Early View

Original article

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Early childhood growth is associated with lung function at seven years: a prospective population-based study

Gabriela P. Peralta[1,2,3], Alicia Abellan[1,2,3,4], Parisa Montazeri[1,2,3], Mikel Basterrechea[3,5], Ana Esplugues[3,6,7], Sandra González-Palacios[3,8], Célina Roda[1,2,3,9], Loreto Santa-Marina[3,5], Jordi Sunyer[1,2,3,10], Martine Vrijheid[1,2,3], Maribel Casas[1,2,3]*, Judith Garcia-Aymerich[1,2,3]*

*Shared last authorship

[1] ISGlobal, Barcelona, Spain

[2] Universitat Pompeu Fabra (UPF), Barcelona, Spain

[3] CIBER Epidemiología y Salud Pública (CIBERESP)

[4] Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain

[5] Public Health Division of Gipuzkoa, Basque Government, San Sebastian, Spain

[6] Epidemiology and Environmental Health Joint Research Unit, FISABIO-Universitat Jaume I, Universitat de Valencia, Valencia, Spain

[7] Nursing Department, Faculty of Nursing and Chiropody, Universitat de València, Valencia, Spain

[8] Department of Public Health, History of Medicine and Gynecology, Miguel Hernández University and Institute for Health and Biomedical Research (ISABIAL Foundation), Alicante, Spain

[9] Université de Paris, CRESS, INSERM – HERA team (Health Environmental Risk Assessment), INRA, F-75004, Paris, France

[10] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

Corresponding author:

Judith Garcia-Aymerich

Barcelona Institute for Global Health (ISGlobal)

Doctor Aiguader, 88

08003 Barcelona, Spain

Email address: judith.garcia@isglobal.org

"Take home" message: Independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at 7 years, but showed airflow limitation. Children with lower birth size and slower BMI gain in early childhood had lower lung function at 7 years.

ABSTRACT

Previous studies have related early postnatal growth with later lung function but their interpretation is limited by the methods used to assess child's growth. We aimed to assess the association of early childhood growth, measured by body mass index (BMI) trajectories up to four years, with lung function at seven years.

We included 1,257 children from the Spanish Infancia y Medio Ambiente population-based birth cohort. Early childhood growth was classified in five categories based on BMI trajectories up to four years previously identified using latent class growth analysis. These trajectories differed in birth size ('lower', 'average', 'higher') and in BMI gain velocity ('slower', 'accelerated'). We related these trajectories with lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 25-75% (FEF_{25-75})) at seven years, using multivariable mixed regression.

Compared to children with average birth size and slower BMI gain (reference), children with higher birth size and accelerated BMI gain had higher percent predicted FVC (3.3% [95% CI: 1.0; 5.6]) and lower percent predicted FEV_1/FVC (-1.5% [-2.9; -0.1]) at seven years. Similar associations were observed for children with lower birth size and accelerated BMI gain. Children with lower birth size and slower BMI gain had lower percent predicted FVC at seven years. No association was found for FEF_{25-75}.

Independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at seven years but showed airflow limitation. Children with lower birth size and slower BMI gain in early childhood had lower lung function at seven years.

BACKGROUND

Early childhood is a critical period for lung function growth [1–3]. The respiratory system starts to develop *in utero* but the airways, particularly the alveoli, continue to develop until early adulthood [1,3,4]. Therefore, early life events can affect normal lung growth and increase the risk of respiratory morbidity in later life [5]. In recent years, several studies have assessed the association between early growth characteristics and lung function in childhood. There is consistent evidence showing that low birth weight is associated with poor lung function (mostly measured by means of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1)) in childhood [6–11]. In addition, previous studies suggested that accelerated weight gain during infancy and childhood is associated with higher FEV_1 and FVC levels but lower FEV_1/FVC ratio, i.e., higher risk of airflow limitation [10–13].

These previous studies are limited by the methods used to assess child's growth. First, some studies calculated the differences between only two time points [6,11]. This approach can only estimate linear growth and does not fully capture growth in early childhood. Second, other studies derived complex growth patterns such as peak height and weight growth velocity [13]. Although these patterns are biologically meaningful, they are also difficult to interpret and apply in clinical settings. Other analytical strategies that integrate repeated weight information and are, at the same time, easy to interpret for paediatricians and the general public, have not yet been tested in relation to lung function.

In the present study we aimed to assess the association of body mass index (BMI) trajectories from birth to four years with lung function at seven years using data from the population-based INfancia y Medio Ambiente (INMA, "Environment and Childhood") birth cohort in Spain. We previously identified BMI z-score trajectories from birth to four years based on repeated measures of weight and height during early childhood from routine paediatric charts [14], which allow for an accurate assessment of early childhood growth and easier interpretation.

METHODS

Study population

Pregnant women (n=2,270) were recruited at prenatal visits at public health care centres or referral hospitals, from 2004 to 2008, in three regions (Sabadell, Valencia and Gipuzkoa) participating in the Spanish INMA birth cohort [15]. Inclusion criteria were: ≥16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues. In the present study, we included children who had available information

for the identification of BMI z-score trajectories from birth to four years and lung function data at seven years (Figure S1).

The study was approved by the hospital and institutional Ethics Committees in each region. All mothers signed a written consent for themselves and their child's participation.

BMI z-score trajectories

Repeated measurements of child height and weight from birth until four years were extracted from routine paediatric charts (mean [SD] number of measurements per child 11 [3.4]). We calculated BMI by dividing weight in kilograms by height squared in centimetres, and age and sex specific BMI z-scores by using the WHO Child Growth Standards [16]. We previously identified five BMI z-score trajectories (hereon referred to as BMI trajectories) using latent class growth analysis [14,17]. These trajectories differed in birth size (labelled for comparison as 'lower', 'average' or 'higher') and in BMI gain velocity (labelled as 'slower' or 'accelerated') (Figure 1). We used the trajectory with average birth size and slower BMI gain as the reference category in our analysis. The distribution of weight and length/height according to the BMI trajectories in our study sample is presented in Table S1.

Lung function

At seven years, trained nurses measured lung function by spirometry according to American Thoracic Society and the European Respiratory Society guidelines [18]. FVC, FEV_1 and forced expiratory flow at 25-75% of the FVC (FEF_{25-75}) were measured, and the FEV_1/FVC ratio was calculated. All children included in the present study had at least one acceptable manoeuvre. We calculated percent predicted lung function parameters by using the Global Lung Function Initiative 2012 prediction equations [19], and we used these variables as the main outcome of the analysis.

