ORIGINAL ARTICLE

The effect of early growth patterns and lung function on the development of childhood asthma: a population based study

Maribel Casas,[1,2,3,4,5] Herman T den Dekker,[1,2,6] Claudia J Kruithof,[1,6] Irwin K Reiss,[7] Martine Vrijheid,[3,4,5] Jordi Sunyer,[3,4,5] Johan C de Jongste,[2] Vincent W V Jaddoe,[1,6,8] Liesbeth Duijts[2,6,7]

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For numbered affiliations see end of article.

Correspondence to
Dr Maribel Casas, The Generation R Study Group, Erasmus MC, University Medical Center, Rotterdam 3015 GD, The Netherlands;
maribel.casas@isglobal.org

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ABSTRACT

Background Infant weight gain is associated with lower lung function and a higher risk of childhood asthma. Detailed individual childhood growth patterns might be better predictors of childhood respiratory morbidity than the difference between two weight and height measurements. We assessed the associations of early childhood growth patterns with lung function and asthma at the age of 10 years and whether the child's current body mass index (BMI) influenced any association.

Methods We derived peak height and weight growth velocity, BMI at adiposity peak, and age at adiposity peak from longitudinally measured weight and height data in the first 3 years of life of 4435 children enrolled in a population-based prospective cohort study. At 10 years of age, spirometry was performed and current asthma was assessed by questionnaire. Spirometry outcomes included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio, and forced expiratory flow after exhaling 75% of vital capacity (FEF_{75}).

Results Greater peak weight velocity was associated with higher FVC but lower FEV_1/FVC and FEF_{75}. Greater BMI at adiposity peak was associated with higher FVC and FEV_1 but lower FEV_1/FVC and FEF_{75}. Greater age at adiposity peak was associated with higher FVC, FEV_1, FEV_1/FVC and FEF_{75}, particularly in children with a small size at birth, and lower odds of current asthma in boys. The child's current BMI only explained the associations of peak weight velocity and BMI at adiposity peak with FVC and FEV_1. Peak height velocity was not consistently associated with impaired lung function or asthma.

Conclusion Peak weight velocity and BMI at adiposity peak were associated with reduced airway patency in relation to lung volume, whereas age at adiposity peak was associated with higher lung function parameters and lower risk of asthma at 10 years, particularly in boys.

Key messages

What is the key question?

► Are individual childhood growth patterns, derived from longitudinally measured weight and height data in the first 3 years of life, good predictors of lung function development and asthma risk in later childhood?

What is the bottom line?

► Greater peak weight velocity and body mass index at adiposity peak are associated with lower airway patency in relation to lung volume at 10 years, independently of the child's current weight status, whereas greater age at adiposity peak favours respiratory health, particularly in boys.

Why read on?

► Using data from a large population-based prospective study, we demonstrate that detailed individual early childhood growth patterns affect respiratory health until the age of 10.

INTRODUCTION

Early infancy is a critical age for the development of respiratory diseases later in life.[1] In recent years, several studies have reported an association between early childhood weight gain and the development of asthma.[2–18] A proposed underlying mechanism is that childhood weight gain leads to developmental adaptations of the lungs and airways resulting in reduced airway calibre and airflow limitation.[19] However, results from studies assessing the influence of childhood weight gain on airway calibre, reflected by lung function values, have been inconsistent.[3 5 14 16–18 20–22] The majority of these studies have observed that infant weight gain is associated with higher lung volume and airflow,[14 18 20–23] but others have reported lower airflow in relation to postnatal weight gain.[3 5 16 17] In these studies weight gain was generally defined as the difference in two growth measurements. Detailed and specific individual longitudinal childhood growth patterns might be better predictors of lung function and the development of asthma later in life. We previously reported that weight gain velocity and particularly body mass index at adiposity peak (BMIAP) were associated with a higher risk of wheezing at pre-school age.[24] Few other studies have used individual growth trajectories to study their influence on childhood respiratory morbidity[3 4 6 10] and only one assessed lung function,[3] showing that airflow limitation at 15 years of age was associated with early life weight gain.[3] This study did not evaluate the influence of BMIAP. Further, it is not clear

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whether allergic sensitisation, a maternal history of asthma or atopy, and the child's current weight status influence the association of early weight gain with lung function and asthma.

We examined the associations of early childhood growth patterns with lung function and asthma at 10 years of age, and examined the potential effect modification of maternal history of asthma or atopy, birth outcomes, the child's allergic sensitisation and body mass index (BMI) at 10 years of age. These early childhood growth patterns included peak height and weight velocities (PHV and PWV, respectively), which occur at around 1 month of age,[25] and BMIAP and age at adiposity peak (AGEAP) which usually occur at around 9 months.[26]

METHODS

Design

The study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onwards conducted in Rotterdam, the Netherlands.[27] Eligible pregnant women were those living in the study area at the moment of delivery who had a delivery date between April 2002 and January 2006. The majority of pregnant women were recruited at their first prenatal visit (gestational age <18 weeks), although enrolment was allowed until delivery. A total of 9778 mothers were enrolled in the study. Pregnant women were followed at each prenatal visit (early, mid and late pregnancy) and at delivery. After birth, children were followed at 2, 3, 4, 6, 11, 12, 14, 18, 24, 30, 36, 45 and 48 months, and at 6 and 9 years. At each follow-up visit, a questionnaire was administered to the parents and a physical examination of the child was performed to evaluate their growth, health, and physical and mental development. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam (MEC 40020.078.12/2012/165).

