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Early childhood weight status in relation to asthma development in high-risk children

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Abstract

Background—Obesity has been proposed to be a risk factor for the development of childhood asthma.

Objective—To examine weight status from birth to age 5 years in relation to the occurrence of asthma at age 6 and 8 years.

Methods—285 full-term high-risk newborns with at least one asthmatic/atopic parent, enrolled in the Childhood Origin of Asthma (COAST) project, were studied from birth to age 8 years. Overweight was defined by weight-for-length percentiles > 85th prior to age 2 years and body mass index percentile > 85th at ages 2–5 years.

Results—No significant concurrent association was found between overweight and wheezing/asthma occurrence at each year of age. In contrast, longitudinal analyses revealed complex relationships between overweight and asthma. Being overweight at age 1 year was associated with a decreased risk of asthma at age 6 (OR=0.32, p=0.02) and 8 years (OR=0.35, p=0.04) as well as better lung function. However, being overweight beyond infancy was not associated with asthma occurrences. In fact, only children who were overweight at age 5 but not at age 1 year had an increased risk of asthma at age 6 years (OR=5.78, p=0.05).

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Conclusion—In children genetically at high risk of developing asthma, overweight at age 1 year was associated with a decreased risk of asthma and better lung function at age 6 and 8 years. However, being overweight beyond infancy did not have any protective effect and even could confer a higher risk for asthma.

Keywords

Asthma; overweight; children; high risk birth cohort

INTRODUCTION

Both asthma and obesity are major public health concerns that often begin in childhood and share some common risk factors. With the increased prevalence of these two conditions in the last 20 years, a natural speculation arose that the development of asthma and obesity might be related.¹ Current evidence favors the association that obesity precedes asthma in adults.² In children, inconsistent findings have been observed^{3–6}; that is, some studies reported an increased risk for asthma in overweight children, whereas others did not. This discrepancy might result from different study designs, especially different ages of the study subjects.

Early childhood is a dynamic period for growth as well as for disease development. For instance, inadequate nutrition during infancy, the period with most rapid growth in life, could lead to consequences that may be lifelong, harming not only the current but also the future growth and development.⁷ Since both asthma and obesity have roots in fetal and early childhood periods^{8, 9}, it is important to examine the associations between these two conditions beginning from birth. A recent longitudinal study conducted in Netherlands found that asthmatic symptoms at age 8 years were related to late overweight at age 6–7 years but not early overweight at age 1–2 years.¹⁰ However, the study did not distinguish the effect of overweight in infancy, i.e., the first year of life, from later years. In addition, the weight and height data were reported by parents, instead of measured by clinicians.

During infancy, human lung parenchyma undergoes a substantial structural remodeling due to alveolar formation and septal restructuring.^{11, 12} Stimuli or Insults during this critical time period can have profound effects on subsequent development of respiratory systems and lung disease processes, including asthma.^{13, 14}

The objective of this study was to examine the age-related associations between weight status from birth to age 5 years and asthma at age 6 and 8 years. The data used for this study are generated from the Childhood Origin of Asthma (COAST)¹⁵ cohort, which comprises of a birth cohort genetically at high risk of developing asthma due to parental history of asthma or respiratory allergies. The frequently collected medical information provided us a unique opportunity for this study.

METHODS

Study Subjects

The design and implementation of the COAST study has been described in detail elsewhere.¹⁵ Briefly, a total of 289 full-term newborns with birth weight > 2000 g were enrolled from November 1998 through May 2000. To qualify, at least one parent was required to have respiratory allergies (defined as one or more positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma. Of these children, 285 were followed for age 1 year. Among them, 259 children at age 6 years and 238 at age 8 years had asthma diagnosis defined, respectively. Height/length and weight data were collected from medical records. Other

information was collected prospectively at each planned clinical visits and sick visits as well. The COAST study was approved by the Human Subjects Committee of the University of Wisconsin.