Other relevant characteristics

We obtained the following additional information: maternal characteristics (age at delivery, pre-pregnancy BMI, smoking status, educational level and history of allergy-related disease [at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis]) using questionnaires during pregnancy; child birth characteristics (sex, gestational age and weight at birth) from medical records; child characteristics (duration of any breastfeeding and lower respiratory tract infections) during the first year by postnatal questionnaires; height at seven years by trained nurses; and asthma at seven years through the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents. As previously agreed in the MeDALL (Mechanisms of the Development of Allergy) project [20], we defined current asthma based on a positive answer to at least two of the following questions: life-time doctor

diagnosis of asthma, use of medicines for asthma or breathing difficulties in the last 12 months, and wheezing or whistling in the chest at any time in the last 12 months (see full questions in the online supplement).

Statistical analysis

We assessed the association of BMI trajectories from birth to four years with lung function (FVC, FEV_1, FEV_1/FVC and FEF_{25-75}) at seven years using multivariable mixed linear regression models with random intercepts for participants nested within regions (Sabadell, Valencia and Gipuzkoa). All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year. We selected covariates based on previous research [10–13] and on subject matter knowledge. We used Direct Acyclic Graphs to identify the minimum set of covariables required to adjust our models (Figure S2).

To assess whether associations differed by sex, we tested for interaction and stratified models by this variable. Specifically, we tested the overall significance of the interaction term using a Wald test, which tested whether interaction terms between each one of the BMI trajectories and sex were collectively different from zero and provided a single p-value for the interaction. We performed several sensitivity analyses to assess the robustness of results to various assumptions regarding inclusion of susceptible subgroups (e.g. children born prematurely or with current asthma) and quality of lung function measures (see the online supplement).

Missing data accounted for 4.9% of total observations. We used a complete case strategy and reported missing data in the Table 1 footnotes. All analyses were conducted in Stata/SE 14.0 (StataCorp, College Station, TX, USA). Statistical significance was set at p-value<0.05 for multivariate analyses, and at p-value<0.2 for interaction tests.

RESULTS

Sample description

We included 1,257 children in the present analysis. Mothers of these children were older at pregnancy, had higher educational level and breastfed for a longer period than mothers of children not included in the present analysis (Table S2). Table 1 shows the main characteristics of the study sample. Approximately 17% of mothers reported that they smoked during pregnancy and 37% had a high educational level (university). Approximately 5% of the children

had low birth weight (<2500 g) and 38% were classified in the BMI trajectory with average birth size and slower BMI gain (reference category).

Associations of early childhood BMI trajectories with lung function at seven years

Figure 2 and Table S3 show the adjusted associations between BMI trajectories up to four years and lung function at seven years. Compared to children with average birth size and slower BMI gain (reference), children with higher birth size and accelerated BMI gain had higher percent predicted FVC (3.3% [95% CI: 1.0 to 5.6]) and lower percent predicted FEV_1/FVC ratio (-1.5% [-2.9 to -0.1]) at seven years. Similarly, children with lower birth size and accelerated BMI gain had higher percent predicted FVC (2.8% [0.5 to 5.0]) and tended to have lower percent predicted FEV_1/FVC ratio (-1.3% [-2.7 to 0.1]) than children in the reference category. In contrast, children with lower birth size and slower BMI gain had lower percent predicted FVC (-3.1% [-5.2 to -0.9]) and tended to have lower FEV_1 (-1.9% [-4.1 to 0.3]), but higher percent predicted FEV_1/FVC (1.1% [-0.2 to 2.4]) than children at the reference category. Finally, children with higher birth size and slower BMI gain did not differ from the reference category in lung function values. We found no significant associations of BMI trajectories with FEF_{25-75}.

We observed a statistically significant interaction by sex of the association between accelerated BMI gain and higher FEV_1, which was only present in girls (p=0.075, Table S4). The association of accelerated BMI gain with FVC was stronger in girls than in boys, while the association with FEV_1/FVC was stronger in boys, without presence of statistical interaction.

The direction of the observed associations remained stable in all sensitivity analyses (Tables S5 to S9). However, exclusion of children with extreme lung function values resulted in the attenuation of some FEV_1/FVC effect estimates (Table S7). Also, models restricted to children with at least two acceptable manoeuvres reproducible within 150 mL showed increased effect estimates for the group with higher birth size and accelerated BMI gain (Table S9).

DISCUSSION

Main findings

In this prospective population-based study we found that BMI trajectories from birth to four years relate to lung function at seven years. Specifically, we found that: (i) children with accelerated BMI gain had higher FVC and lower FEV_1/FVC ratio at seven years either if they departed from lower or higher birth size, (ii) children with lower birth size and slower BMI gain had lower FVC and FEV_1, but higher FEV_1/FVC ratio at seven years (although the effect

estimates for FEV_1 and FEV_1/FVC were imprecise), and (iii) we found no associations of BMI trajectories with FEF_{25-75} at seven years.

Comparison with previous studies

Our finding that accelerated BMI gain in the first four years of life is associated with higher FVC and lower FEV_1/FVC ratio at seven years is in line with previous longitudinal studies [10–13], which measured early childhood growth using different parameters. The most recent study using data from the Generation R Study showed that peak weight velocity and BMI at adiposity peak, derived from individual growth trajectories in the first three years of life, were associated with higher FVC and FEV_1 but lower FEV_1/FVC ratio at ten years [13]. Peak weight velocity and BMI at adiposity peak represent accelerated BMI gain particularly in the first year of life, which is the period of fastest growth, as reflected in our trajectories (Figure 1). Similarly, another study using data from the same cohort found that accelerated foetal growth followed by accelerated infant weight growth up to one year (defined as growth percentile change between time periods) were associated with higher FVC and FEV_1/FVC ratio at ten years [12]. An important contribution from our study is that, because we distinguished two patterns of accelerated BMI gain (departing from higher and lower birth size), we were able to demonstrate that the effects of accelerated weight gain on lung function do not depend on birth size. Specifically, we observed that accelerated BMI gain was associated with higher FVC at 7 years even if children departed from low birth size. This finding is in line with a previous study showing that children with intrauterine growth restriction who showed weight catch-up growth in the first nine years of life (calculated as the difference between two time points) had higher spirometry measures at age nine years than those without catch-up [6]. Another study also showed that weight gain during the first year of life (defined as the difference between two time points) was associated with higher adult lung function independently of birth weight [21].

We also found that children in the trajectory with lower birth size and slower BMI gain had lower FVC and FEV_1 at seven years than the reference trajectory (although the estimate for FEV_1 was imprecise), which is consistent with existing literature. Previous studies have reported that children with low birth weight or smaller birth size have decreased lung function compared to children with normal birth weight in childhood [6–11]. In addition, these children had higher FEV_1/FVC ratio at seven years (although the estimate was imprecise), which is in line with previous research reporting an association between smaller birth size and higher ratio in childhood [10,11].