Longitudinal early childhood growth patterns

Well-trained staff obtained weight and height at ages 1, 2, 3, 4, 6, 11, 14, 18, 24 and 36 months based on the national care programme in the Netherlands. The median number of postnatal growth measurements (ie, weight and height) was 5 (90% range: 3–8); children with less than three measurements were excluded from modelling. PHV and PWV in early childhood were derived using the Reed1 model for boys and girls separately, considering growth measurements from 0 to 3 years of age, including birth weight and length. BMIAP and AGEAP were derived using a cubic mixed effects model fitted on log(BMI) from 14 days to 1.5 years, including sex as covariate, as described previously.[25] For each child, the maximum of the curve (ie, maximum adiposity peak) was taken to obtain the BMIAP and the AGEAP. The adiposity peak is defined as the age at maximum BMI between 14 days and 1.5 years[26]; therefore, the measurements after 1.5 were not included when modelling these data. This is in contrast to PWV and PHV which are considered to peak at different ages. A detailed description of these models is provided in the online supplementary file. PHV, PWH, BMIAP and AGEAP were expressed as SD scores (SDS).

Childhood lung function and asthma

Spirometry was performed at 10 years of age (mean: 9.8 years; SD: 0.3) according to the American Thoracic Society/European Respiratory Society guidelines. Lung function parameters included forced vital capacity (FVC) as a measure of lung volume, and forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, and forced expiratory flow after exhaling 75% of vital capacity (FEF_{75}), which reflect reduced airway patency in obstructive lung diseases such as asthma.[28 29] Lung function variables were converted into sex-, height-, age- and ethnicity-adjusted z-scores according to the Global Lung Function Initiative reference values.[30] Information on ever physician-diagnosed asthma was obtained at 10 years of age through questionnaires. We defined current asthma as ever been diagnosed with asthma by a doctor with either wheezing in the past 12 months or inhalant medication use in the past 12 months.

Covariates

Information on maternal characteristics including age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, pet keeping, psychological distress during pregnancy, parity and smoking during pregnancy was obtained from questionnaires during pregnancy. Maternal psychological distress during pregnancy was obtained by questionnaire at 20 weeks of gestation (range 18–25 weeks) by using the Brief Symptom Inventory (BSI),[31] a short version of the Symptom Checklist 90 (SCL-90). The BSI is a self-report instrument with good reliability and validity. For the current study, the 6-item depression scale was used, which has previously been published in detail.[32] Based on the Dutch cut-off values,[33] mothers were categorised as being sensitive for clinically significant psychological distress (yes/no) when having a score greater than 0.71 on the overall distress scale. Maternal gestational hypertensive disorders, gestational diabetes, and child's sex, gestational age and weight at birth were obtained from midwife and hospital records. Ethnicity was based on country of birth of the parents.[34] Postnatal questionnaires provided information on breastfeeding, day care attendance, lower respiratory tract infections and passive smoking in the first year. At the age of 10 years, inhalant allergic sensitisation for the five most common inhalant allergens (house dust mite, grass, birch, cat and dog) was determined by a skin prick test (ALK-Abelló, Almere, the Netherlands), using the 'scanned area' method.[35] Length and weight at 10 years of age were measured and BMI (in kg/m^2) adjusted for age and sex was calculated.[36]

Statistical analysis

We used linear and logistic regression models to assess the association of early childhood growth patterns with lung function and current asthma, respectively. All models were first adjusted for the sex and age of the child at the time of assessment of respiratory outcomes (minimally adjusted model), and then sequential adjustments for maternal characteristics (maternal age at enrolment, pre-pregnancy BMI and parity), socioeconomic characteristics (maternal educational level, child's ethnicity and maternal smoking during pregnancy), maternal history of asthma or atopy, maternal psychological distress during pregnancy, birth outcomes (birth weight and gestational age) and child's characteristics (day care attendance, lower respiratory tract infections and passive smoking at 1 year) were performed. Covariates were included based on previous literature[3 10 12 24] and whether they were associated with the exposures and the outcomes ($p<0.05$) (online supplementary figure S1). Because both childhood growth patterns and lung function parameters depend on sex, we stratified all analyses by sex. Effect modification by maternal history of asthma or atopy, preterm birth, small for gestational age, and child's inhalant allergic sensitisation was assessed by inclusion of the interaction terms in the model and stratified analysis ($p<0.05$). We defined preterm birth as being born before 37 weeks of gestation and being small for gestational age (below the 10th percentile of birth weight