Wheezing and asthma

Wheezing respiratory illness and asthma were defined as previously described.¹⁶ A wheezing illness during the first 5 years was defined as meeting one or more of the following criteria: 1) physician-diagnosed wheezing at an office visit; 2) an illness for which the child was prescribed short or long-acting beta agonists and/or long term controller medications; or 3) an illness given the following specific diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation. Current asthma was defined based on the documented presence of one or more of the following characteristics in the previous year: 1) physician-diagnosed asthma, 2) use of albuterol for coughing or wheezing episodes (prescribed by physician), 3) use of a daily controller medication, 4) step-up plan including use of albuterol or short-term use of inhaled corticosteroids during illness, and 5) use of prednisone for asthma exacerbation. Four separated investigators, blinded to any antecedent histories concerning viral illnesses or patterns of aeroallergen sensitization, independently evaluated each subject for the presence or absence of asthma based on the above criteria.

Pulmonary function test

Pulmonary function tests were conducted yearly beginning at age 5. Three primary indicators of lung function - forced vital capacity (FVC) and forced expiratory volume (FEV) at timed intervals of 0.5 second (FEV_{0.5}), and 1.0 second (FEV₁) at ages 6 and 8 years were analyzed. Percent predicted values for FVC (FVC%) and FEV₁ (FEV₁%) were calculated according to the equations developed by Wang et al.¹⁷

Weight status

Height/length and weight data were retrieved from physician records obtained during routine well-child visits at age 2, 4, 6, 9, 12, 18, 24, 30, 36 months and every annual visit after age 3 years. Absolute height/length and weight were converted to gender- and age-specific percentiles by using the 2000 CDC growth references.¹⁸ Weight-for length percentile for children at age 2 years or younger and body mass index (BMI) percentile for children at age 3 years or older were calculated. A value greater than 85th percentile was defined as being overweight.¹⁹

Birth weight was categorized into 3 groups: (1) low, <15th weight-for-age percentile (only 5 participants had birth weight <2500 g), (2) average, 15th-85th percentile and (3) high, >85th percentile. Rapid weight gain during infancy was defined as an increase in weight-for-age z-scores of greater than 0.67 SD from birth to 6 months, which is equivalent to crossing one percentile channel on the CDC growth chart.

Statistical analyses

All analyses were performed using SAS (version 9.1.3, SAS Institute, Inc., Cary NC, 2001) and R (equivalent to S-Plus, downloadable from <http://www.r-project.org>). Student t-test or simple regression was used to compare group differences for continuous variables. Chi-square or fisher exact test was used in univariate analyses to compute frequency distributions and test differences in proportions for categorical variables. The associations between asthma and overweight were examined using logistic regression. Other factors that may contribute to the development of wheezing/asthma were also included in logistic regression models; these included breastfeeding, gender, self-reported maternal asthma, as

well as various environmental factors during first year of life: dog and cat in household at birth, smoke exposure, daycare attendance, having older children (including siblings and other children) in the household, wheezing with Rhinovirus infection (RV wheezing). Breastfeeding groups were defined based on the duration of exclusively breastfeeding of <2 months, 2–4 months or ≥ 4 months. More detailed descriptions of these factors have been described previously.^{20–22} Statistical significance was set at an α of 0.05 for all analysis.

RESULTS

Study population

Among 285 COAST children followed up to age 1 year, 259 children (91%) at age 6 years and 238 (84%) at age 8 had sufficient data to be evaluated for asthma using preset criteria. No significant difference was found between these subsets of children and overall 285 children with respect to the descriptive statistics in Table I.

Prevalence of overweight and wheezing from birth to age 8 years

The prevalence of overweight increased from 15% at age 1 year to 22% at age 3 years then stayed about the same between 3–8 years (Figure 1). Proportionately more children with birth weight less than 15th percentile experienced rapid weight gain during the first six month of life (34%) compared to those with average birth weight (20%) and high birth weight (2%), $p=0.0005$. As a result, a similar percentage of children were found to be overweight at age 1 year among all birth weight groups (11%, 15% and 20% in low, average and high birth weight groups, respectively, $p=0.51$).

The prevalence of wheezing illnesses decreased from 29% in the first year of life to 14% at age 5 (Figure 1). Asthma was diagnosed in 28% of children at age 6 and 33% of children at age 8 years. There were no significant concurrent associations between overweight and wheezing/asthma at any given age (all p -values >0.05).

