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Early childhood growth is associated with lung function at 7 years: a prospective population-based study

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ABSTRACT Previous studies have related early postnatal growth with later lung function but their interpretation is limited by the methods used to assess a child's growth. We aimed to assess the association of early childhood growth, measured by body mass index (BMI) trajectories up to 4 years, with lung function at 7 years.

We included 1257 children from the Spanish Infancia y Medio Ambiente population-based birth cohort. Early childhood growth was classified into five categories based on BMI trajectories up to 4 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 to lung function (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 25%–75% of FVC ($FEF_{25–75\%}$)) at 7 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 a higher FVC % pred (3.3%, 95% CI 1.0%–5.6%) and a lower FEV_1/FVC % pred (−1.5%, 95% CI −2.9%–−0.1%) at 7 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 FVC % pred at 7 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 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.

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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 s (FEV_1)) in childhood [6–11]. In addition, previous studies have 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 a 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 difficult to interpret and apply in clinical settings. Other analytical strategies that integrate repeated weight information but are 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 4 years with lung function at 7 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 4 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=2270) 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 as follows: age ⩾16 years, 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 4 years and lung function data at 7 years (supplementary 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 4 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 using the World Health Organization 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 or height according to the BMI trajectories in our study sample is presented in supplementary table S1.

Lung function

At 7 years, trained nurses measured lung function by spirometry according to the American Thoracic Society and European Respiratory Society guidelines [18]. FVC, FEV_1 and forced expiratory flow at 25%–75% of 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 % pred lung function parameters 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 7 years by trained nurses; and asthma at 7 years through the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents. As previously agreed in the Mechanisms of the Development of Allergy (MeDALL) project [20], 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 (see full questions in the supplementary material).

Statistical analysis

We assessed the association of BMI trajectories from birth to 4 years with lung function (FVC, FEV_1, FEV_1/FVC and $FEF_{25-75\%}$) at 7 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, 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 co-variables required to adjust our models (supplementary 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 (supplementary material).

Missing data accounted for 4.9% of total observations. We used a complete case strategy and report 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 $p<0.05$ for multivariate analyses, and at $p<0.2$ for interaction tests.

Results

Sample description

We included 1257 children in the present analysis. Mothers of these children were older at pregnancy, had a higher educational level and breastfed for a longer period than mothers of children not included in the present analysis (supplementary 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 7 years

Figure 2 and supplementary table S3 show the adjusted associations between BMI trajectories up to 4 years and lung function at 7 years. Compared to children with average birth size and slower BMI gain (reference), children with higher birth size and accelerated BMI gain had higher FVC % pred

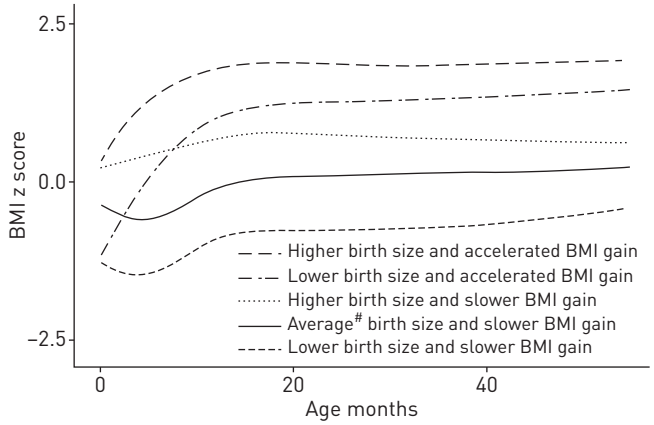

FIGURE 1 Body mass index (BMI) z-score trajectories from birth to 4 years. Birth size recorded as BMI. Adapted from [14] with permission. #: reference category.

(3.3%, 95% CI 1.0%–5.6%) and lower FEV_1/FVC ratio % pred (−1.5%, 95% CI −2.9%–−0.1%) at 7 years. Similarly, children with lower birth size and accelerated BMI gain had higher FVC % pred (2.8%, 95% CI 0.5%–5.0%) and tended to have lower FEV_1/FVC % pred (−1.3%, 95% CI −2.7%–0.1%) than children in the reference category. In contrast, children with lower birth size and slower BMI gain had lower FVC % pred (−3.1%, 95% CI −5.2%–−0.9%) and tended to have lower FEV_1 (−1.9%, 95% CI −4.1%–0.3%), but higher FEV_1/FVC % pred (1.1%, 95% CI −0.2%–2.4%) than children in 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, supplementary table S4). The association of