adjusted for gestational age). We also assessed potential mediation by wheezing patterns[24] and the child's BMI at 10 years of age. First, we tested whether these variables met the conditions to act as mediators: (i) the mediator is associated with the exposure; (ii) the mediator is associated with the outcome; and (iii) a previously significant association between the exposure and the outcome is no longer significant when the mediator is included as a confounder in the models; in our case, we established that a coefficient had to change more than 10% to perform mediation analysis. Second, since lung function parameters are potentially correlated, we constructed a structural equation model to better estimate the effect of mediation (online supplementary figure S2). Finally, we assessed the sensitivity of the estimated average causal mediation effect (ACME) to the effect of unmeasured mediator-outcome confounding. This sensitivity analysis estimates how large the correlation (r) between the unmeasured confounders and the residual variance of the mediator-outcome model has to be for the ACME to disappear (ACME=0). The larger the r value, the less sensible the ACME is to the effect of unmeasured confounding. We also conducted sensitivity analysis to assess the robustness of the lung function results by excluding those children who were unable to perform reproducible spirometry curves, those who received asthma drugs in the past 12 months or 48 hours before spirometry, and children with asthma. Because we performed a total of 20 comparisons (four exposures×five outcomes), we had 64% probability of observing at least one significant effect due to chance [1 (1–0.05)^20]. We therefore applied Bonferroni correction adjusting the alpha level to 0.003 (0.05/20). To account for potential selection bias due to follow-up losses when only participants with available information on exposures and outcomes were included, we used inverse probability weighting. In brief, we used information available for all participants with written informed consent at 10 years of age to predict the probability of inclusion in the analysis, and used the inverse of those probabilities as weights in the analyses so that results would be representative for the populations of the cohort at 10 years of age. To reduce the likelihood of bias due to missing data, we performed multiple imputation of missing values for the covariates where 10 completed datasets were generated and analysed using the standard combination rules for multiple imputations.[37 38] No major differences in covariate distributions between the observed and the imputed datasets were found (table 1). Effect estimates are presented as z-scores of FVC, FEV_1, FEV_1/FVC and FEF_{75}, or OR for current asthma with their 95% CI. All statistical analyses were conducted with Stata 14.0 statistical software (Stata Corporation, College Station, TX, USA).

RESULTS

Of the 5861 children whose parents gave written informed consent at 10 years, 4435 were included in the present analysis (online supplementary figure S3). The characteristics of mothers and their children are given in table 1. Current asthma was reported in 8% of children at 10 years of age. All covariates differed between those included and those excluded from this study, apart from maternal history of asthma or atopy, pet keeping, gestational hypertension disorders, child's sex, breastfeeding, lower respiratory tract infections and passive smoking age 1 year (online supplementary table S1).

A greater PHV was associated with a lower FEF_{75} z-score in boys (−0.01 (95% CI −0.01 to −0.00) per SDS increase) but not in girls (−0.00 (95% CI −0.01 to 0.00) per SDS increase), although sex differences were not significant (p=0.68) (figure 1 and online supplementary table S2). A greater PWV was associated with a higher FVC z-score (0.03 (95% CI 0.02 to 0.05)) and lower FEV_1/FVC and FEF_{75} z-score (−0.05 (95% CI −0.07 to −0.03) and −0.05 (95% CI −0.06 to −0.03) per SDS increase, respectively). No differences were observed between boys and girls (p>0.05) (figure 1 and online supplementary table S2). A greater BMIAP was associated with a higher FVC (0.15 (95% CI 0.11 to 0.19)), particularly in girls (0.18 (95% CI 0.12 to 0.24) per SDS increase) (p=0.05), and higher FEV_1 only in girls (0.10 (95% CI 0.05 to 0.16) per SDS increase) (p=0.04). A greater BMIAP was also associated with a lower FEV_1/FVC and FEF_{75} (−0.15 (95% CI −0.19 to −0.10) and −0.09 (95% CI −0.13 to −0.05) per SDS increase, respectively) in both boys and girls (p=0.94 and p=0.54, respectively) (figure 1 and online supplementary table S2). Among boys, a greater AGEAP was associated with a higher FVC and FEV_1 (0.09 (95% CI 0.03 to 0.15) and 0.16 (95% CI 0.09 to 0.22) per SDS increase, respectively) (p<0.01) and a higher FEV_1/FVC and FEF_{75} (0.08 (95% CI 0.02 to 0.15) and 0.11 (95% CI 0.05 to 0.17) per SDS increase, respectively), although the sex differences were not significant (p=0.58 and p=0.16, respectively) (figure 1 and online supplementary table S2). Among boys, a greater AGEAP was associated with a lower odds of current asthma (OR=0.75 (95% CI 0.59 to 0.96) per SDS increase) (p=0.03) (figure 1 and online supplementary table S2). We are only presenting the fully adjusted models because they yielded similar results to the minimally adjusted ones (online supplementary table S3). Effect estimates did not change after exclusion of those children with non-reproducible spirometry curves, those who took medication in the past 12 months or 48 hours before spirometry, and those who had current asthma at the time of spirometry (data not shown). Complete case analyses revealed similar results, although the associations of PHV with FEF_{75} and of AGEAP with FVC in boys did not reach statistical significance (data not shown). Inverse probability weighting showed no differences on effect estimates and therefore obtained results were representative for the whole population of the Generation R Study at the age of 10 years (data not shown). After applying Bonferroni correction, all p-values exceeded 0.003 except the association of AGEAP and current asthma in boys (p=0.022) (online supplementary table S4).

