

Fetal and Infant Growth and Asthma Symptoms in Preschool Children

The Generation R Study

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Rationale: Low birth weight is associated with an increased risk of wheezing in childhood.

Objectives: We examined the associations of longitudinally measured fetal and infant growth patterns with the risks of asthma symptoms in preschool children.

Methods: This study was embedded in a population-based prospective cohort study among 5,125 children. Second- and third-trimester fetal growth characteristics (head circumference, femur length, abdominal circumference, and weight) were estimated by repeated ultrasounds. Infant growth (head circumference, length, and weight) was measured at birth and at the ages of 3, 6, and 12 months. Parental report of asthma symptoms until the age of 4 years was yearly obtained by questionnaires.

Measurements and Main Results: Both fetal restricted and accelerated growth, defined as a negative or positive change of more than 0.67 standard deviation score, were not associated with asthma symptoms until the age of 4 years. Accelerated weight gain from birth to 3 months following normal fetal growth was associated with increased risks of asthma symptoms (overall odds ratio for wheezing: 1.44 [95% confidence interval: 1.22, 1.70]; shortness of breath: 1.32 [1.12, 1.56]; dry cough: 1.16 [1.01, 1.34]; persistent phlegm: 1.30 [1.07, 1.58]), but not with eczema (0.95 [0.80, 1.14]). These associations were independent of other fetal growth patterns and tended to be stronger for children of atopic mothers than for children of nonatopic mothers.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Low birth weight and preterm birth are associated with an increased risk of asthma symptoms. Little is known about the association between specific fetal and infant growth patterns and the risk for the development of asthma in childhood.

What This Study Adds to the Field

Fetal growth restriction and acceleration were not associated with asthma symptoms in childhood. However, accelerated infant weight gain during the first 3 months after birth was associated with higher risks of asthma symptoms in childhood, independent of fetal growth patterns.

Conclusions: Weight-gain acceleration in early infancy was associated with increased risks of asthma symptoms in preschool children, independent of fetal growth. Early infancy might be a critical period for the development of asthma.

Keywords: cohort studies; dyspnea; eczema; pediatrics; wheezing

(Received in original form July 14, 2011; accepted in final form January 4, 2012)

The Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, and the Netherlands Organization for Health Research and Development. The researchers are independent from the funders. The study sponsors had no role in study design, data analysis, interpretation of data, or writing of this report. Dr. Vincent Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159). Dr. Liesbeth Duijts is the recipient of a European Respiratory Society/Marie Curie Joint Research Fellowship—Number MC 1226-2009. The research leading to these results has received funding from the European Respiratory Society and the European Community's Seventh Framework Program FP7/2007-2013—Marie Curie Actions under grant agreement RESPIRE, PCOFUND-GA-2008-229571, and from the Seventh Framework Program, project CHICOS (HEALTH-F2-2009-241504).

Author Contributions: A.S., V.J., J.J., and L.D. contributed to the conception and design, acquisition of data, and analyses and interpretation of the data, drafted the article, revised it critically for important intellectual content, and gave final approval of the version to be published. H.R., H.M., and A.H. contributed to the conception and design and acquisition of data, revised the article critically for important intellectual content, and gave final approval of the version to be published.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 185, Iss. 7, pp 731–737, Apr 1, 2012

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Originally Published in Press as DOI: 10.1164/rccm.201107-1266OC on January 20, 2012

Internet address: www.atsjournals.org

Low birth weight is associated with increased risks of asthma, chronic obstructive airway disease, and impaired lung function, such as lower FEV₁ and FVC in adults (1). In children, low birth weight is associated with increased risks of respiratory morbidity, including asthma and respiratory tract infections (2), but results are not consistent (3–6). The developmental plasticity hypothesis suggests that the associations between low birth weight and common diseases in adulthood are explained by early adaptive mechanisms in response to various adverse exposures in fetal and early postnatal life (7). These adaptive mechanisms might lead to impaired lung development, smaller airways, and impaired lung function (8), and might lead to an increased susceptibility of development of respiratory diseases, including asthma and chronic obstructive pulmonary disease (9, 10). Low birth weight *per se* is not likely to be the causal factor leading to asthma. The same birth weight might be the result of various growth patterns and different fetal exposures (11). Information about fetal growth characteristics in different periods of pregnancy enables identification of critical periods for specific exposures and development of asthma in postnatal life (12, 13). Also, children with a low birth weight tend to have a postnatal catch-up growth, which has also been suggested to be associated with respiratory morbidity, including childhood asthma (12, 14, 15). Studies so far focused on early growth patterns, and showed inconsistent results. This might partly be due to methodological issues including differences in definitions of fetal and infant growth patterns or asthma-related outcomes and the adjustment for gestational age and other potential confounders.