Associations between weight status 0–5 years and asthma at age 6 and 8 years

We conducted a longitudinal analysis to determine whether weight status at any age was associated with the subsequent development of asthma ascertained at age 6 or 8 years (Tables II for univariate analyses and III for multiple regressions). The analyses in Table III show that neither birth weight nor rapid weight gain between 0–6 months was associated with asthma. However, overweight at age 1 year was associated with a lower rate of asthma at age 6 years (p -value=0.02) and asthma at age 8 years (p -value=0.04). Overweight beyond age 1 year (i.e., age 2, or 3 or 5 years) was not related to higher risk of asthma either at age 6 or 8 years (all p -values >0.05).

We next tested weight change between age 1 and 5 years in relation to the subsequent development of asthma. We discovered that children who were overweight at age 5 years but not at age 1 year had an increased risk of asthma at age 6 years compared to children overweight at age 1 only (p -value=0.05, Table III). Those children overweight at age 5 years only had the highest asthma rate (38% [age 6 years, Table II]), followed by those with normal weight at both age 1 and 5 years (30%), then children overweight at both ages (21%), and the lowest (11%) in those overweight at age 1 year only.

Associations between weight status at age 1 year and lung function at age 6 and 8 years

Weight-for-length at age 1 year was positively correlated with pulmonary function test values at age 6 and 8 years (Table IV). In general, weight-for-length at age 1 was positively correlated with FVC, FEV_{0.5}, and FEV₁ at age 6 and 8 years. These correlations remained

significant after adjusting for length status, i.e., on percent predicted FVC and percent predicted FEV1 at age 8 (Table IV).

DISCUSSION

The prospectively followed birth cohort in the COAST project provided us with an excellent opportunity to investigate the associations between weight status in the first five years and having asthma at age 6 and 8 years. The findings demonstrate that in the COAST children, who are genetically at high risk of developing asthma, overweight at age 1 year was associated with decreased risk of asthma and greater lung function at age 6 and 8 years. Beyond age 1, being overweight at 2–5 years of age was no longer protective for asthma development at age 6 or 8 years. In fact, in our study population, late onset of overweight, i.e., overweight at age 5 but not age 1 year, was associated with a higher risk for developing asthma at age 6 and 8 years. These findings provide evidence of the complex relationships between age, overweight status, and wheezing/asthma development.

The effect of overweight status on the subsequent development of asthma during childhood has been previously reported.^{3–6, 10, 23} Many of the studies focused on weight status at birth, during preschool age, or school age. Very few of them examined overweight status during infancy.⁸ One study conducted in a general population in the Netherlands⁸ found that a high BMI between 1–2 year of age was not associated with later asthma symptoms if the weight status became normal. Whether or not being heavier at age 1 year has a protective effect was not analyzed separately in this study.⁸ However, the study showed that the late onset of overweight at age 6–7 years, instead of “persistent high BMI” between 1–2 years and 6–7 years, was associated with a significantly increased risk of asthma symptoms at age 8, which might indicate protective effects of early overweight status at age 1 and/or 2 years on asthma development.⁸ Similar findings were observed in our cohort for asthma at age 6 and 8, although the result at age 8 did not reach statistical significance. One possible reason for the insignificant test at age 8 is that some of the children in “Overweight at 1 y only” group became overweight at 6–7 year (data not shown), which might increase their risk of asthma at age 8. As noticed in our study, the percentage of asthmatic children in “Overweight at 1 y only” group at age 8 year was almost doubled compared to age 6 (11% at age 6 vs. 21% at age 8).

It is interesting to speculate why overweight status at age 1 year was associated with a decreased risk of asthma at age 6 and 8 years. One possible explanation is that children on the top 15th percentile of growth chart at age 1 year were in general well nourished, and this promoted maximum postnatal lung development and alveolarization. Accordingly, children with weight-to-height >85% also had increased lung function at age 6 and 8 years. Alveolar development begins during gestation and continues through age 1 and 1.5 years, or even longer.^{11, 12} Most of the alveoli are added through multiplication during this time.²⁴ Therefore, nutritional influences on alveolarization during infancy could have profound and long lasting effects on lung function, and perhaps the development of lung disease, far beyond infancy. The concept of “programming”, in which growth in early life exerts long-term effects on the structure and function of particular organs and tissues, is well established in epidemiological and animal studies.^{7, 25} For example, small body size at birth or in infancy has been associated with an increased risk of asthma^{26–30} and low lung function.^{31–34} In addition, low weight gain during infancy was found to be associated with modest reductions in adult lung function.³⁵ On the other hand, abundant nutrition during infancy that would encourage maximum physical growth and development, might reduce the risk of subsequent lung disease.

