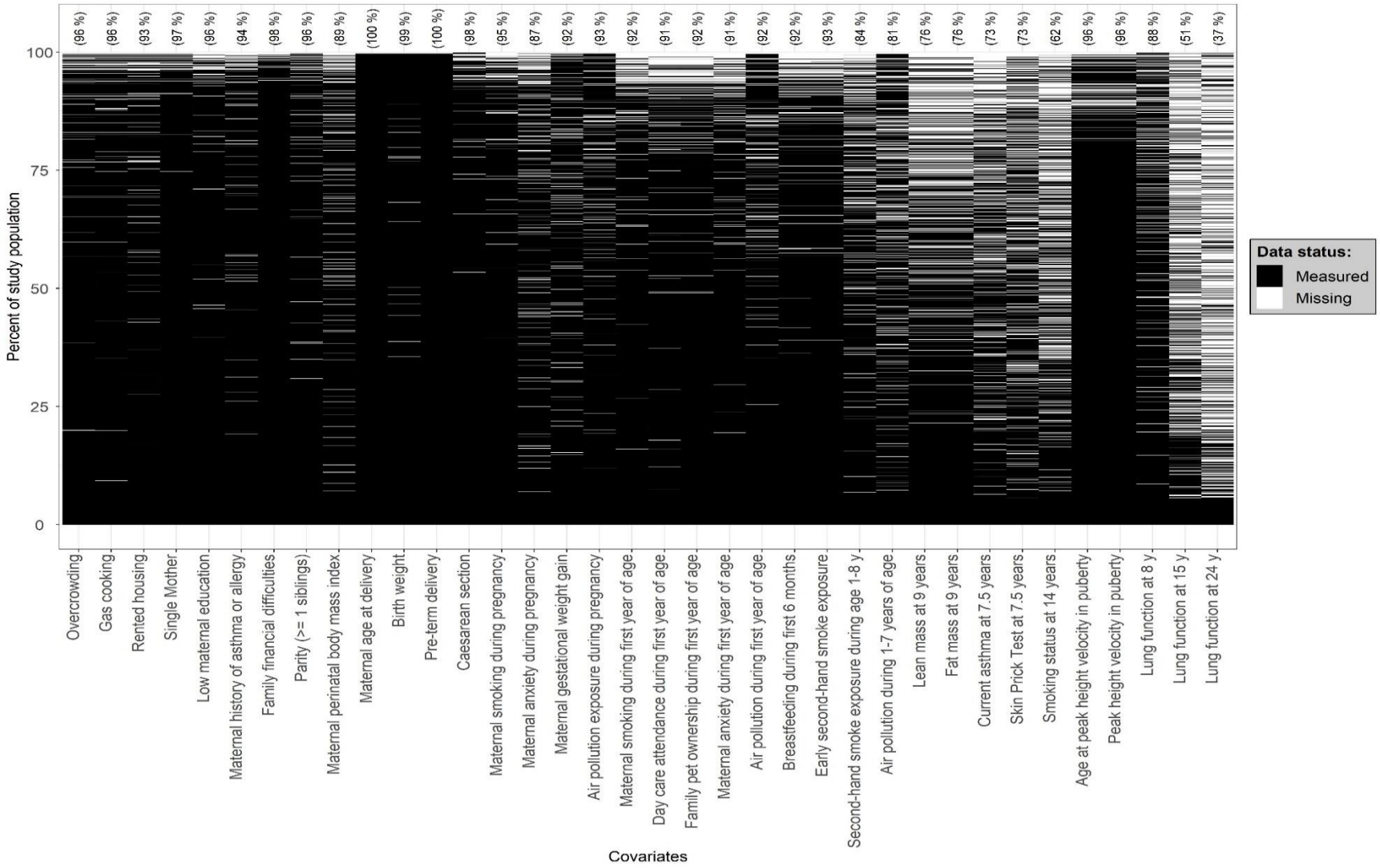

Figure S1. Layout of missing data among study population (N=7,545), with percent of observed data shown above corresponding characteristic's column