A greater BMIAP was associated with a higher odds of asthma at 10 years of age among children whose mothers had a history of asthma or atopy, but not among children whose mothers did not have a history of asthma or atopy (p=0.03) (figure 2 and online supplementary table S2). Among small for gestational age infants (ie, not normal birth weight infants), a greater PWV was associated with a higher FVC (p=0.04), and a greater AGEAP was associated with a higher FEV_1/FVC and FEF_{75} (p=0.03 and p=0.01, respectively) (figure 2 and online supplementary table S2). Among children who did not have allergic sensitisation at 10 years of age, a greater AGEAP was associated with a lower odds of current asthma (p<0.01) (figure 2 and online supplementary table S2). Finally, we tested the potential role of wheezing patterns and child's BMI at 10 years of age on the previously observed associations of PHV, PWV, BMIAP and AGEAP with lung function parameters (FVC, FEV_1, FEV_1/FVC and FEF_{75}) and current asthma. Child's BMI at 10 years of age only met the conditions to act as a mediator for the associations of PWV and BMIAP with lung function parameters FVC, FEV_1 and FEV_1/FVC (data not shown). Thus, we only performed mediation analyses for these associations. Subsequent mediation analysis showed that the child's BMI at 10 years of age completely explained the associations of PWV with FVC and FEV_1. After considering BMI at 10 years of age, a greater PWV was associated with a lower

Table 1 Observed and imputed characteristics of mothers and children (n=4435)

	Data missing (%)	Observed dataset	Imputed dataset
Maternal characteristics			
Age at enrolment (years)	0.0	31.4 (4.7)	31.4 (4.7)
Pre-pregnancy body mass index (kg/m^2)	9.2	24.4 (4.2)	24.4 (4.1)
Educational level	5.9		
Primary or secondary		44.8	45.2
Higher		55.2	54.8
History of asthma or atopy, yes	12.7	44.9	46.2
Pet keeping, yes	20.8	33.3	33.2
Psychological distress during pregnancy, yes	22.1	7.2	7.7
Parity, multiparous	2.8	42.0	42.2
Smoked during pregnancy, yes	11.3	22.6	22.6
Gestational hypertensive disorders, yes	12.3	4.1	4.3
Gestational diabetes, yes	3.3	0.7	0.7
Infant characteristics			
Sex, female	0.0	50.3	50.3
Gestational age (weeks)*	0.4	40.1 (26.7–43.4)	40.1 (26.7–43.4)
Birth weight (g)	0.0	3455 (543)	3456 (543)
Ethnicity, non-European	1.5	28.5	28.6
Breastfeeding, never	6.5	7.6	7.6
Day care attendance age 1 year, yes	28.6	63.3	61.0
Lower respiratory tract infections age 1 year, yes	17.0	13.2	13.3
Passive smoking age 1 year, yes	17.3	16.1	17.6
Peak height velocity (PHV; cm/year)	2.2	49.3 (8.5)	–
Peak weight velocity (PWV; kg/year)	0.0	12.1 (2.1)	–
Body mass index at adiposity peak (BMIAP; kg/m^2)	7.8	17.6 (0.8)	–
Age at adiposity peak (AGEAP; months)	7.8	8.3 (0.7)	–
Child characteristics			
Age at the time of respiratory outcomes (years)	0.0	9.8 (0.3)	–
Allergic sensitisation, yes	19.1	33.0	33.1
Spirometry	7.1		
FVC (L)		2.33 (0.4)	–
FEV_1 (L)		2.02 (0.3)	–
FEV_1/FVC (%)		86.7 (5.7)	–
FEF_{75} (L/s)		1.14 (0.3)	–
Current asthma, yes	15.3	7.8	–
Body mass index age 10 years (z-score)	0.2	0.2 (1.0)	0.2 (1.0)

Values are percentages for categorical variables and means (SD) or medians (range) for continuous variables.
Data on early childhood growth patterns (PHV, PWV, BMIAP, AGEAP) and respiratory outcomes (spirometry parameters and current asthma) were not imputed.

FEV_1 and consequently lower FEV_1/FVC ratio (table 2). Also, the child's BMI at 10 years of age explained half of the associations of a greater BMIAP with a higher FVC but fully explained the association of a greater BMIAP with FEV_1. Hence, the effect of the child's BMI at 10 years of age on the association of BMIAP with the FEV_1/FVC ratio was minimal (table 2). In the sensitivity analysis of mediation, we obtained an average r value of 0.22.

DISCUSSION

Our results suggest that a greater PWV and BMIAP were associated with higher FVC and FEV_1 but lower FEV_1/FVC and FEF_{75}, and that a greater AGEAP was associated with higher FVC, FEV_1, FEV_1/FVC and FEF_{75} and lower odds of current asthma among boys. The child's weight status at 10 years completely explained the associations of childhood growth patterns with FEV_1, part of the associations with FVC, and just a small proportion of the associations with FEV_1/FVC and current asthma. The associations of PWV with FVC and AGEAP with FEV_1/FVC were stronger among small for gestational age infants. We also observed that the associations of BMIAP and AGEAP with current asthma were stronger among children whose mothers had a history of asthma or atopy or if they had no allergic sensitisation at 10 years, respectively.