TABLE 1 Characteristics of the study sample

	Result
Subjects n	1257
Maternal characteristics[#]	
Age at delivery years	30.9±0.1
Pre-pregnancy BMI kg·m^{-2}	22.6 (20.8–25.2)
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[+]	
Female sex	622 (49.5)
Birth weight g	3258±458
Low birth weight (<2500 g)	65 (5.2)
Gestational age weeks	39.9 (38.9–40.7)
Preterm birth (<37 weeks)	48 (3.8)
Duration of any breastfeeding weeks	25.9 (10.7–43.4)
Lower respiratory tract infections during the first year	438 (35.4)
Age at 7 years	7.5 (7.0–7.8)
Height at 7 years cm	124.7 (6.3)
Asthma at 7 years[§]	115 (9.2)
BMI trajectories from birth to 4 years	
Higher birth size and accelerated BMI gain	137 (10.9)
Lower birth size and accelerated BMI gain	145 (11.6)
Higher birth size and slower BMI gain	332 (26.4)
Average birth size and slower BMI gain (Reference)	483 (38.4)
Lower birth size and slower BMI gain	160 (12.7)
Lung function at 7 years[f]	
FVC % pred	101.8 (12.0)
FEV_1 % pred	104.8 (11.9)
FEV_1/FVC % pred	96.7 (7.5)
$FEF_{25–75\%}$ % pred	95.1 (23.8)

Data are presented as n (%), mean±SD or median (25th–75th percentile), unless otherwise stated. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow at 25%–75% of FVC. [#]: missing values: 6 in age at delivery, 8 in pre-pregnancy BMI, 1 in allergy-related disease, 18 in smoking, 14 in educational level; [¶]: defined as reporting at least one of the following: allergic asthma, atopic dermatitis, eczema or allergic rhinitis; [+]: missing values: 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; [§]: 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; [f]: calculated using Global Lung Function Initiative 2012 prediction equations.

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 (supplementary tables S5–S9). However, exclusion of children with extreme lung function values resulted in the attenuation of some FEV_1/FVC effect estimates (supplementary 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 (supplementary table S9).

