# 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”

## At a Glance Commentary

**Scientific Knowledge on the Subject:** Low lung function at the physiological plateau in early-adulthood is associated with chronic obstructive pulmonary disease in later life. Lung development influences maximally attained lung function in early-adulthood. Early-life events, environmental, and health behaviour characteristics as well as pubertal growth play crucial roles – with different levels of relevance - in this process. Several early-life characteristics, such as maternal smoking during pregnancy, birth weight, and childhood respiratory disease have been associated with lung function, but little is known about the relative importance of each of these characteristics on lung function in early-adulthood.

**What This Study Adds to the Field:** This population based, birth cohort study with information on a large number of exposures, estimated the relative contribution of characteristics associated with lung function in early-adulthood, around its physiological maximum. Perinatal and childhood characteristics explained relatively larger variation in the lung function in early-adulthood compared with other investigated characteristics. Birth weight, childhood lean mass and fat mass at age 9 years explained $\mathbf{0.5}\% - \mathbf{7.7}\%$ of the variation in forced expiratory volume in one-second ($FEV_1$) as well as forced vital capacity (FVC) in early-adulthood. Maternal perinatal body mass index, maternal smoking during pregnancy, childhood asthma at age 7 years, and lean mass at age 9 years contributed the most to the explained variance of the $FEV_1$/FVC ratio at age 24 years explaining $\mathbf{0.5}\% - \mathbf{0.8}\%$ of its

At a glance commentary word count: 213

## ‘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 ($\mathbf{RI}$) 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 $\mathbf{RI}$ ($\mathbf{0.5}\% - \mathbf{7.7}\%$) for decreased FVC. Having no-siblings, lower birthweight, lower lean mass, and higher fat mass were associated with decreased $FEV_1$ ($\mathbf{RI}$: $\mathbf{0.5}\% - \mathbf{4.6}\%$). Higher lean mass and childhood-asthma were associated with decreased $FEV_1$/FVC ($\mathbf{RI}$: $\mathbf{0.6}\% - \mathbf{0.8}\%$).

**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 (99.2%) 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 $\leq 0.1$. 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 and derived the relative importance of sociodemographic, environmental, lifestyle and physiological characteristics from prenatal to adolescence in lung function at age 24 years, around its physiological maximum. 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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## 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) | $2\times10^{-4}$ | | 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) | $1\times10^{-16}$ | | 7.707 | |
| | Fat mass at age 9 years (SD-score) | -0.051 (-0.073 to -0.028) | $1\times10^{-4}$ | | 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 | | 0.104 | |
| | 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 | 1.21 | 0.039 | 0.89 |
| | 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) | $5\times10^{-5}$ | | 0.524 | |
| Perinatal characteristics | Maternal perinatal body mass index (Kg/m²) | 0.006 (-0.004 to 0.015) | 0.263 | | 0.086 | |
| | 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 | 1.06 | 0.027 | 1.59 |
| | 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 (μg/m³) | -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 | | 0.025 | |
| | 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 | 0.27 | 0.076 | 1.59 |
| | Air pollution during first year of age (μg/m³) | -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 | | 0.011 | |
| | Air pollution during 1-7 years of age (μg/m³) | -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) | $3\times10^{-15}$ | 5.26 | 4.579 | 6.63 |
| | Fat mass at age 9 years (SD-score) | -0.045 (-0.063 to -0.026) | $3\times10^{-5}$ | | 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 | | 0.162 | |
| | Age at peak height velocity in puberty (years) | 0.009 (-0.019 to 0.037) | 0.542 | 0.19 | 0.019 | 6.79 |
| | 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 ($\mu g/m^3$) | 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 ($\mu g/m^3$) | 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 ($\mu g/m^3$) | 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) | $6\times10^{-6}$ | | 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 (μg/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 (μg/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 (μg/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) | $2\times10^{-5}$ | | 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