We found no association between early childhood growth and FEF_{25-75} at seven years. This finding is in contrast with a previous study showing that rapid weight gain during the first three months of life (derived from individual growth trajectories) was associated with a decreased

FEF_{25-75} at eight years [10]. This discrepancy may be attributed to different definitions of childhood growth and different exposure assessment periods (i.e. first three months *vs.* first four years), as well as to differences in sample size.

Interpretation of results

There are three potential mechanisms to explain the associations of accelerated BMI gain in early childhood with higher FVC and lower FEV_1/FVC in later childhood. First, it is possible that accelerated BMI gain during early childhood has greater influence on lung volume than airway growth. This phenomenon is known as dysanapsis and reflects an incongruence between (faster) growth in lung volume and airway length, and (slower) increase in airway calibre [22,23]. Dysanapsis has been linked with clinical alterations in children with asthma [23] and may be a risk factor for respiratory diseases in later life. Second, it is plausible that accelerated BMI gain is accompanied by accumulation of adipose tissue, which could lead to airflow limitation (as measured by a lower FEV_1/FVC) by means of inflammatory processes. Adipose tissue is a source of pro-inflammatory factors, which can have local effects on the lungs causing structural alterations of the airways [24–26]. This inflammatory hypothesis is supported by a previous longitudinal study showing that higher fat mass during childhood was associated with lower FEV_1/FVC levels in adolescence [27], and by another study showing that subjects with higher BMI had higher adipose tissue and inflammatory cells within the airway wall [26]. Finally, we cannot rule out the possibility that the association of accelerated BMI gain with lower FEV_1/FVC ratio is due to mathematical artefact, since accelerated BMI gain was more strongly associated with FVC than with FEV_1 in the present study. Further studies with available measures of early growth, inflammatory markers, adipose tissue levels and lung structure are needed to understand the potential underlying mechanisms of this association.

A potential explanation for the association of lower birth size and slower BMI gain with lower FVC and FEV_1 at seven years is restricted foetal growth, since it may be a common cause of both lower birth size and disrupted lung function. Although the respiratory system continues developing until early adulthood, the majority of airway and alveoli development takes place *in utero* [3,28]. Several animal studies have reported that restricted foetal growth affects normal lung development causing structural alterations [29,30], which may affect lung function in childhood. In contrast to children with lower birth size and accelerated BMI gain, children with lower birth size and slower BMI gain may not be able to compensate for these lung alterations during the first years of life.

Implications

The findings of the present study have important implications for research and public health. Our study shows that early childhood BMI trajectories are a useful tool to identify growth

patterns associated with poor respiratory health. BMI trajectories, which can be estimated using information collected routinely in medical records, represent an accurate way to study early growth that can be easily interpreted for paediatricians and the general public. In addition, our findings, together with existing literature, support that early childhood growth impacts lung function development, and therefore may affect future respiratory health. Since weight growth is affected by modifiable factors, public health interventions promoting healthy lifestyles (e.g. healthy eating and physical activity) in early childhood may help to improve lung function and reduce respiratory morbidity in adulthood.

Strengths and limitations

Strengths of the present study are the longitudinal design and the population-based nature of the INMA cohort. Also, the availability of BMI trajectories from birth to four years allowed us to estimate the association of early growth with lung function accounting simultaneously for birth size and BMI gain. In addition, by using BMI trajectories as a marker of early growth we took into account weight and height changes during the first years of life simultaneously, while most of previous studies have focused only on weight growth [11,12], or have analysed weight and height separately [10,13].

Our study also has some limitations, which include the potential selection bias due to the fact that mothers of children included in the study were older at pregnancy and had a higher educational level than mothers of children not included but participated in the INMA birth cohort. Although we were able to account for a wide range of potential confounders (including gestational age), residual confounding may be a concern as we did not have information on physical activity or diet before four years nor on non-allergic maternal asthma, all of which could be related to BMI growth and lung function. Another potential limitation of this study is the regional basis of the sample which may not allow the generalizability of our results to populations with different environmental and lifestyle factors. Finally, we used BMI as a marker of body growth but BMI is limited by its inability to distinguish between muscle and fat mass, which have different effects on lung function [27]. Although BMI trajectories in early childhood could be a good predictor of later body composition [31], further research using detailed measures of body composition is needed to provide insight into the effect of body composition during early childhood on later respiratory health.

Conclusion

In conclusion, we found that, independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at seven years, but also showed airflow limitation. In contrast, children with lower birth size and slower BMI gain in early childhood had lower lung function at seven years. This study shows that BMI trajectories during the first years of life can

identify growth patterns associated with poor respiratory health in later childhood. Our results, together with existing literature, support that early postnatal growth is likely to play a role in lung function development during childhood, and therefore can affect respiratory health in later life. Public health strategies aiming to reduce respiratory health problems may need to target early weight growth.

COMPETING INTERESTS

JG-A reports personal fees from Esteve, Chiesi and AstraZeneca, outside the submitted work. Other authors declare no competing interests related to this work

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Figure 1. Body mass index (BMI) z-score trajectories from birth to four years

Adapted from Montazeri P., et al. Obesity 2018

† Reference category

Figure 2. Adjusted associations of early childhood body mass index (BMI) trajectories with lung function at seven years.

Abbreviations: FEF_{25-75}: forced expiratory flow 25-75%; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient; 95% CI: 95% confidence intervals.

All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year.

Due to missing values in the covariates, the study sample included in the multivariable analysis was 1,195 for FVC, FEV_1 and FEV_1/FVC, and 1,193 for FEF_{25-75}.

* p-value <0.05

Table 1. Characteristics of the study sample (n=1,257)*

	n (%), mean (SD) or median (P_{25}-P_{75})
Maternal characteristics	
Age at delivery (years)	30.9 (0.1)
Pre-pregnancy BMI (kg/m^2)	22.6 (20.8 to 25.2)
History of allergy-related disease [†]	335 (26.7%)
Smoking during pregnancy	
Never smoker	573 (46.2%)
Smoking before pregnancy	458 (37.0%)
Smoking during pregnancy	208 (16.8%)
Educational level	
Primary or less	263 (21.2%)
Secondary	515 (41.4%)
University	465 (37.4%)
Child characteristics	
Sex: girl	622 (49.5%)
Birth weight (g)	3,258 (458)
Low birth weight (<2,500 g)	65 (5.2%)
Gestational age (weeks)	39.9 (38.9 to 40.7)
Preterm birth (<37 weeks)	48 (3.8%)
Duration of any breastfeeding (weeks)	25.9 (10.7 to 43.4)
Low respiratory tract infections during the first year	438 (35.4%)
Age at 7 years (years)	7.5 (7.0 to 7.8)
Height at 7 years (cm)	124.7 (6.3)
Asthma at 7 years [**]	115 (9.2%)
BMI trajectories from birth to four years	
Higher birth size – accelerated BMI gain	137 (10.9%)
Lower birth size – accelerated BMI gain	145 (11.6%)
Higher birth size – slower BMI gain	332 (26.4%)
Average birth size – slower BMI gain (Reference)	483 (38.4%)
Lower birth size – slower BMI gain	160 (12.7%)
Lung function at 7 years[‡]	
Percent predicted FVC (%)	101.8 (12.0)
Percent predicted FEV$_1$ (%)	104.8 (11.9)
Percent predicted FEV$_1$/FVC (%)	96.7 (7.5)
Percent predicted FEF$_{25-75}$ (%)	95.1 (23.8)