Therefore, we examined the associations of fetal and infant growth patterns with the risk of asthma symptoms in the first 4 years of life in a population-based prospective cohort study among 5,125 children who were followed up from fetal life. Some of the results of this study has been previously reported in the form of an abstract at the European Respiratory Society Conference 2011 (16).

METHODS

Design and Setting

This study was embedded in the Generation R Study, a population-based prospective cohort study of pregnant women and their children in Rotterdam, The Netherlands (17). The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants. A total of 5,125 children were included for the current analyses (*see* Figure E1 in the online supplement).

Growth Characteristics

Fetal growth characteristics were measured in the first trimester (crown-rump length) (18), and in the second and third trimester (head circumference [HC], abdominal circumference, and femur length) (19, 20). Estimated fetal weight was calculated using the Hadlock formula (21, 22). HC, length, and weight at birth were obtained from community midwife and hospital registries. Infant growth characteristics (HC, length, and weight) were measured at the ages of 3, 6, and 12 months. All growth characteristics were converted into standard deviation scores (SDS) using fetal and infant reference growth charts (19, 22) (Growth Analyzer 3.0, Dutch Growth Research Foundation). We calculated growth (change in SDS) between various age intervals. Growth restriction and acceleration (from 2nd trimester to birth and birth to 3 mo of age) were defined as a change, either decrease or increase, of more than 0.67 SDS, representing the width of each percentile band on standard growth charts (23, 24).

Asthma Symptoms

Information on asthma symptoms (wheezing, shortness of breath, dry cough at night, and persistent phlegm [no, yes]) and doctor-attended eczema (no, yes) was obtained by questionnaires, adapted from the International Study on Asthma and Allergy in Childhood (25) at the ages of 1, 2, 3, and 4 years. Response rates for these questionnaires were 71, 76, 72, and 73%, respectively (26).

Covariates

Maternal anthropometrics were obtained during first visit, and education, history of asthma and atopy, smoking habits, parity, and children's ethnicity and pet keeping were obtained by questionnaire, completed by the mother at enrollment. Maternal gestational hypertension, diabetes, and children's gestational age and sex were obtained from midwife and hospital registries at birth. Postal questionnaires at the ages of 6 and 12 months provided information about breastfeeding and day-care attendance (17).

Statistical Analysis

We used adjusted generalized estimating equations to examine the longitudinal effects of fetal and infant growth and their interaction with each asthma symptom from the age of 1 to 4 years. With generalized estimating equation analyses, repeatedly measured asthma symptoms over time were analyzed, taking correlations within the same subject into account. We calculated the overall effect (age 1 to 4 yr combined) of fetal and infant growth on asthma symptoms. Missing data in covariates and outcomes were imputed using the multiple imputation procedure (27). All measures of association are presented as odds ratio (OR) with 95% confidence intervals. Statistical analyses were performed using Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc., Chicago, IL) and SAS 9.2 (SAS Institute, Cary, NC). An

extensive description of the methods is provided in the online supplement (Text E1).

RESULTS

Characteristics of children and their mothers are presented in Table 1. Children were born after median pregnancy duration of 40.1 weeks (range 25.3–43.4) with a mean birth weight of 3,440 g (SD 551 g) (Table 1). Wheezing was the most prevalent asthma symptom, and its prevalence declined with increasing age (*see* Table E1).

Birth Weight and Gestational Age

We observed from crude analyses that birth weight was inversely associated with the risks of asthma symptoms, but these associations attenuated and became nonsignificant after adjustment for gestational age (wheezing OR, 0.97 [0.92, 1.02]; shortness of breath OR, 0.96 [0.91, 1.01]; dry cough OR, 1.01 [0.97, 1.06]; persistent phlegm OR, 0.93 [0.87, 0.99]; and eczema OR 1.01 [0.96, 1.07]) (Table 2). Similar changes in effect estimates were observed for children with low birth weight (<2,500 g) with and without adjustment for gestational age and the risk of asthma symptoms. As compared with term birth, preterm birth (<36 wk of gestational age) was positively associated with the risks of wheezing (OR, 1.55 [1.30, 1.84]), shortness of breath (OR, 1.54 [1.28, 1.85]), and persistent phlegm (OR, 1.30 [1.03, 1.64]).

Fetal and Infant Growth

No consistent associations of fetal length and weight growth during different trimesters with asthma symptoms were observed (Table 3). Crown-rump length in first trimester (data not shown) and growth of fetal abdominal and head circumference were also not associated with asthma symptoms (Table E2 in the online supplement). Infant weight gain between birth and 3 months, expressed as SDS increase in weight, was positively associated with the risks of wheezing, shortness of breath, and persistent phlegm (OR, 1.17 [1.11, 1.23], 1.13 [1.08, 1.20], and 1.15 [1.08, 1.23], respectively) in the first 4 years of life. Length growth was not associated with any asthma symptom (Table 3).