Comparison with previous studies

The majority of previous studies assessing the association of early childhood weight gain with lung function later in life have

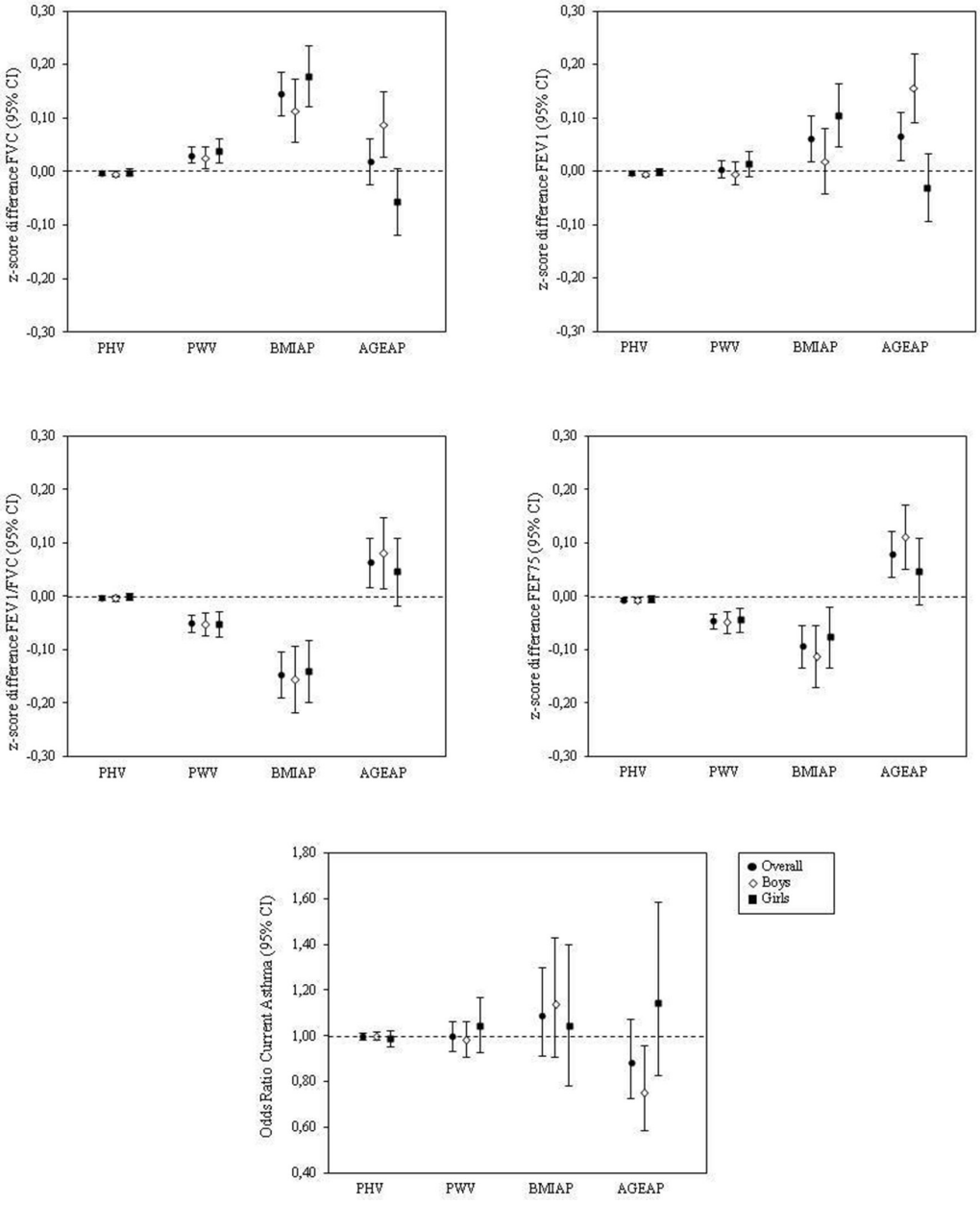

Figure 1 Associations of early childhood growth patterns with lung function and current asthma in the overall population, in boys and in girls. Values represent changes in z-scores or OR with their 95% CIs per standard deviation (SD) score increase in childhood growth patterns, and were obtained from linear or logistic regression models. 1 SD of PHV equals 8.4 cm/year, of PWV 2.1 kg/year, of BMIAP 0.8 kg/m^2 and of AGEAP 0.7 months (around 21 days). Models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress during pregnancy, parity, smoking during pregnancy, and child's sex (only the overall population models), gestational age, birth weight, ethnicity, day care attendance, lower respiratory tract infections, passive smoking at 1 year and age at the time of respiratory outcomes. AGEAP, age at adiposity peak; BMIAP, body mass index at adiposity peak; PHV, peak height velocity; PWV, peak weight velocity.