Current evidence shows that children who were overweight during infancy tend to be overweight in later years,^{36, 37} and a similar trend was observed in our study population (data not shown). Establishing a pattern of overweight status could be problematic given that overweight/obesity is a major risk factor for many metabolic diseases.³⁶ However, many of the association studies did not evaluate when children became overweight, and this could lead to biased assumptions about weight status in infancy. It is not clear if health is impaired for children who were overweight in infancy and then subsequently developed normal weight. More studies are needed to thoroughly understand the role of growth during infancy on subsequent health.

The longitudinal design of the COAST study enabled us to examine age related differences in the relationship between weight and asthma risk, and the excellent retention in this cohort added to the validity of the results. Limitations in the present study include the fact that this is a high-risk population for allergic diseases and results from this study need to be confirmed in the general population. Second, the sample size was relatively small and limited subgroup analyses. Third, overweight status was defined by BMI (weight-for-length if a child was younger than 2 years old) instead of the actual percent of body fat. However, in children, using BMI to define overweight has been endorsed by major organizations and it shows a high degree of correlation with percent of body fat.^{38, 39} Last, parental weight status was not taken into account. This is not likely to introduce bias in the study because evidence shows that parental obesity is not a significant contributor to early childhood obesity, especially in the first two years of life.^{40, 41}

In conclusion, our findings suggest that association between weight and childhood asthma changes with age. While obesity may promote asthma in later life, these findings suggest the possibility that nutrition during infancy should be optimized to promote lung growth and development, and that this could have effects in reducing asthma risk later in childhood. On the other hand, after the first year of life, the attention needs to be focused on balanced nutrition to prevent overweight and obesity beyond infancy, which might be a potential risk factor for asthma. Again, further studies are needed to validate these findings in both high-risk and general populations as well in children premature and/or with very low birth weight.

KEY MESSAGE

High body weight at age 1 year is associated with a decreased risk of asthma and better lung function at age 6 and 8 years in children with parental history of asthma or atopy.

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ABBREVIATIONS

BMI	Body mass index
COAST	Childhood origin of asthma project
FEV0.5	- Forced expiratory volume (FEV) at timed interval of 0.5 second
FEV1	Forced expiratory volume (FEV) at timed interval of 1.0 second
FEV1%	Percent predicted value for FEV1
FVC	Forced vital capacity

FVC%	Percent predicted value for FVC
RV wheezing	wheezing with Rhinovirus infection

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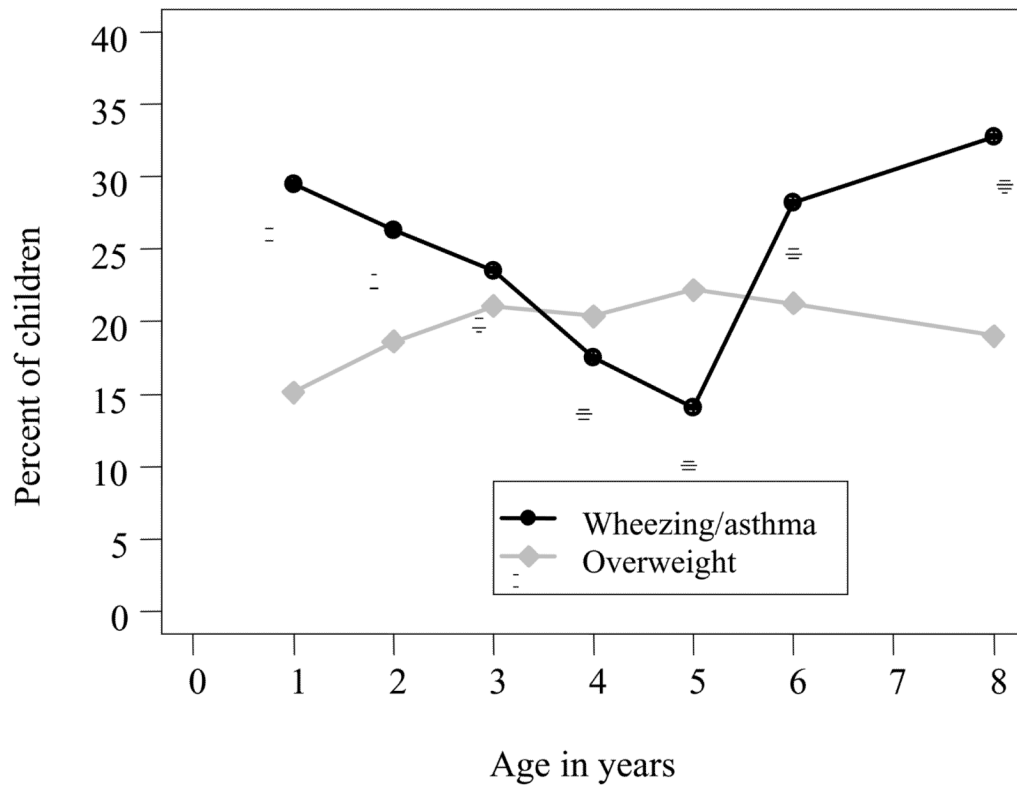