Further exploration of fetal and infant growth patterns showed that, as compared with children with a normal fetal and infant growth pattern, those with a normal fetal but accelerated infant growth pattern had an increased risk of wheezing (OR, 1.44 [1.22, 1.70]), shortness of breath (OR, 1.32 [1.12, 1.56]), dry cough (OR, 1.16 [1.01, 1.34]), and persistent phlegm (OR, 1.30 [1.07, 1.58]), but not of eczema (Figures 1A–1E). We observed a protective effect of a restricted fetal and infant growth pattern, compared with a normal growth pattern, for wheezing and shortness of breath (Figures 1A and 1B). The results did not materially change when preterm-born infants were excluded from the analyses or when the associations of fetal and infant growth patterns for each year separately were analyzed (Table E3). Analysis stratified for maternal atopy showed that the effect estimates tended to be stronger for atopic mothers than nonatopic mothers, but the *P* for interaction was not significant (Figure E2).

DISCUSSION

Our results suggest that fetal growth during different periods of pregnancy was not associated with the overall risk of asthma symptoms until the age of 4 years. However, we observed associations between early infant growth acceleration and increased risks of asthma symptoms. These associations seem to be independent of fetal growth.

Birth Weight and Preterm Birth

Previous child cohort studies reported inconsistent associations of birth weight with wheezing or asthma in childhood (2–5). After adjustment for gestational age, we only observed an association of birth weight with persistent phlegm, not with wheezing or other asthma symptoms. Differences with previous published studies might be due to our assessment of the outcomes at a young age at which an asthma diagnosis is not possible and asthma symptoms are common, but nonspecific and often transient (28, 29). Also, it might be that not low birth weight but preterm birth is the main risk factor for increased risks of asthma symptoms (30, 31). This is supported by our consistent associations of gestational age and preterm birth with wheezing, shortness of breath, and persistent phlegm.

Fetal and Infant Growth

Earlier studies used birth weight as a proxy for fetal growth (4–6, 32) and showed inconsistent associations between either low or high birth weight and the risk of asthma symptoms, asthma diagnosis, or a reduced lung function. Assessing fetal and infant growth characteristics related to birth weight might help to identify specific critical periods. Two recent studies focused on the associations of fetal growth characteristics in different trimesters and the risk of childhood asthma and atopy (12, 13). Pike and colleagues observed no association of fetal growth characteristics and “ever wheezing” until the age of 3 years (12). The authors did observe an association of abdominal circumference growth between 19 and 34 weeks with atopic wheezing (relative risk [95% confidence interval], 0.80 [0.65, 1.00]) and of head circumference growth between 11 and 19 weeks and nonatopic wheezing (relative risk, 0.90 [0.81, 1.00]). They suggest that the association with atopic wheezing might be the effect of an impaired thymic development, while nonatopic wheezing might be caused by mechanical changes in growth-restricted children. Turner and colleagues recently showed that crown–rump length in first trimester was inversely associated with “ever wheezing” (OR, 0.96 [0.93, 0.99]) at the age of 5 years and diagnosed asthma (OR, 0.94 [0.89, 0.99]) and lung function at the ages of 5 and 10 years (13), independent of atopy. In our study, in a larger number of children, we used ultrasound measurements in each trimester of pregnancy and observed no associations of fetal growth, including multiple growth parameters and patterns, with asthma symptoms in preschool children. We were, however, not able to differentiate between atopic and nonatopic children, as we had no direct measures of sensitization. When we stratified our analysis for atopic and nonatopic mothers, a proxy for atopic status of children (33), the effect estimates of the association of fetal growth characteristics and patterns with asthma symptoms tended to be stronger for children with atopic mothers than nonatopic mothers.

Previous studies in children reported a slightly increased risk of wheezing (ORs up to 1.05 [1.01, 1.09]) and reduced lung function for weight gain in the first year and no associations with length growth (12, 15, 34, 35). In adulthood, no effect on airway obstruction, but a modest reduction of lung volume, was observed if children had either a lower or higher weight gain in the first 3 years of life (36). Due to our extensive anthropometric measurements after birth, we were able to specify the critical time period in which weight gain had an effect on asthma symptoms and found that accelerated weight gain between birth and 3 months of age was associated with asthma symptoms in childhood. Furthermore, we observed that this effect was independent of fetal growth. These results are in line with Pike and colleagues, who observed that low third-trimester abdominal circumference with high weight gain and adiposity in the first 6 months was associated with a higher proportion of atopic