reported higher values for FVC and FEV_1.[14 18 20–23] Those studies that also assessed FEV_1/FVC reported a lower ratio associated with weight gain during the first year of life.[3 14 22] Interestingly, the magnitude of deficits in the FEV_1/FVC ratio in these studies is similar to that in the present study regarding PWV and BMIAP. Previous studies showed that weight gain in the first 3 months of life was associated with a −0.13 lower FEV_1/FVC z-score at 8 years,[14] a greater PWV with a −0.13 lower FEV_1/FVC z-score at 15 years,[3] and weight gain during the first year of life with a −0.08 lower FEV_1/FVC z-score between 4 and 19 years of age.[22] In our study we showed that BMIAP had a stronger effect on FVC, FEV_1 and the FEV_1/FVC ratio than PWV, and that this association was consistent after the analysis was restricted to children without asthma. To the best of our knowledge, this is the first time that the relationship between BMIAP and lung function has been assessed. Our results agree with findings from the same cohort at earlier ages, where PWV and BMIAP were associated with a higher risk of wheezing at 6 years of age.[24] No previous studies have assessed AGEAP in relation to respiratory outcomes in childhood. We observed here that the later the AGEAP, the higher the increase in lung function parameters at 10 years of age, particularly in boys and in small for gestational age infants. These results agree with previous findings from the Generation R cohort where children with a restricted fetal and

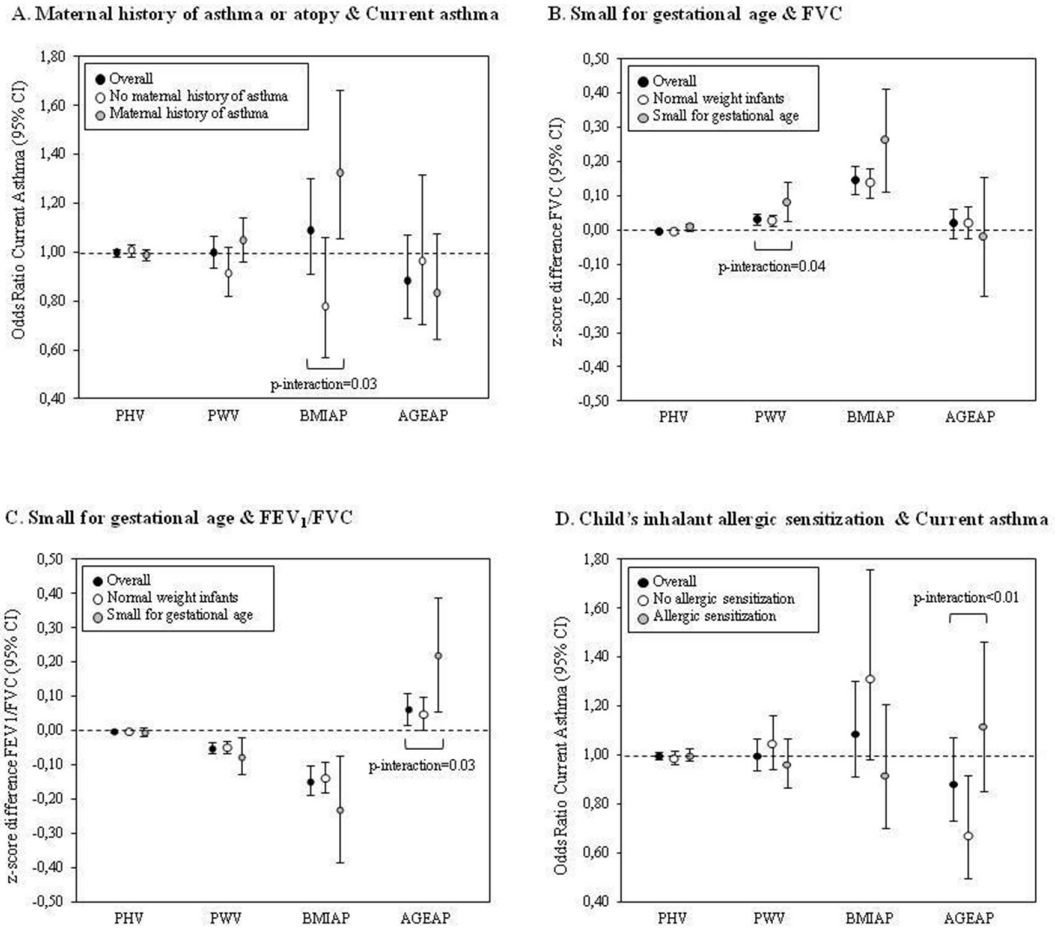

Figure 2 Effect modification by maternal history of asthma and atopy (A), small for gestational age (B and C), and child's inhalant allergic sensitisation (D) on the association of early childhood growth patterns with lung function and current asthma. Values represent changes in z-scores or OR with their 95% CIs per SD score increase in childhood growth patterns and were obtained from linear or logistic regression models. 1 SD of PHV equals 8.4 cm/year, of PWV 2.1 kg/year, of BMIAP 0.8 kg/m^2, and of AGEAP 0.7 months (around 21 days). Models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress during pregnancy, parity, smoking during pregnancy, and child's sex, gestational age, birth weight, ethnicity, day care attendance, lower respiratory tract infections, passive smoking at 1 year, and age at the time of respiratory outcomes. AGEAP, age at adiposity peak; BMIAP, body mass index at adiposity peak; PHV, peak height velocity; PWV, peak weight velocity.