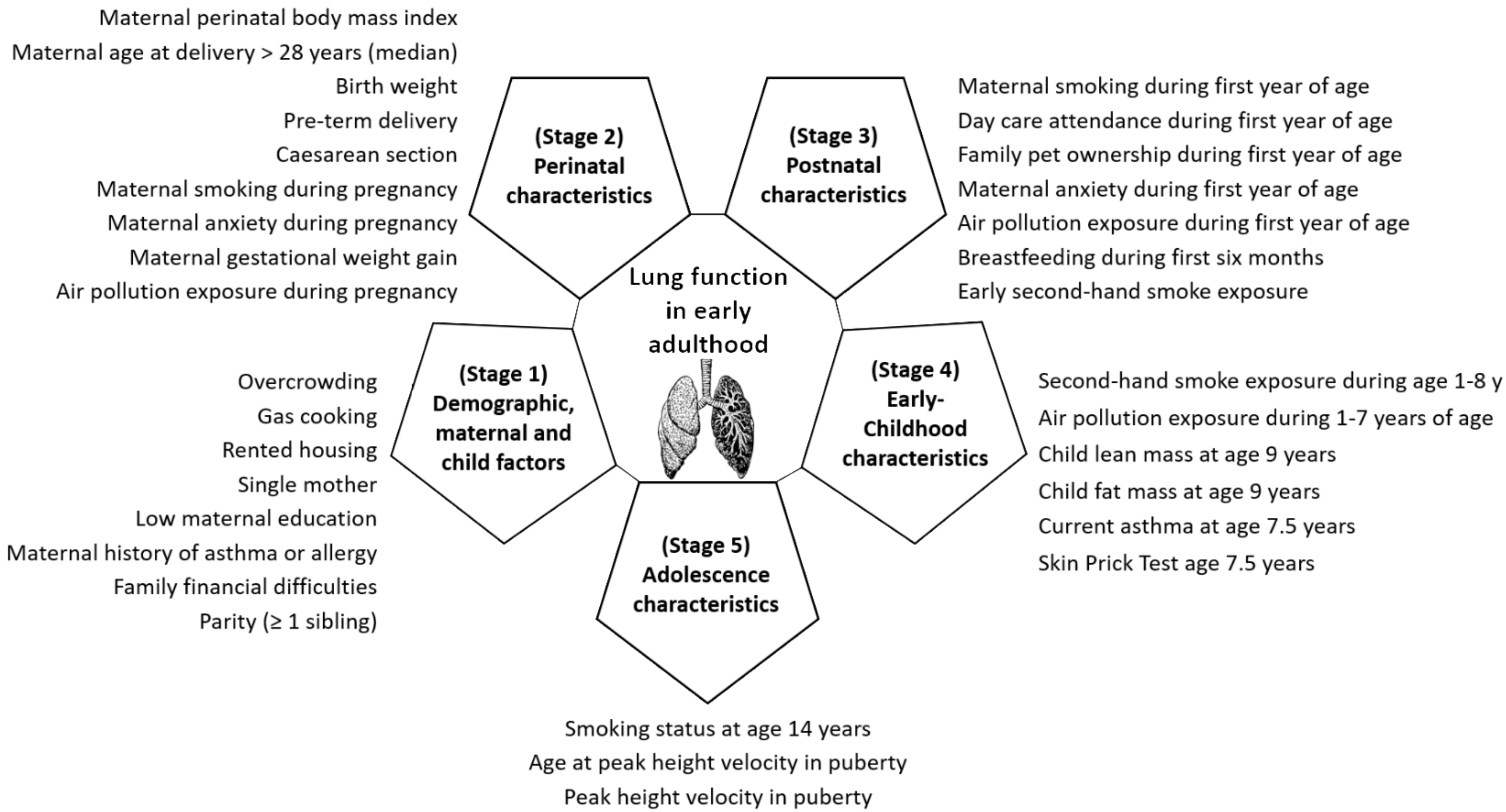


Figure 1. Characteristics examined for association and relative importance with lung function at age 24 years (Detailed description presented in Table 1).