TABLE 1. CHARACTERISTICS OF CHILDREN AND THEIR MOTHERS

	Population of Analysis (<i>n</i> = 5,125)
Maternal characteristics	
Age, %	
<20 yr	2.1 (107)
20–25 yr	12.2 (624)
25–30 yr	26.4 (1,353)
30–35 yr	42.4 (2,173)
≥35 yr	16.9 (868)
Missing	—
Height, cm	168.0 (7.5)
Weight, kg	69.4 (12.8)
Body mass index	
<20 kg/cm ²	8.9 (457)
20–25.0 kg/cm ²	54.5 (2,791)
25–30.0 kg/cm ²	24.9 (1,278)
≥30 kg/cm ²	11.1 (568)
Missing	0.6 (31)
Education, %	
Primary, or secondary	46.7 (2,394)
Higher	48.9 (2,504)
Missing	4.4 (227)
History of asthma, %	
No	56.7 (2,906)
Yes	31.9 (1,637)
Missing	11.4 (582)
Smoking during pregnancy, %	
No	76.5 (3,919)
Yes	12.4 (633)
Missing	11.2 (573)
Parity, %	
0	62.1 (3,181)
1–2	34.3 (1,756)
≥3	3.1 (161)
Missing	0.5 (27)
Gestational hypertension, %	
No	91.8 (4,704)
Yes	4.1 (208)
Missing	4.2 (213)
Gestational diabetes, %	
No	96.9 (4,964)
Yes	0.7 (37)
Missing	2.4 (124)
Child characteristics	
Male sex, %	50.1 (2,567)
Gestational age at birth, wk	40.1 (37.1–42.1)
Birth weight, g	3,440 (551)
Ethnicity, %	
European	66.8 (3,421)
Non-European	30.7 (1,573)
Missing	2.6 (131)
Breastfeeding, %	
No	7.2 (370)
Yes	88.6 (4,542)
Missing	4.2 (213)
Day care attendance 1st yr, %	
No	40.1 (2,054)
Yes	43.5 (2,229)
Missing	16.4 (842)
Pet keeping, %	
No	58.8 (3,015)
Yes	29.6 (1,519)
Missing	11.5 (591)

Values are means (SD), medians (5th–95th percentile), or percentages (absolute numbers).

wheezing (12). Whether their highest weight-gain group in the first 6 months showed consistently increased effect estimates for wheezing, independent of fetal growth, was not presented.

Our results suggest that the effect of infant weight gain on asthma symptoms is not due to “catch up” growth of fetal growth–restricted infants only. The underlying mechanisms are unclear. Accelerated

TABLE 2. BIRTH CHARACTERISTICS AND ASTHMA SYMPTOMS

	Odds Ratios (95% Confidence Interval)				
	Wheezing	Shortness of Breath	Dry Cough	Persistent Phlegm	Eczema
Birth weight					
Weight (500 g)	0.92 (0.89, 0.96)***	0.93 (0.89, 0.96)***	1.02 (0.99, 1.06)	0.90 (0.86, 0.95)***	1.01 (0.97, 1.06)
Gestational age adjusted weight (500 g)	0.97 (0.92, 1.02)	0.96 (0.91, 1.01)	1.01 (0.97, 1.06)	0.93 (0.87, 0.99)*	1.01 (0.96, 1.07)
Low birth weight (<2500 g)	1.34 (1.12, 1.62)**	1.24 (1.02, 1.52)*	0.87 (0.72, 1.05)	1.32 (1.05, 1.66)*	1.01 (0.81, 1.27)
Gestational age adjusted low birth weight (<2500 g)	1.07 (0.85, 1.34)	0.99 (0.78, 1.27)	0.91 (0.74, 1.12)	1.05 (0.80, 1.39)	1.05 (0.81, 1.35)
Gestational age					
Gestational age (wk)	0.94 (0.92, 0.97)***	0.95 (0.93, 0.97)***	1.02 (0.99, 1.04)	0.94 (0.92, 0.97)***	1.01 (0.98, 1.04)
Preterm birth (<37 wk)	1.55 (1.30, 1.84)***	1.54 (1.28, 1.85)***	0.90 (0.74, 1.08)	1.30 (1.03, 1.64)*	1.00 (0.79, 1.25)

Values are odds ratios (95% confidence interval) and, if continuously measured, reflect the risk of asthma symptoms per 500 grams or week of gestational age increase. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ using longitudinal generalized estimating equation models. Models were adjusted for maternal age, body mass index, education, history of asthma or atopy, smoking habits, parity, gestational hypertension, gestational diabetes, children's sex, ethnicity, breastfeeding status, daycare attendance, and pet keeping.

weight growth in the first 3 months of life might adversely affect lung growth, including a change in alveolar numbers, lung weight, and the developing immune system (37–39). It was suggested that early infant weight gain is associated with a higher body mass index in childhood with overweight and obesity in later life (24, 40) and subsequently may have a modifying effect on asthma, asthma symptoms, and lung function during childhood and in the long term (41, 42). Also, adverse changes of the immune system in early life due to increased weight gain might affect the development of childhood asthma (38, 39, 43).