Table 2 Mediation analysis showing associations of peak weight velocity (PWV) and body mass index at adiposity peak (BMIAP) with lung function considering the BMI of the child at age 10 years in the overall population

	FVC z-score (95% CI)	FEV_1 z-score (95% CI)	FEV_1/FVC z-score (95% CI)
PWV			
Indirect effect	0.03 (0.02 to 0.03)	0.02 (0.02 to 0.03)	−0.01 (−0.01 to -0.01)
Direct effect	0.01 (0.00 to 0.01)	−0.02 (−0.02 to -0.01)	−0.04 (−0.05 to -0.04)
Total effect	0.03 (0.03 to 0.04)	0.01 (0.00 to 0.01)	−0.05 (−0.05 to -0.04)
BMIAP			
Indirect effect	0.08 (0.07 to 0.08)	0.08 (0.07 to 0.08)	−0.02 (−0.02 to -0.01)
Direct effect	0.07 (0.06 to 0.08)	−0.00 (−0.02 to 0.01)	−0.13 (−0.14 to -0.11)
Total effect	0.15 (0.14 to 0.16)	0.07 (0.06 to 0.08)	−0.14 (−0.16 to -0.13)

Values represent differences in z-scores with their 95% CIs per SD score increase in childhood growth patterns, and were obtained from linear regression models. 1 SD of PWV equals 2.1 kg/year and of BMIAP 0.8 kg/m^2. Models were adjusted for maternal age at enrolment, pre-pregnancy BMI, educational level, history of asthma or atopy, psychological distress during pregnancy, parity, smoking during pregnancy, and child's sex, gestational age, birth weight, ethnicity, day care attendance, lower respiratory tract infections, passive smoking at 1 year, and age at the time of respiratory outcomes. The table displays the estimates of the indirect effect, the direct effect and the total effect (indirect+direct).

infant growth pattern (ie, equivalent to a later AGEAP) had a lower risk of wheezing and shortness of breath at 4 years of age compared with children with normal fetal and infant growth patterns.[12] Three studies examined the association between early height gain and lung function.[3 14 17] Height gain during the first 3 years of life was more strongly associated with lower lung volume measures at 15 years of age than at 8 years.[14] In our study, we observed an association of greater PHV with lower FEF_{75}, but it was a small effect and the association was no longer significant in the complete case analysis.

Several prospective birth cohort studies have assessed the association of early childhood weight gain with asthma-related symptoms later in life.[2 4 6 8–14 16–18 20 22] Those that used individual longitudinal childhood growth patterns observed that PWV was associated with a higher risk of asthma at 7 and 10 years of age,[4 6] and that *size* and weight *velocity* (PWV) but not the *time* at which PWV occurred, were associated with a higher risk of wheezing at 18 months.[10] Using the difference between two growth measurements instead, a study showed that a lower lung function partly explained the association of early weight gain and childhood asthma.[22] In our study we observed that children with a greater BMIAP whose mothers had a history of

asthma or atopy had a higher odds of asthma compared with the children of mothers without asthma or atopy. We also observed that a delay in the time of the adiposity peak is associated with lower odds of asthma at school age, particularly in boys and in children with no allergic sensitisation. As far as we know, no previous studies have explored the potential effect modification of maternal history of asthma or atopy, birth outcomes, and allergic sensitisation in the association between these specific early infant growth patterns and childhood asthma.

Interpretation of results

One of the most important findings of this study is that a greater PWV and particularly BMIAP are associated with lower FEV_1/FVC at 10 years of age, and that these associations are independent of wheezing patterns and the current weight status of the child. Our findings suggest dysanapsis in which FVC is higher relative to FEV_1 as a result of a possible imbalance between alveolar and airway growth. In consequence, airways are small with respect to the total lung volume.[19] Dysanapsis may be a risk factor for the development of respiratory diseases later in life.[39] Although the growth and development of the respiratory system are largely programmed in utero,[39 40] both airways and specially alveoli continue to grow and develop until adolescence. Therefore, postnatal factors such as early childhood weight gain could modify normal development leading to dysanapsis. Although the mechanisms are not fully understood, it is suggested that factors involved in alveolarization and resulting from the adipose tissue may play a role.[19] This includes immunological and pro-inflammatory factors and energy-regulating hormones such as leptin and adiponectin. In our population, we observed that children with a small size at birth followed by a greater PWV and BMIAP are especially at risk of this disproportionate growth of the lungs and airways.

In the Generation R cohort, greater PWV and BMIAP are associated with higher risks of overweight at 6 years of age[41] and greater BMI at this age is associated with higher respiratory resistance and a higher risk of wheezing at 6 years.[42] When considering the child's weight status at 10 years of age, we observed that infant weight gain had a greater influence on the growth of the alveoli than of the airways and that the reduction in FEV_1/FVC ratio persists. This suggests that the dysanapsis due to infant weight gain during the first years of life persists up to the age of 10 years. Follow-up studies at older ages are needed to elucidate whether these structural changes of the lung continue into adolescence and adulthood.