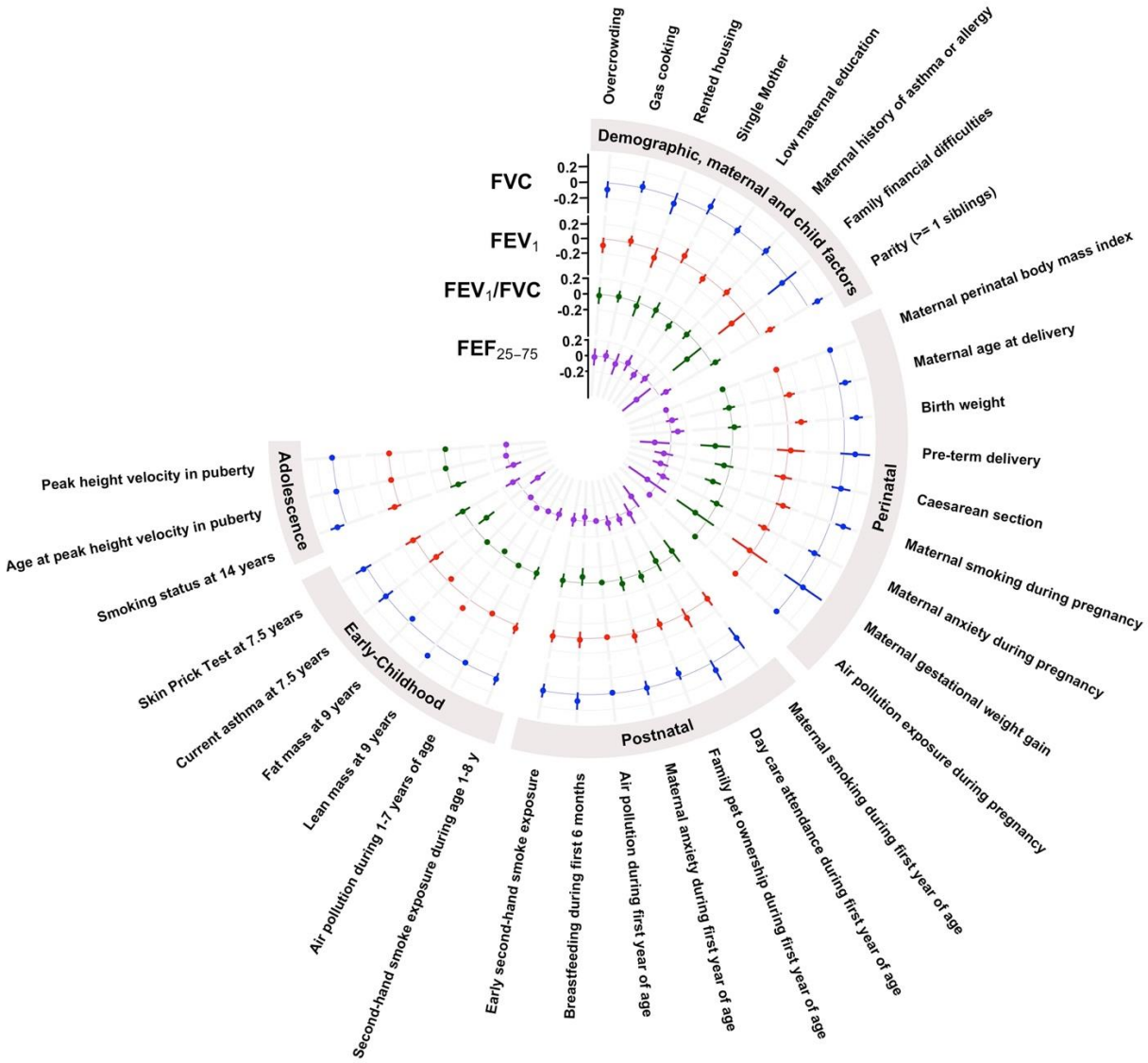

Figure S2. Circular plot of characteristics' association (point estimates and 95% confidence intervals) with measured (non-imputed) lung function parameters at age 24 years (N=2800). The raw data used for generating this plot are reported in Tables S6-S9.