We observed that children with fetal and infant growth deceleration had a decreased risk of wheezing and shortness of breath up to the fourth year. A protective effect of fetal and infant growth deceleration was also observed in an earlier study on atopic wheezing, but not for nonatopic wheezing (12). Pike and colleagues observed that children with a normal fetal growth and a restricted infant growth tended to have a lower risk of wheezing than children with normal infant growth (12). The underlying mechanisms for these associations were not shown. According to animal studies, it might be that fetal growth restriction lead

to impaired growth of bronchial walls, affecting the airway compliance, alterations in mucus-producing tissues, decrease in number of alveoli, thicker interalveolar septa, and a greater volume density of lung tissue (44–46). However, some of these adaptations resolved within weeks after birth. Hence, we speculate that at least a part of the effects on the lungs in children with a restricted fetal growth is caught up before the age of 1 to 4 years, and this might have reduced our effect estimates. If fetal growth indeed leads to respiratory symptoms via an effect on lung development, this might be of influence later in childhood.

Strengths and Limitations

This study was embedded in a population-based prospective cohort study with a large number of subjects being studied from early fetal life onwards with detailed and frequently prospectively measured information about fetal and infant anthropometrics. We adjusted for a large number of confounders, and the results did not differ between nonimputed and imputed analyses. Nonresponse would lead to biased effect estimates if the associations of fetal

TABLE 3. FETAL AND INFANT GROWTH (CHANGE IN SDS) AND ASTHMA SYMPTOMS

	Overall Odds Ratios (95% Confidence Interval)				
	Wheezing	Shortness of Breath	Dry Cough	Persistent Phlegm	Eczema
Length					
2nd–3rd trimester n = 4,803	1.02 (0.98, 1.07)	1.00 (0.95, 1.05)	0.96 (0.93, 1.00)	0.99 (0.94, 1.05)	0.98 (0.93, 1.03)
3rd trimester – birth n = 3,270	0.99 (0.95, 1.03)	1.01 (0.97, 1.06)	0.99 (0.95, 1.03)	0.98 (0.93, 1.03)	1.00 (0.96, 1.05)
Birth–3 mo n = 2,031	1.02 (0.96, 1.08)	0.99 (0.94, 1.06)	1.03 (0.98, 1.09)	0.98 (0.90, 1.06)	0.98 (0.92, 1.04)
3–6 mo n = 2,619	1.04 (0.95, 1.14)	1.08 (0.98, 1.19)	1.00 (0.92, 1.09)	0.98 (0.86, 1.11)	0.91 (0.83, 1.01)
6–12 mo n = 3,425	0.93 (0.85, 1.01)	0.97 (0.88, 1.06)	0.99 (0.91, 1.06)	1.00 (0.89, 1.12)	0.98 (0.88, 1.08)
Weight					
2nd–3rd trimester n = 4,766	1.04 (0.99, 1.08)	1.01 (0.96, 1.05)	1.00 (0.96, 1.04)	0.99 (0.93, 1.05)	1.04 (0.99, 1.10)
3rd trimester – birth n = 5,023	1.00 (0.96, 1.04)	1.02 (0.98, 1.07)	0.99 (0.95, 1.03)	0.95 (0.89, 1.00)	0.99 (0.94, 1.04)
Birth–3 mo n = 3,558	1.17 (1.11, 1.23)***	1.13 (1.08, 1.20)***	1.04 (1.00, 1.09)	1.15 (1.07, 1.22)***	0.93 (0.88, 0.98)*
3–6 mo n = 3,391	0.97 (0.88, 1.06)	0.96 (0.87, 1.07)	1.04 (0.95, 1.13)	0.91 (0.80, 1.03)	0.88 (0.79, 0.99)*
6–12 mo n = 3,875	0.95 (0.86, 1.04)	0.95 (0.86, 1.04)	0.96 (0.89, 1.04)	0.90 (0.79, 1.02)	0.90 (0.81, 1.00)*

Values are odds ratios (95% confidence interval) and reflect the risk of asthma symptoms per standard deviation score (SDS) increase of length and weight. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ using longitudinal generalized estimating equation models. Models were adjusted for maternal age, body mass index, education, history of asthma or atopy, smoking habits, parity, gestational hypertension, gestational diabetes, children's sex, gestational age, ethnicity, breastfeeding status, daycare attendance, and pet keeping.