Abbreviations: BMI: body mass index; FEV$_1$: forced expiratory volume in 1 second; FEF$_{25-75}$: forced expiratory flow at 25-75% of the pulmonary volume; FVC: forced vital capacity

*Some variables had missing values: Maternal characteristics: 6 in age at delivery, 8 in pre-pregnancy BMI, 1 in allergy-related disease, 18 in smoking, 14 in educational level; Child characteristics: 3 in birth weight, 17 in duration of any breastfeeding, 18 in lower respiratory tract infections during the first year, 3 in asthma at 7 years, 2 in FEF_{25-75} at 7 years

† Defined as reporting at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis

** We defined current asthma based on a positive answer to at least two of the following questions: lifetime doctor diagnosis of asthma, use of medicines for asthma or breathing difficulties in the last 12 months, and wheezing or whistling in the chest at any time in the last 12 months.

‡ Calculated by using Global Lung Function Initiative (GLI) 2012 prediction equations
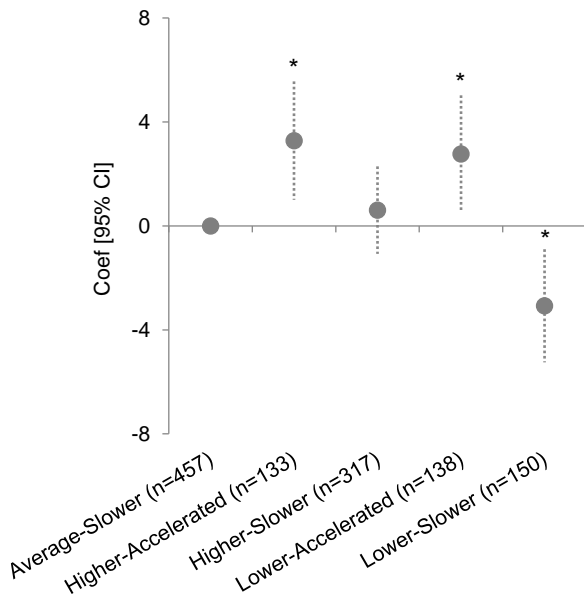
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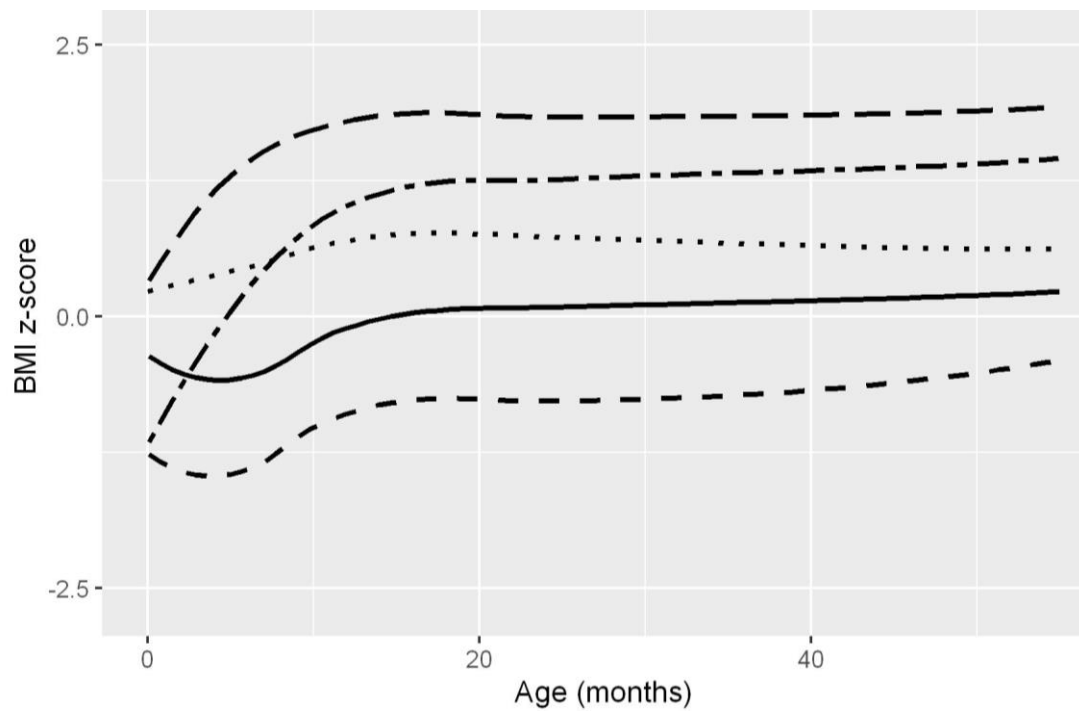
	Description	
Birth size (BMI)		**BMI gain**
Higher		Accelerated
Lower		Accelerated
Higher		Slower
† Average		Slower
Lower		Slower

Percent predicted FVC (%)
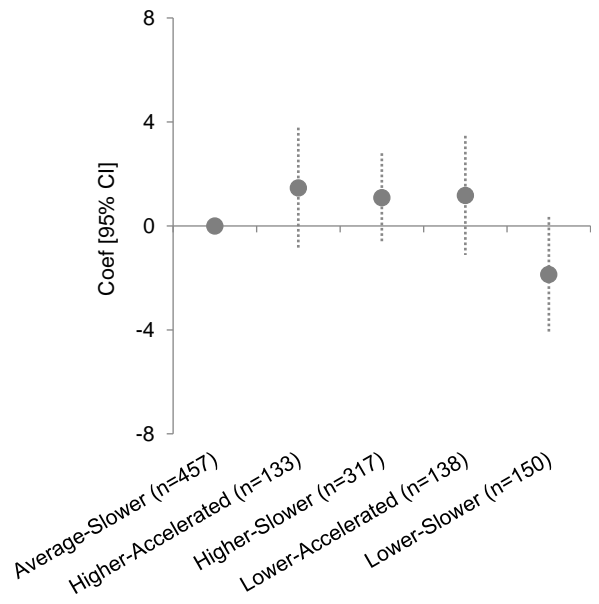
Coef [95% CI]

Average-Slower (n=457) Higher-Accelerated (n=133) Higher-Slower (n=317) Lower-Accelerated (n=138) Lower-Slower (n=150)