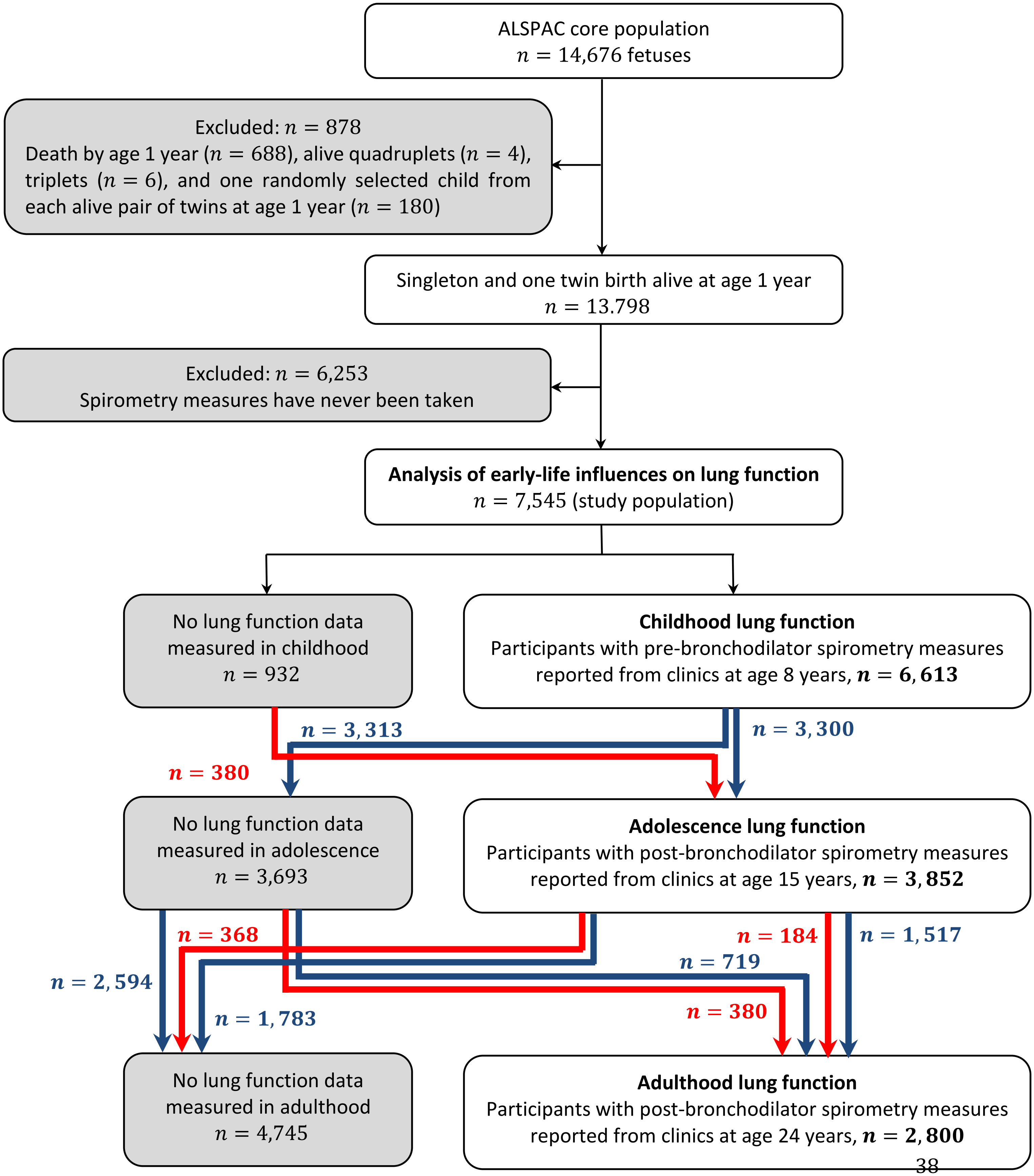




Figure 2. Flow chart of study participants. The blue and red arrows refer to different follow-up paths for spirometry clinics at ages 8, 15 and 24 years. For example, the blue arrow from 'Childhood' to 'Adolescence' lung function boxes represents participants ($n$ = 3,300) whose lung function was measured 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 of the box of 'Adolescence lung function'). ALSPAC = Avon Longitudinal Study of Parents and Children.