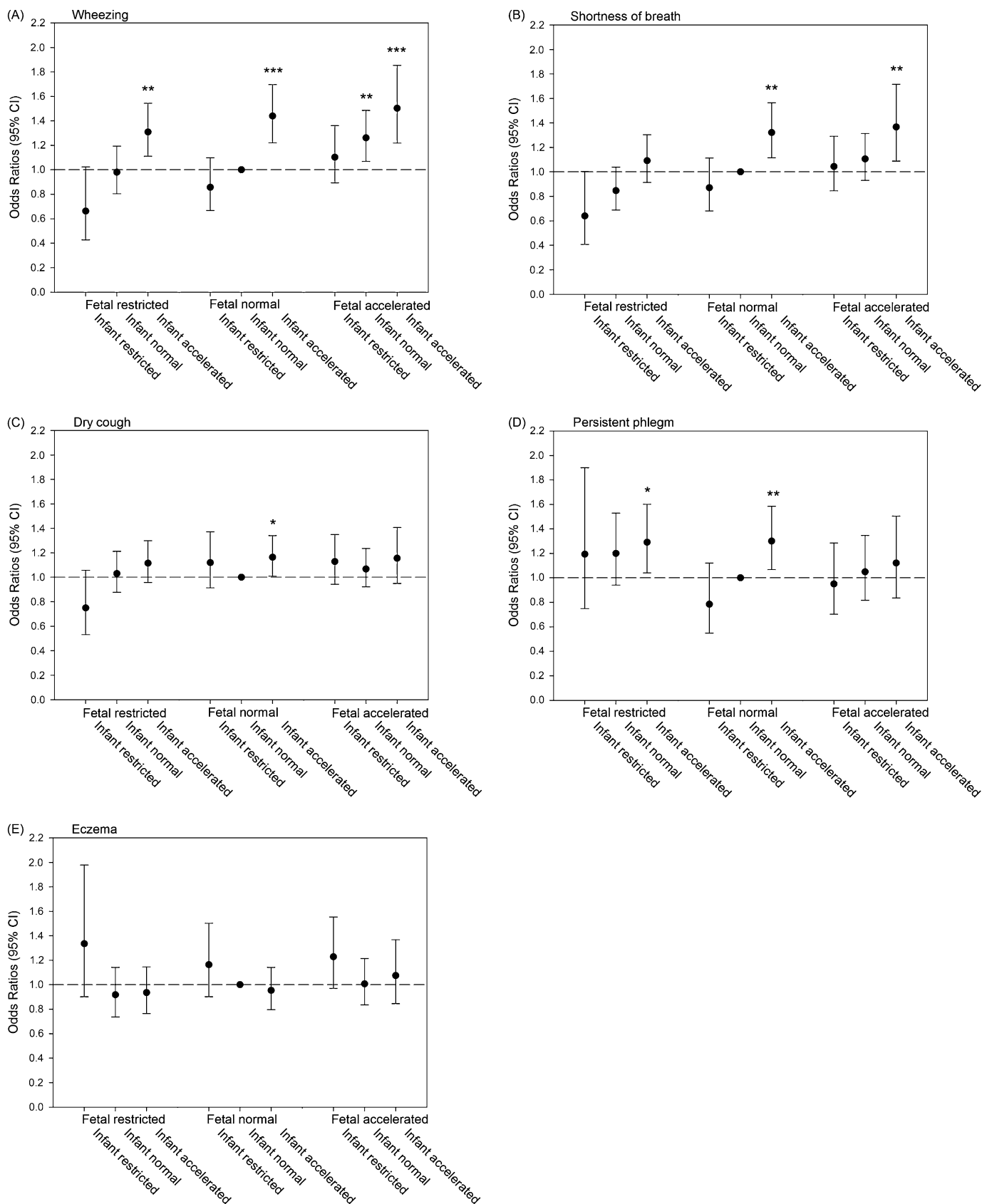


Figure 1. Weight growth patterns and asthma symptoms: (A) wheezing; (B) shortness of breath; (C) dry cough; (D) persistent phlegm; and (E) eczema. Values are odds ratios (95% confidence interval). Normal fetal and normal infant growth pattern is used as reference category. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ based on longitudinal generalized estimating equation models. Models were adjusted for maternal age, body mass index, education, history of asthma or atopy, smoking habits, parity, gestational hypertension, gestational diabetes, children's sex, gestational age, ethnicity, breastfeeding status, daycare attendance, and pet keeping.