BMI trajectories

Percent predicted FEV$_1$ (%)

Coef [95% CI]

Average-Slower (n=457) Higher-Accelerated (n=133) Higher-Slower (n=317) Lower-Accelerated (n=138) Lower-Slower (n=150)

BMI trajectories

Percent predicted FEV$_1$/FVC (%)

Coef [95% CI]

Average-Slower (n=457) Higher-Accelerated (n=133) Higher-Slower (n=317) Lower-Accelerated (n=138) Lower-Slower (n=150)

BMI trajectories

Percent predicted FEF$_{25-75}$ (%)

Coef [95% CI]

Average-Slower (n=455) Higher-Accelerated (n=133) Higher-Slower (n=317) Lower-Accelerated (n=138) Lower-Slower (n=150)
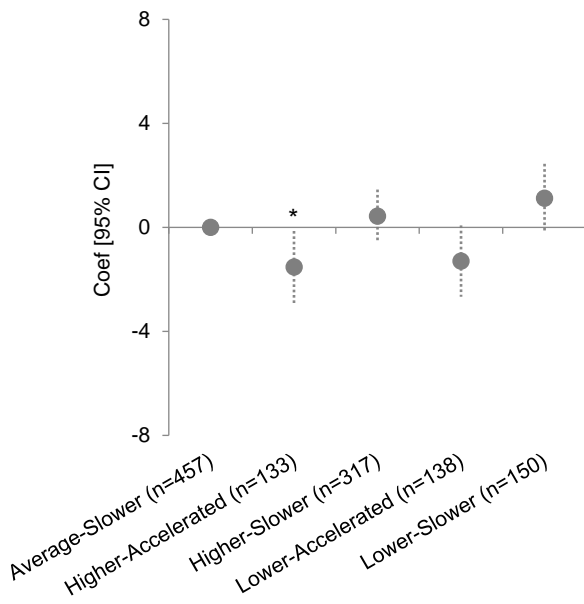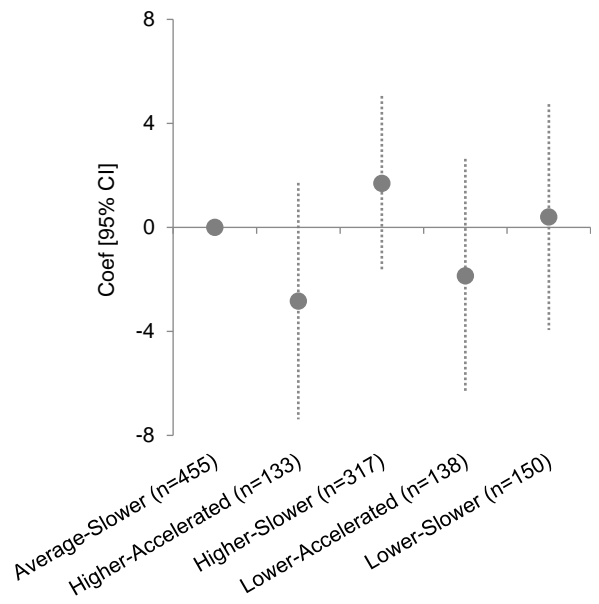
BMI trajectories

Early childhood growth is associated with lung function at seven years: a prospective population-based study

Gabriela P. Peralta, Alicia Abellan, Parisa Montazeri, Mikel Basterrechea, Ana Esplugues, Sandra González, Célina Roda, Loreto Santa-Marina, Jordi Sunyer, Martine Vrijheid, Maribel Casas*, Judith Garcia-Aymerich*

*Shared last authorship

SUPPLEMENTARY INFORMATION

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Definition of asthma at 7 years

Information on asthma at seven years was collected through the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents. As previously agreed in the MeDALL (Mechanisms of the Development of Allergy) project, we defined current asthma based on a positive answer to at least two of the following questions: 1) 'Has your child ever been diagnosed by a doctor as having asthma?'; 2) 'Has your child taken any medicines for asthma (including inhalers, nebulizers, tablets or liquid medicines) or breathing difficulties (chest tightness, shortness of breath) in the last 12 months?'; 3) Has your child had wheezing or whistling in the chest at any time in the last 12 months?'[1].

Reference:

1   Hohmann C, Keller T, Gehring U, *et al.* Sex-specific incidence of asthma, rhinitis and respiratory multimorbidity before and after puberty onset: individual participant meta-analysis of five birth cohorts collaborating in MeDALL. *BMJ Open Resp Res* 2019;6:460. doi:10.1136/bmjresp-2019-000460

Methods: Sensitivity analyses

To assess the robustness of our results we performed several sensitivity analyses. We excluded children with current asthma at seven years, children from mothers who smoked during pregnancy, children with extreme lung function values (below percentile one and above percentile 99) and children born prematurely in separate analyses to assess whether the observed associations were influenced by these subsamples. We also restricted models to children with at least two acceptable manoeuvres reproducible within 150 mL to account for potential misclassification in lung function.