Since a lower FEV_1/FVC might contribute to asthma-like symptoms, we would expect greater PWV and BMIAP to be associated with higher odds of current asthma. However, we only observed such associations in children whose mothers had a history of asthma or atopy. Interestingly, a maternal history of asthma or atopy did not modify the association between childhood growth and FEV_1/FVC. This may indicate that the mechanisms involved in the association between early childhood weight gain and lung function and asthma may differ. The first could be the result of dysanapsis, whereas the second could be due to potentiation of airway inflammation through immunological and pro-inflammatory factors derived from adipose tissue, hence increasing the probability of developing asthma later in life. We also found that a delay in the age at adiposity peak, that is, decelerated infant weight gain, was associated with higher airway patency and a lower risk of asthma at 10 years of age. These associations were particularly important among boys and in children with no allergic sensitisation. Potential underlying mechanisms need to be explored.

Strengths and limitations

The present study is embedded in a population-based prospective study with a large number of participants followed from fetal life until 10 years of age and with detailed information on growth and respiratory outcomes. We used individual growth trajectories rather than the difference in two measurements of weight and height and used objective measurements of lung function. We also performed advanced statistical analysis to deal with follow-up losses and missing data, including inverse probability weighting and multiple imputation. Further, we applied Bonferroni correction and all associations, except the association of AGEAP with current asthma in boys, remained significant. However, this association was consistent with the findings observed in relation to the association of AGEAP with a higher FEV_1/FVC in boys. We also should consider that statistical correction for multiple comparisons is useful to avoid errors due to false positive findings (type I errors) but increases false negative findings (type II errors). This could have adverse consequences for public health. Also, statistical correction for multiple comparisons assumes that the hypothesis tests are statistically independent, which may not be the case in our study since all the early childhood patterns are related, as are the lung function parameters.

However, our study has some limitations that should be addressed. First, the mothers of the children not included in the analysis were younger, with a lower educational level, non-European, more stressed, smoked more during pregnancy and had children with a lower birth weight than the mothers of the children included in the analysis (online supplementary table S1). This could have led to biased effect estimates if these variables had a strong influence on our associations between growth patterns and respiratory outcomes, but they did not (online supplementary table S3). Inverse probability weighting also showed no differences in effect estimates when the children not included in the analysis were considered. However, our results may not be generalisable to the general population. Second, the Reed1 model smoothes the growth curves over the whole growth period, missing extreme growth changes over very short time periods that might be more relevant for respiratory outcomes. Also it does not allow the modelling of individual growth trajectories for those subjects with only one weight and height measurement available. Future studies might consider the superimposition by translation and rotation model approach (SITAR) because this permits growth trajectories to be estimated for all children regardless of the number of measurements available, detects inflection points, and allows the identification of the three important growth parameters of size, velocity and tempo.[43] Hence, the use of the Reed1 model in our study may have introduced some exposure misclassification. However, we assume that such misclassification is likely to be random with respect to our outcomes, and would thus have biased our results towards the null. Third, children with asthma often have spirometry within the normal range, leading to misclassification of the outcome. Bronchodilator and bronchial responsiveness tests that demonstrate reversibility or airway hyperresponsiveness, respectively, may be more specific for asthma but lack sensitivity.[3 14 44] Moreover, these tests are time consuming and giving healthy children a bronchoactive agent with potential side effects is less feasible in a large cohort. Additionally, although we defined current asthma as a combination of doctor diagnosis, medication and wheezing in the last 12 months, we cannot rule out some outcome misclassification due to under- or over-reporting of asthma, which may have led to attenuation or overestimation

of the results. Fourth, the effect estimates for some of the associations of childhood growth patterns with lung function were small, and need to be carefully interpreted. A z-score change of ±0.05 is considered clinically relevant on a population level. However, smaller changes are highly relevant from an aetiological perspective. Finally, we cannot exclude potential residual confounding by unmeasured factors, including the child's diet and various environmental chemicals. Unmeasured confounders seem to be especially relevant in our mediation analysis since we obtained an r value close to 0, which suggests that a weak unmeasured confounder would be enough to destabilise the model.

In conclusion, our results suggest that PWV and BMIAP are associated with a disproportionate increase in FVC with respect to FEV_1 at 10 years of age, leading to smaller airways in relation to lung capacity. In boys, AGEAP is associated with better lung function and a lower risk of asthma at school age. These results suggest that weight gain during the first years of life appears to be important for lung development. Further studies should explore whether the lower airway patency in relation to lung volume associated with PWV and BMIAP persists in adolescence and whether it leads to a higher risk of asthma.

Author affiliations
[1]The Generation R Study Group, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[2]Department of Pediatrics, Division of Respiratory Medicine and Allergology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[3]ISGlobal, Barcelona, Spain
[4]Universitat Pompeu Fabra (UPF), Barcelona, Spain
[5]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[6]Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[7]Department of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[8]Department of Pediatrics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

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