and infant growth with asthma symptoms would be different between those included and not included in the analyses. However, this seems unlikely because biased estimates mainly arise from loss to follow-up rather than from nonresponse at baseline (47). Although we used the established Hadlock formula for calculation of the estimated fetal weight, we cannot exclude that there may be a random measurement error in this estimation, especially in late third trimester, which might have led to underestimation of the effect estimates. Although we showed that the intraobserver and interobserver intraclass correlations for assessing fetal growth in early pregnancy were high, measurement error is expected to be higher for fetal growth measurements than for infant growth measurements (20). We categorized growth patterns by a change of more than 0.67 SD, a well-known recognized threshold value in studies on growth (23). Other studies categorized fetal and infant growth by separating groups in tertiles (12), or used a longer time interval for the SD change, which might explain some differences from our results (48). The main outcomes in our study were self-reported symptoms. This method is widely accepted in epidemiological studies and reliably reflects the incidence of asthma symptoms in young children (49). In preschool children, a diagnosis of asthma is based on symptoms (50). Objective tests, including spirometry or bronchial hyperresponsiveness, are difficult to perform in young children, and have limited applicability. We were not able to assign phenotypes based on patterns of wheezing, including transient, late-onset, persistent, or other wheezing phenotypes, due to the follow-up of children until the age of 4 years only (28, 29). Follow-up studies at older ages that include more detailed assessments of asthma and atopy phenotypes are needed. We did not apply Bonferroni correction because we used repeated-measurements analyses and correlated outcomes of both the exposure and outcomes. However, we observed consistent associations of infant weight gain independent of fetal growth with all asthma symptoms.

In conclusion, our results suggest that not fetal growth, but accelerated growth in the first 3 months of life is associated with an increased risk of asthma symptoms during the first 4 years of life. The results of this study should be considered as hypothesis generating. Further studies are needed to replicate these findings and to explore underlying mechanisms of the effect of growth acceleration on respiratory health, in particular on the various phenotypes of asthma in later life.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam; the Municipal Health Service Rotterdam area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (STAR), Rotterdam. The authors gratefully acknowledge the contribution of participating parents, children, general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

References

- Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, Zitting P, Patel S, Little MP, Jarvelin MR. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. *Thorax* 2007;62:396–402.
- Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, Hoekstra M, Gerritsen J, de Jongste JC. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA birth cohort. *Am J Respir Crit Care Med* 2007;175:1078–1085.
- Kindlund K, Thomsen SF, Stensballe LG, Skytthe A, Kyvik KO, Backer V, Bisgaard H. Birth weight and risk of asthma in 3–9-year-old twins: exploring the fetal origins hypothesis. *Thorax* 2010;65:146–149.
- Taveras EM, Camargo CA Jr, Rifas-Shiman SL, Oken E, Gold DR, Weiss ST, Gillman MW. Association of birth weight with asthma-related outcomes at age 2 years. *Pediatr Pulmonol* 2006;41:643–648.
- Yuan W, Basso O, Sorensen HT, Olsen J. Fetal growth and hospitalization with asthma during early childhood: a follow-up study in Denmark. *Int J Epidemiol* 2002;31:1240–1245.
- Shaheen SO, Sterne JA, Tucker JS, Florey CD. Birth weight, childhood lower respiratory tract infection, and adult lung function. *Thorax* 1998;53:549–553.
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;359:61–73.
- Shaheen S, Barker DJ. Early lung growth and chronic airflow obstruction. *Thorax* 1994;49:533–536.
- Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British women's heart and health study and a meta-analysis. *Thorax* 2005;60:851–858.
- Lopuhaa CE, Roseboom TJ, Osmond C, Barker DJ, Ravelli AC, Bleker OP, van der Zee JS, van der Meulen JH. Atopy, lung function, and obstructive airways disease after prenatal exposure to famine. *Thorax* 2000;55:555–561.
- Milani S, Bossi A, Bertino E, di Battista E, Coscia A, Aicardi G, Fabris C, Benso L. Differences in size at birth are determined by differences in growth velocity during early prenatal life. *Pediatr Res* 2005;57:205–210.
- Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, The Southampton Women's Survey Study G, Roberts G, Godfrey KM. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax* 2010;65:1099–1106.
- Turner S, Prabhu N, Danielian P, McNeill G, Craig L, Allan K, Cutts R, Helms P, Seaton A, Devereux G. First and second trimester fetal size and asthma outcomes at age ten years. *Am J Respir Crit Care Med* 2011;184:407–413.
- Tai A, Volkmer R, Burton A. Association between asthma symptoms and obesity in preschool (4–5 year old) children. *J Asthma* 2009;46:362–365.
- van der Gugen AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. *Eur Respir J* 2012;39:403–410.
- Sonnenschein-van der Voort A, de Jongste J, Hofman A, Moll H, Steegers E, Jaddoe V, Duijts L. Fetal and infant growth is associated with wheezing in preschool children. The generation R study. *Eur Respir J* 2011;38:270s–271s.
- Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC, Hofman A. The generation R study: design and cohort update 2010. *Eur J Epidemiol* 2010;25:823–841.
- Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, Jaddoe VW. Risk factors and outcomes associated with first-trimester fetal growth restriction. *JAMA* 2010;303:527–534.
- Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, Moll HA, Jaddoe VW, Witteman JC. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol* 2008;31:388–396.
- Verburg BO, Mulder PG, Hofman A, Jaddoe VW, Witteman JC, Steegers EA. Intra- and interobserver reproducibility study of early fetal growth parameters. *Prenat Diagn* 2008;28:323–331.
- Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight: the value of femur length in addition to head and abdomen measurements. *Radiology* 1984;150:535–540.
- Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). *Acta Paediatr Scand* 1991;80:756–762.
- Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 2000;320:967–971.
- Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr* 2006;95:904–908.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483–491.
- Sonnenschein-van der Voort AMM, Jaddoe VWV, Van der Valk RJP, Willemsen SP, Hofman A, Moll HA, de Jongste JC, Duijts L. Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms. *Eur Respir J* 2012;39:81–89.