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┌─────────────────────────────────────────────────────────────────────┐
│   Pregnant women recruited in Gipuzkoa, Sabadell and Valencia regions │
│                            n=2,270                                    │
└─────────────────────────────────────────────────────────────────────┘
                                   │
                                   ▼
┌─────────────────────────────────────────────────────────────────────┐
│                      Children recruited at birth                      │
│                            n=2,140                                    │
└─────────────────────────────────────────────────────────────────────┘
                                   │
                                   ▼
┌─────────────────────────────────────────────────────────────────────┐
│  Children with BMI measures available to derive BMI z-score           │
│  trajectories from birth to four years                                │
│                                                                       │
│                            n=1,912                                    │
└─────────────────────────────────────────────────────────────────────┘
                                   │
                                   ▼
┌─────────────────────────────────────────────────────────────────────┐
│  Children with available lung function data (FEV1 or FVC or FEF 25-75)│
│  at seven years                                                       │
│                                                                       │
│                            n= 1,257                                   │
└─────────────────────────────────────────────────────────────────────┘
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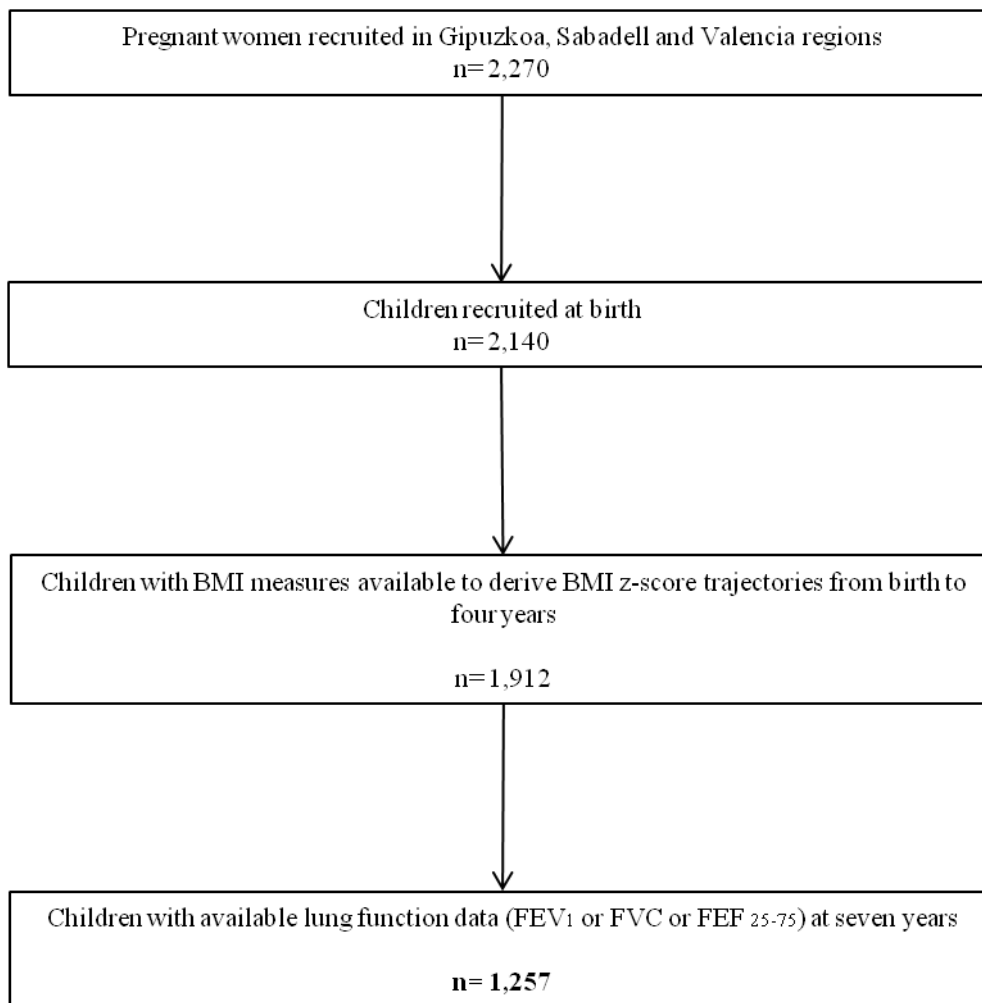
Figure S1. Flowchart of the study sample

Abbreviations: BMI, body mass index; FEV_1: forced expiratory volume in 1 second; FEF_{25-75}: forced expiratory flow at 25-75% of the pulmonary volume; FVC: forced vital capacity
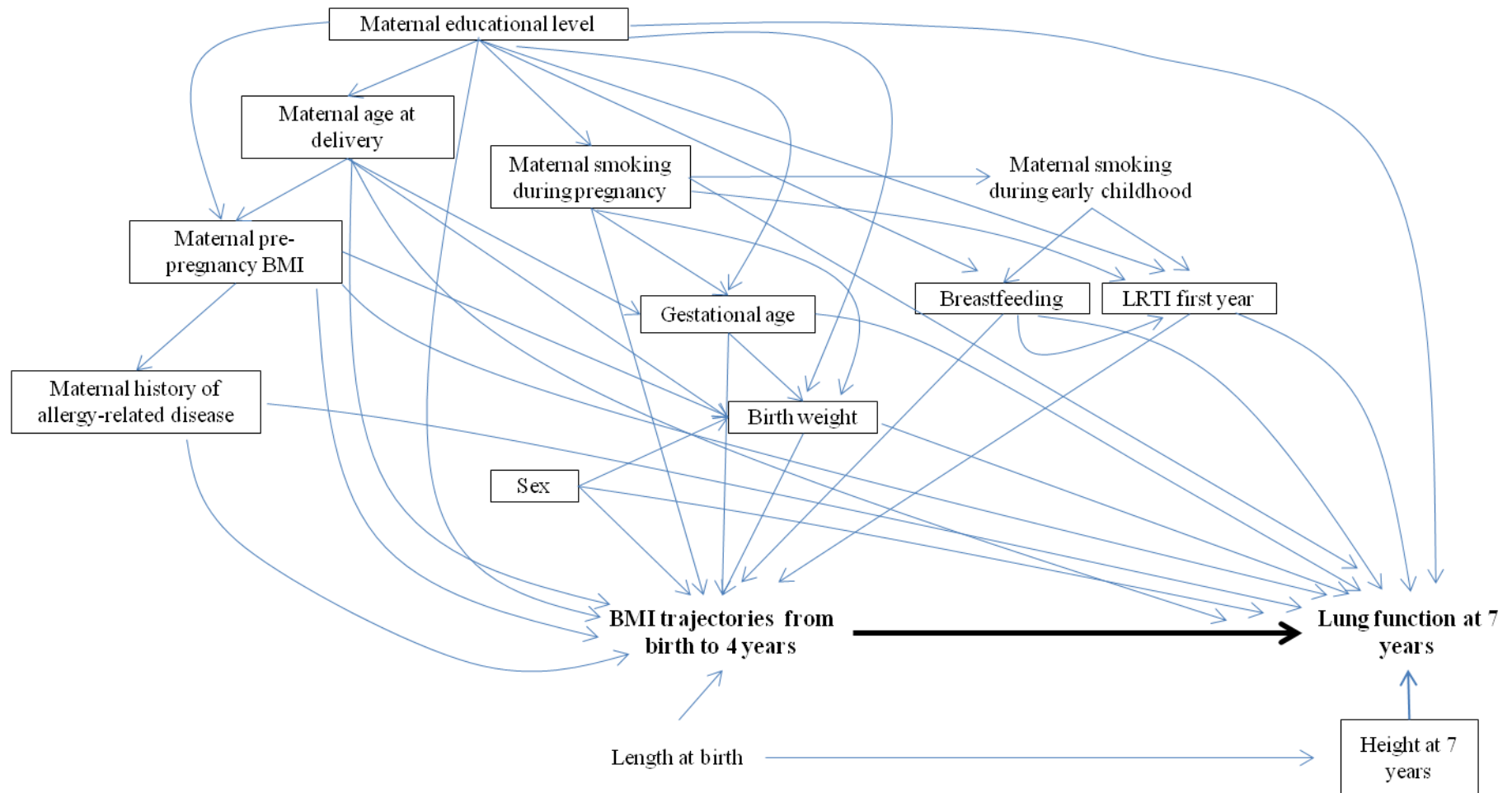
Figure S2. Directed acyclic graph of hypothesised associations between study variables