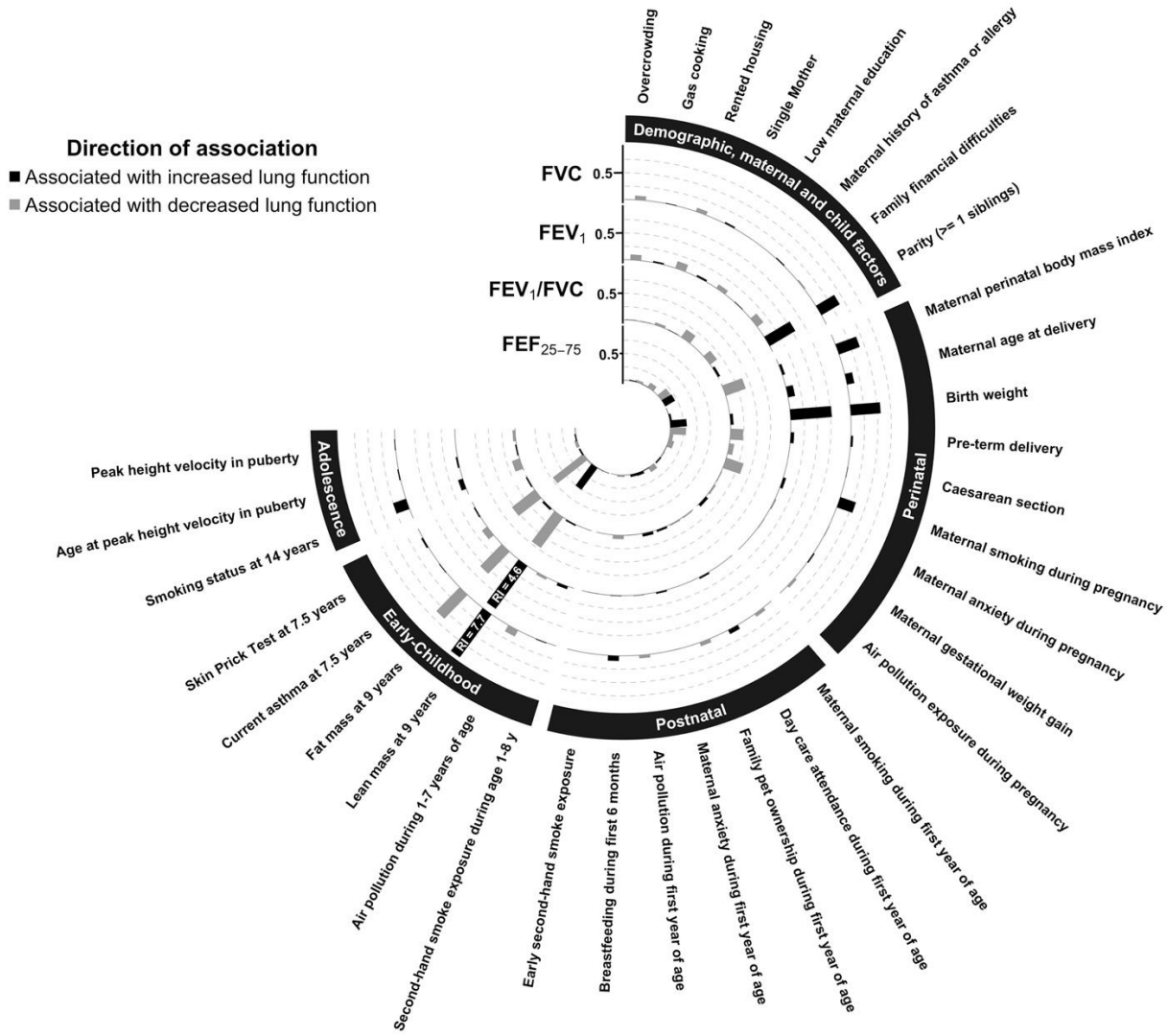

Figure S3 Circular plot of characteristics' relative importance (RI), on measured (non-imputed) lung function parameters at age 24 years (N=2800). Associations with higher and lower lung function were highlighted in black and grey colours respectively. Bars' height represents levels of RI, expressed in %, except for characteristics whose RI > 1%, where exact RI values are displayed on their corresponding bars