27. Spratt M, Carpenter J, Sterne JA, Carlin JB, Heron J, Henderson J, Tilling K. Strategies for multiple imputation in longitudinal studies. *Am J Epidemiol* 2010;172:478–487.
28. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, Shaheen SO, Sterne JA. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–980.
29. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: the group health medical associates. *N Engl J Med* 1995;332:133–138.
30. Metsala J, Kilkkinen A, Kaila M, Tapanainen H, Klaukka T, Gissler M, Virtanen SM. Perinatal factors and the risk of asthma in childhood—a population-based register study in Finland. *Am J Epidemiol* 2008;168:170–178.
31. Raby BA, Celedon JC, Litonjua AA, Phipatanakul W, Sredl D, Oken E, Ryan L, Weiss ST, Gold DR. Low-normal gestational age as a predictor of asthma at 6 years of age. *Pediatrics* 2004;114:e327–e332.
32. Leadbitter P, Pearce N, Cheng S, Sears MR, Holdaway MD, Flannery EM, Herbison GP, Beasley R. Relationship between fetal growth and the development of asthma and atopy in childhood. *Thorax* 1999;54:905–910.
33. Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. *PLoS ONE* 2010;5:e10134.
34. Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. *Thorax* 2005;60:549–554.
35. Turner S, Zhang G, Young S, Cox M, Goldblatt J, Landau L, Le Souef P. Associations between postnatal weight gain, change in postnatal pulmonary function, formula feeding and early asthma. *Thorax* 2008;63:234–239.
36. Hancox RJ, Poulton R, Greene JM, McLachlan CR, Pearce MS, Sears MR. Associations between birth weight, early childhood weight gain and adult lung function. *Thorax* 2009;64:228–232.
37. Rao L, Tiller C, Coates C, Kimmel R, Applegate KE, Granroth-Cook J, Denski C, Nguyen J, Yu Z, Hoffman E, *et al.* Lung growth in infants and toddlers assessed by multi-slice computed tomography. *Acad Radiol* 2010;17:1128–1135.
38. Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy* 2007;62:1205–1213.
39. Martinez FD. Maturation of immune responses at the beginning of asthma. *J Allergy Clin Immunol* 1999;103:355–361.
40. Durmus B, Mook-Kanamori DO, Holzhauser S, Hofman A, van der Beek EM, Boehm G, Steegers EA, Jaddoe VW. Growth in foetal life and infancy is associated with abdominal adiposity at the age of 2 years: the generation R study. *Clin Endocrinol (Oxf)* 2010;72:633–640.
41. Kim KW, Shin YH, Lee KE, Kim ES, Sohn MH, Kim KE. Relationship between adipokines and manifestations of childhood asthma. *Pediatr Allergy Immunol* 2008;19:535–540.
42. Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, Postma DS, Kerkhof M, Smit HA. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. *J Allergy Clin Immunol* 2009;123:1312–1318.e2.
43. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001;56:ii64–ii73.
44. Joyce BJ, Louey S, Davey MG, Cock ML, Hooper SB, Harding R. Compromised respiratory function in postnatal lambs after placental insufficiency and intrauterine growth restriction. *Pediatr Res* 2001;50:641–649.
45. Maritz GS, Cock ML, Louey S, Joyce BJ, Albuquerque CA, Harding R. Effects of fetal growth restriction on lung development before and after birth: a morphometric analysis. *Pediatr Pulmonol* 2001;32:201–210.
46. Wignarajah D, Cock ML, Pinkerton KE, Harding R. Influence of intrauterine growth restriction on airway development in fetal and postnatal sheep. *Pediatr Res* 2002;51:681–688.
47. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006;17:413–418.
48. Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S. Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. *Am J Respir Crit Care Med* 2010;181:969–974.
49. Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, Holst DP, Choi K, Giles GG. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25:609–616.
50. Edwards CA, Osman LM, Godden DJ, Douglas JG. Wheezy bronchitis in childhood: a distinct clinical entity with lifelong significance? *Chest* 2003;124:18–24.

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