Variables with black squares represent the minimal adjustment set of covariables required to study the association of BMI trajectories from birth to four years with lung function at seven years. Abbreviations: BMI, body mass index; LRTI, lower respiratory tract infections

Table S1. Distribution of weight and length/height at birth and at one and four years according to BMI trajectories

	n	Higher birth size - accelerated BMI gain n = 137 (10.9%)	Higher birth size - slower BMI gain n= 145 (11.6%)	Lower birth size - accelerated BMI gain n = 332 (26.4%)	Average birth size - slower BMI gain n = 483 (38.4%)	Lower birth size - slower BMI gain n = 160 (12.7%)	Overall n = 1,257 (100%)
Weight							
Birth weight (kg)	1,254	3.5 (0.5)	3.4 (0.4)	3.1 (0.4)	3.2 (0.4)	3.0 (0.5)	3.3 (0.5)
Weight at 1 year (kg)	1,143	11.5 (1.1)	10.3 (0.9)	11.0 (1.1)	9.7 (0.9)	9.1 (0.9)	10.1 (1.2)
Weight at 4 year (kg)	1,200	20.7 (2.9)	18.2 (2.1)	20.2 (3.1)	17.6 (2.1)	16.1 (1.9)	18.2 (2.7)
Height							
Birth length (cm)	1,224	49.8 (2.0)	49.9 (1.9)	49.1 (2.4)	49.6 (2.1)	49.0 (2.6)	49.6 (2.2)
Height at 1 year (cm)	1,143	77.7 (3.0)	76.7 (2.9)	77.2 (3.3)	76.4 (2.9)	76.3 (3.0)	76.7 (3.0)
Height at 4 year (cm)	1,200	106.7 (4.4)	105.2 (4.3)	107.2 (4.7)	105.5 (4)	104.6 (4.4)	105.6 (4.3)

Values are means and standard deviations. Abbreviations: BMI: body mass index

Table S2. Characteristics of included and non-included participants

	Participants (n=1,257)	Non-participants (n=1,013)	*p*-value*
	n (%), mean (SD) or median (P_{25}-P_{75})	n (%), mean (SD) or median (P_{25}-P_{75})	
Maternal characteristics			
Age at delivery (years)	30.9 (0.1)	29.7 (0.2)	<0.001
Pre-pregnancy BMI (kg/m^2)	22.6 (20.8 to 25.2)	22.5 (20.7 to 25.1)	0.559
History of allergy-related disease †	335 (26.7%)	246 (25.2%)	0.417
Smoking during pregnancy			
Never smoker	573 (46.2%)	361 (41.5%)	0.061
Smoking before pregnancy	458 (37.0%)	334 (38.5%)	
Smoking during pregnancy	208 (16.8%)	173 (20.0%)	
Educational level			
Primary or less	263 (21.2%)	312 (33.4%)	<0.001
Secondary	515 (41.4%)	376 (40.3%)	
University	465 (37.4%)	245 (26.3%)	
Child characteristics			
Sex: girls	622 (49.5%)	415 (47.2%)	0.302
Birth weight (grams)	3,258 (458)	3,256 (521)	0.764
Low birth weight (<2,500 g)	65 (5.2%)	45 (5.2%)	0.994
Gestational age (weeks)	39.9 (38.9 to 40.7)	39.9 (38.9 to 40.6)	0.959
Preterm birth (<37 weeks gestation)	48 (3.8%)	40 (4.6%)	0.390
Duration of any breastfeeding (weeks)	25.9 (10.7 to 43.4)	21.8 (5.7 to 39)	0.001
Low respiratory tract infections during the first year	438 (35.4%)	240 (34.3%)	0.637

Abbreviations: BMI: body mass index

†Defined as reporting at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis

*p-value for chi-squared, t-test or U-Mann Witney tests

Table S3. Adjusted associations of early childhood BMI trajectories with lung function at seven years

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
n	1,195		1,195		1,195		1,193	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	3.3 (1.0 to 5.6)	0.005	1.5 (-0.9 to 3.8)	0.215	-1.5 (-2.9 to -0.1)	0.031	-2.8 (-7.4 to 1.7)	0.222
Higher birth size - Slower BMI gain	0.6 (-1.1 to 2.3)	0.480	1.1 (-0.6 to 2.8)	0.214	0.4 (-0.6 to 1.5)	0.407	1.7 (-1.7 to 5.1)	0.325
Lower birth size - Accelerated BMI gain	2.8 (0.5 to 5.0)	0.016	1.2 (-1.1 to 3.5)	0.315	-1.3 (-2.7 to 0.1)	0.064	-1.9 (-6.4 to 2.6)	0.417
Lower birth size - Slower BMI gain	-3.1 (-5.2 to -0.9)	0.006	-1.9 (-4.1 to 0.3)	0.098	1.1 (-0.2 to 2.4)	0.096	0.4 (-3.9 to 4.7)	0.858

All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF$_{25-75}$: forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S4. Adjusted associations of early childhood BMI trajectories with lung function at seven years - Stratified by sex

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
Girls								
n	590		590		590		588	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	5.6 (2.2 to 8.9)	0.001	4.5 (1.2 to 7.7)	0.007	-0.9 (-2.8 to 1.0)	0.370	0.3 (-5.9 to 6.5)	0.928
Higher birth size - Slower BMI gain	1.9 (-0.5 to 4.3)	0.120	1.6 (-0.8 to 4)	0.186	-0.2 (-1.6 to 1.2)	0.806	0.8 (-3.7 to 5.3)	0.732
Lower birth size - Accelerated BMI gain	4.5 (1.2 to 7.8)	0.007	3.2 (0 to 6.5)	0.051	-1.0 (-2.9 to 0.9)	0.316	0.5 (-5.7 to 6.7)	0.883
Lower birth size - Slower BMI gain	-3.3 (-6.6 to -0.1)	0.045	-2.1 (-5.4 to 1.1)	0.193	1.4 (-0.4 to 3.3)	0.134	-0.9 (-7.1 to 5.2)	0.768
Boys								
n	605		605		605		605	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	1.3 (-1.8 to 4.4)	0.420	-1.4 (-4.7 to 1.9)	0.395	-2.3 (-4.4 to -0.3)	0.025	-6.3 (-13 to 0.3)	0.062
Higher birth size - Slower BMI gain	-0.3 (-2.7 to 2.1)	0.803	0.8 (-1.7 to 3.2)	0.543	1.0 (-0.5 to 2.6)	0.190	2.4 (-2.6 to 7.4)	0.340
Lower birth size - Accelerated BMI gain	1.3 (-1.7 to 4.4)	0.388	-0.6 (-3.8 to 2.6)	0.727	-1.5 (-3.5 to 0.5)	0.146	-3.9 (-10.4 to 2.6)	0.239
Lower birth size - Slower BMI gain	-3.2 (-6.1 to -0.3)	0.030	-2.3 (-5.3 to 0.8)	0.148	0.7 (-1.2 to 2.6)	0.471	-0.2 (-6.3 to 6.0)	0.957
*p-value for sex interaction**		0.216		0.075		0.385		0.410