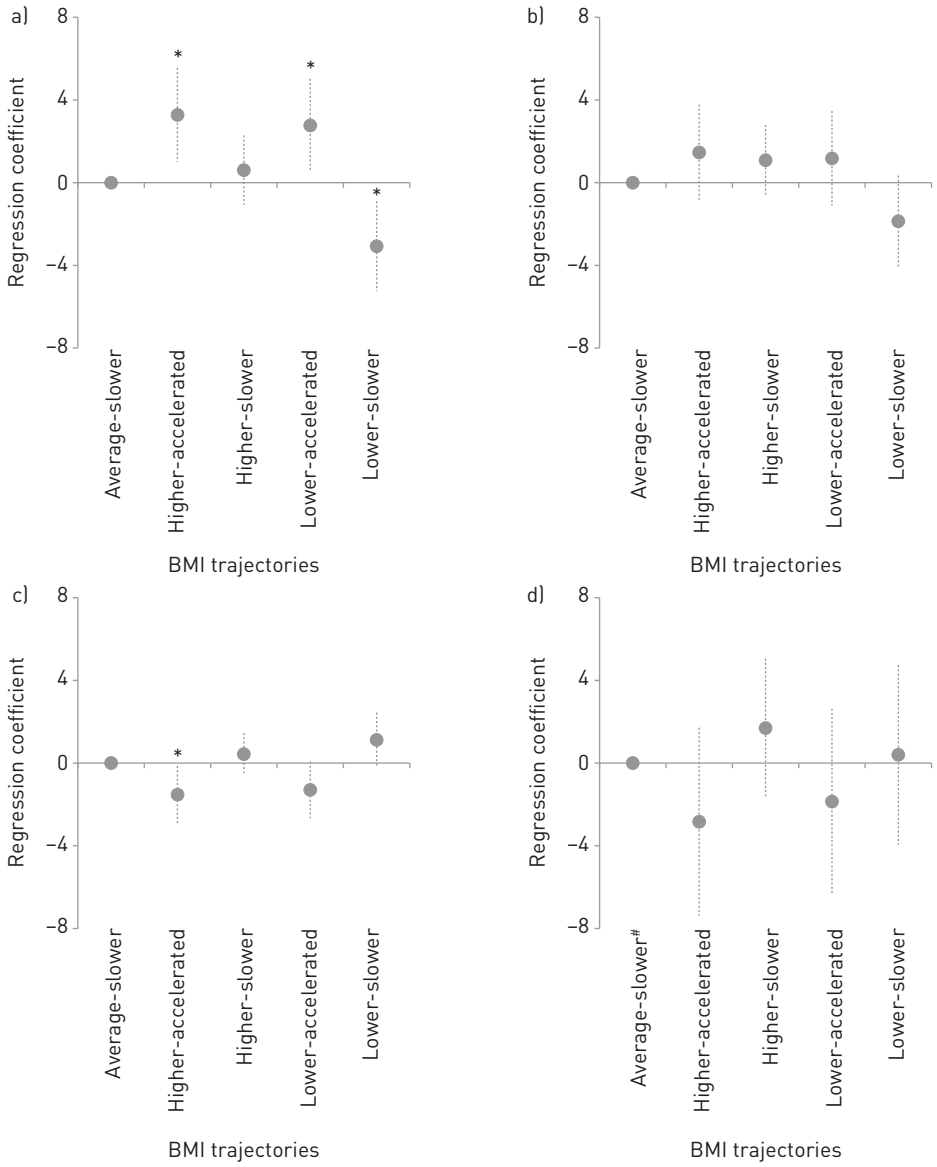

FIGURE 2 Adjusted associations of early childhood body mass index (BMI) trajectories with lung function at 7 years. Trajectories are described as average birth size and slower BMI gain (average-slower), n=457; higher birth size and accelerated BMI gain (higher-accelerated), n=133; higher birth size and slower BMI gain (higher-slower), n=317; lower birth size and accelerated BMI gain (lower-accelerated), n=138; and lower birth size and lower BMI gain (lower-slower), n=150. a) Forced vital capacity (FVC) % pred; b) forced expiratory volume in 1 s (FEV_1) % pred; c) FEV_1/FVC % pred; d) forced expiratory flow at 25%–75% of FVC ($FEF_{25–75\%}$) % pred. All models were adjusted for maternal age at delivery, pre-pregnancy BMI, history of allergy-related disease, educational level, smoking during pregnancy, child's gestational age, duration of any breastfeeding and lower respiratory tract infections during the first year. Owing to missing values in the covariates, the study sample included in the multivariable analysis was 1195 for FVC, FEV_1 and FEV_1/FVC, and 1193 for $FEF_{25–75\%}$. #: n=455; *: p<0.05.

Discussion

Main findings

In this prospective population-based study we found that BMI trajectories from birth to 4 years related to lung function at 7 years. Specifically, we found 1) both children with a lower and a higher birth size plus accelerated BMI gain had higher FVC and lower FEV_1/FVC ratio at 7 years; 2) children with lower birth size and slower BMI gain had lower FVC and FEV_1, but higher FEV_1/FVC ratio at 7 years (although the effect estimates for FEV_1 and FEV_1/FVC were imprecise); and 3) no associations of BMI trajectories with $FEF_{25–75\%}$ at 7 years.

Comparison with previous studies

Our finding that accelerated BMI gain in the first 4 years of life is associated with higher FVC and lower FEV_1/FVC ratio at 7 years is in line with previous longitudinal studies [10–13] that 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 3 years of life, were associated with higher FVC and FEV_1 but lower FEV_1/FVC ratio at 10 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 fetal growth followed by accelerated infant weight growth up to 1 year (defined as growth percentile change between time periods) was associated with higher FVC and lower FEV_1/FVC ratio at 10 years [12]. An important contribution from our study is that, because we distinguished two patterns of accelerated BMI gain (starting from higher or lower birth size), we have been 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 had a 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 9 years of life (calculated as the difference between two time points) had higher spirometry measures at age 9 years than those without catch-up [6]. Another study 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 7 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 ratios at 7 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 7 years. This finding is in contrast to a previous study showing that rapid weight gain during the first 3 months of life (derived from individual growth trajectories) was associated with a decreased $FEF_{25–75\%}$ at 8 years [10]. This discrepancy may be attributed to different definitions of childhood growth and different exposure assessment periods (*i.e.* first 3 months *versus* first 4 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 an 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 is associated with lower FEV_1/FVC levels in adolescence [27], and by another study showing that subjects with higher BMI have higher quantities of 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, given that 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 7 years is restricted fetal growth, because 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 fetal growth affects normal lung development, thus causing structural alterations [29, 30] that 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 by paediatricians and the general public. In addition, our findings, together with existing literature, provide evidence that early childhood growth impacts lung function development, and therefore may affect future respiratory health. Because 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. The availability of BMI trajectories from birth to 4 years allowed us to account simultaneously for birth size and BMI gain when estimating the association of early growth and lung function. By using BMI trajectories as a marker of early growth, we were able to take into account weight and height changes during the first years of life simultaneously, while most 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 who 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 because we did not have information on physical activity or diet before 4 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 generalisability 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

We found that, independently of birth size, children with accelerated BMI gain in early childhood had higher lung function at 7 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 7 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, provide evidence 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.

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Author contributions: G.P. Peralta, M. Casas and J. Garcia-Aymerich designed the study. G.P. Peralta conducted the statistical analyses and wrote the initial draft. M. Casas and J. Garcia-Aymerich had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data

for the work, revised the manuscript for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

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