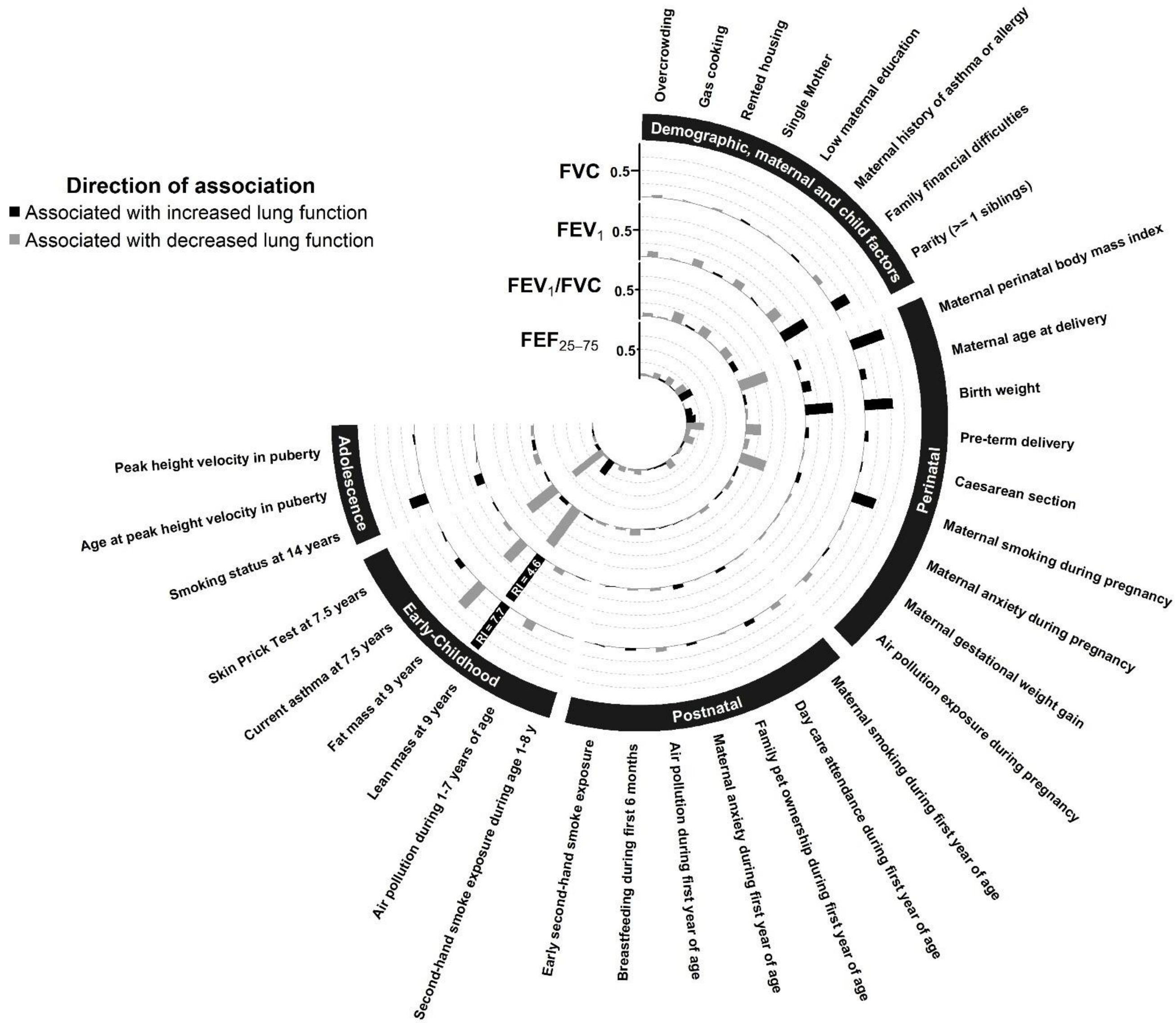


Figure 3. Circular plot of characteristics' relative importance (RI), on lung function parameters at age 24 years. Associations with higher and lower lung function were highlighted in black and grey colours respectively. Bars' height represented levels of RI, expressed in %, except for characteristics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