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF$_{25-75}$, forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

* p-value for the Wald test, which tests the overall significance of the interaction for all trajectory groups

Table S5. Adjusted associations of early childhood BMI trajectories with lung function at seven years - Excluding children with current asthma at seven years

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
n	1,087		1,087		1,087		1,085	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	3.6 (1.2 to 5.9)	0.003	1.8 (-0.6 to 4.2)	0.149	-1.5 (-3.0 to -0.1)	0.038	-3.0 (-7.7 to 1.7)	0.214
Higher birth size - Slower BMI gain	0.9 (-0.9 to 2.6)	0.323	1.1 (-0.6 to 2.9)	0.209	0.2 (-0.8 to 1.3)	0.662	1.3 (-2.2 to 4.8)	0.466
Lower birth size - Accelerated BMI gain	3.1 (0.8 to 5.4)	0.009	1.5 (-0.9 to 3.9)	0.215	-1.3 (-2.7 to 0.1)	0.069	-1.8 (-6.5 to 2.9)	0.453
Lower birth size - Slower BMI gain	-2.7 (-4.9 to -0.4)	0.020	-1.9 (-4.2 to 0.4)	0.108	0.7 (-0.7 to 2.1)	0.307	-0.4 (-5.0 to 4.1)	0.846

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF$_{25-75}$, forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S6. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Excluding children from mothers who smoked during pregnancy

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
n	995		995		995		993	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	2.7 (0.2 to 5.3)	0.036	1.0 (-1.6 to 3.6)	0.448	-1.5 (-3.0 to 0.1)	0.064	-3.0 (-8.1 to 2.1)	0.247
Higher birth size - Slower BMI gain	0.6 (-1.2 to 2.5)	0.511	0.9 (-1.0 to 2.8)	0.352	0.2 (-0.9 to 1.4)	0.683	0.8 (-2.9 to 4.5)	0.664
Lower birth size - Accelerated BMI gain	2.4 (-0.1 to 5.0)	0.064	1.6 (-1.0 to 4.2)	0.228	-0.7 (-2.2 to 0.9)	0.402	-0.4 (-5.4 to 4.7)	0.886
Lower birth size - Slower BMI gain	-2.8 (-5.1 to -0.4)	0.020	-1.4 (-3.8 to 0.9)	0.236	1.2 (-0.2 to 2.6)	0.086	1.2 (-3.4 to 5.8)	0.615

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF$_{25-75}$, forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S7. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Excluding children with extreme lung function values (<p1 & >p99)

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
n	1,172		1,171		1,174		1,172	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	2.7 (0.6 to 4.8)	0.013	1.3 (-0.9 to 3.4)	0.247	-0.8 (-2.1 to 0.5)	0.230	-0.9 (-5.3 to 3.4)	0.672
Higher birth size - Slower BMI gain	0.2 (-1.4 to 1.7)	0.825	0.8 (-0.7 to 2.4)	0.293	0.6 (-0.4 to 1.5)	0.218	1.0 (-2.2 to 4.2)	0.534
Lower birth size - Accelerated BMI gain	2.7 (0.6 to 4.8)	0.011	1.6 (-0.5 to 3.7)	0.136	-0.9 (-2.2 to 0.4)	0.157	-0.3 (-4.6 to 4.0)	0.889
Lower birth size - Slower BMI gain	-2.8 (-4.8 to -0.8)	0.007	-1.6 (-3.6 to 0.4)	0.107	1.3 (0.1 to 2.6)	0.033	1.0 (-3.1 to 5.1)	0.637

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF $_{25-75}$, forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence intervals

Table S8. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Excluding preterm children

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
n	1,151		1,151		1,151		1,149	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	2.8 (0.5 to 5.1)	0.015	1.1 (-1.2 to 3.5)	0.335	-1.4 (-2.8 to 0.0)	0.046	-2.8 (-7.4 to 1.7)	0.222
Higher birth size - Slower BMI gain	0.6 (-1.1 to 2.3)	0.495	1.2 (-0.5 to 2.9)	0.181	0.5 (-0.5 to 1.6)	0.315	2.1 (-1.3 to 5.4)	0.235
Lower birth size - Accelerated BMI gain	2.8 (0.5 to 5.1)	0.017	1.4 (-1.0 to 3.7)	0.257	-1.2 (-2.6 to 0.2)	0.103	-1.4 (-6.0 to 3.2)	0.546
Lower birth size - Slower BMI gain	-3.0 (-5.2 to -0.8)	0.008	-1.6 (-3.9 to 0.6)	0.161	1.3 (-0.1 to 2.6)	0.064	1.2 (-3.2 to 5.7)	0.581

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF$_{25-75}$, forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval

Table S9. Adjusted associations of early childhood BMI trajectories with lung function at seven years – Restricting models to children with at least two acceptable manoeuvres reproducible within 150 mL

BMI trajectories	Percent predicted FVC (%)		Percent predicted FEV$_1$ (%)		Percent predicted FEV$_1$/FVC (%)		Percent predicted FEF$_{25-75}$ (%)	
	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value	Coef (95% CI)	*p*-value
n	939		939		939		939	
Average birth size - Slower BMI gain	Reference		Reference		Reference		Reference	
Higher birth size - Accelerated BMI gain	4.9 (2.4 to 7.4)	<0.001	2.7 (0.2 to 5.2)	0.033	-1.9 (-3.4 to -0.4)	0.014	-2.4 (-7.4 to 2.6)	0.354
Higher birth size - Slower BMI gain	0.0 (-1.8 to 1.8)	0.994	0.2 (-1.6 to 2.0)	0.809	0.2 (-0.9 to 1.3)	0.711	0.7 (-2.9 to 4.2)	0.701
Lower birth size - Accelerated BMI gain	2.4 (0.0 to 4.8)	0.046	0.9 (-1.5 to 3.3)	0.453	-1.4 (-2.8 to 0.1)	0.062	-2.6 (-7.4 to 2.2)	0.280
Lower birth size - Slower BMI gain	-2.6 (-4.9 to -0.3)	0.025	-1.7 (-3.9 to 0.6)	0.154	0.9 (-0.5 to 2.2)	0.210	0.0 (-4.6 to 4.6)	0.997

All models were adjusted for maternal age at pregnancy, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, and child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year

Abbreviations: BMI: body mass index; FEF $_{25-75}$, forced expiratory flow 25-75%; FEV$_1$: Forced expiratory volume in 1 second; FVC: forced vital capacity; Coef: regression coefficient: 95% CI; 95% confidence interval