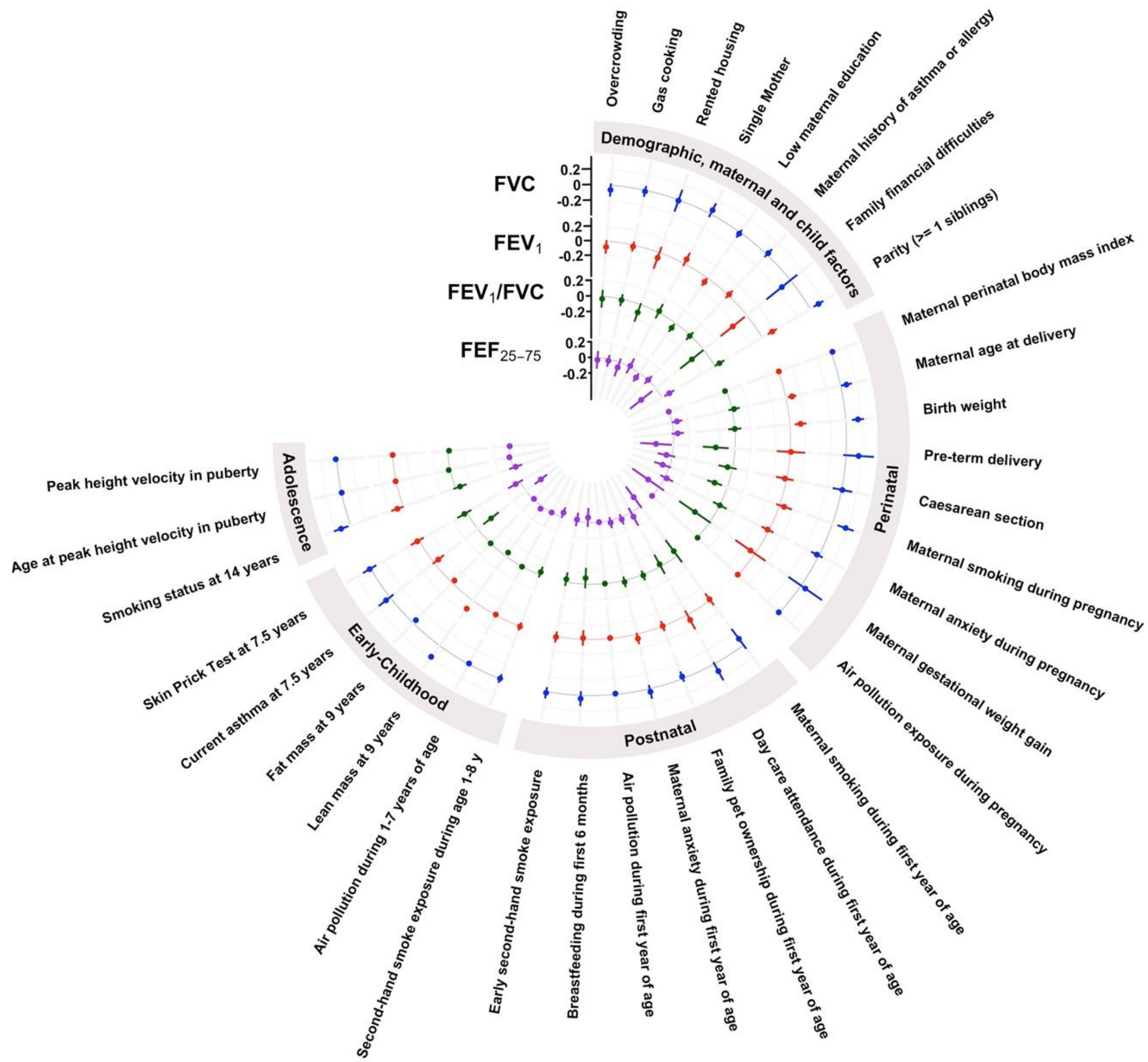


Figure 4. Circular plot of characteristics' association (point estimates and 95% confidence intervals) with lung function parameters at age 24 years for our study population (N=7,545). The raw data used for generating this plot are reported in Table 2 - Table 5