Figure 1. Prevalence of overweight and wheezing/asthma during the first 8 years of life. Asthma diagnosis was not available for age 5 years or younger. Therefore, the prevalence of wheezing was plotted. At age 6 and 8 years, the prevalence of asthma was plotted.

TABLE I

Descriptive statistics of the study population

	Age 1 y (n = 285)	Age 6 y (n = 259)	Age 8 y (n = 238)
Gender			
Male (%)	56% (161)	57% (147)	57% (135)
Female (%)	44% (124)	43% (112)	43% (103)
Maternal allergy			
Yes	83% (230)	83% (207)	83% (195)
No	17% (48)	17% (44)	17% (39)
Maternal asthma			
Yes	42% (115)	43% (106)	41% (93)
No	58% (160)	57% (143)	59% (135)
Exclusive breastfeeding			
<2mo	43% (122)	42% (110)	41% (98)
2-4mo	22% (64)	22% (57)	21% (51)
≥4mo	35% (99)	36% (92)	37% (89)
Smoking exposure during infancy			
Yes	25% (71)	25% (64)	24% (56)
No	75% (214)	75% (195)	76% (182)
Daycare attendance during infancy			
Yes	54% (153)	55% (142)	55% (130)
No	46% (132)	45% (117)	45% (108)
Having older children in the household during infancy			
Yes	58% (166)	59% (154)	60% (143)
No	42% (119)	41% (105)	40% (95)
Dog in household at birth			
Yes	35% (101)	36% (92)	36% (85)
No	65% (184)	64% (167)	64% (153)
Cat in household at birth			
Yes	29% (84)	29% (76)	29% (68)
No	71% (201)	71% (183)	71% (170)
RV wheezing during infancy			
Yes	16% (47)	17% (45)	17% (41)
No	84% (238)	83% (214)	83% (197)
Birth weight percentile	53.3 ± 29.1	53.6 ± 29.0	53.5 ± 28.9
Weight-for-length percentile at 1 y	49.0 ± 30.6	48.8 ± 30.5	49.0 ± 30.3
Weight-for-length percentile at 2 y	49.7 ± 32.2	50.1 ± 32.3	49.8 ± 32.0
BMI percentile at 3 y	55.8 ± 28.6	56.5 ± 28.5	56.5 ± 28.2
BMI percentile at 5 y	59.3 ± 28.2	59.4 ± 28.1	59.0 ± 27.7

* p-value < 0.05 from chi-square test.

TABLE II

Occurrence of asthma at age 6 and 8 y by weight status at different ages

	Asthma 6 y		Asthma 8 y	
	%	No.	%	No.
Birth weight				
< 15 th percentile	30%	10 (n=33)	42%	13 (n=31)
15–85 th percentile	27%	47 (n=177)	30%	49 (n=162)
≥ 85 th percentile	33%	16 (n=49)	36%	16 (n=45)
Rapid weight gain 0–6 mo				
< 0.67 z-score	27%	57 (n=209)	32%	62 (n=192)
≥ 0.67 z-score	30%	14 (n=46)	32%	14 (n=44)
Weight-for-length at 1 y				
< 15 th percentile	31%	16 (n=52)	38%	18 (n=48)
15 – 85 th percentile	30%	51 (n=169)	33%	52 (n=456)
≥ 85 th percentile	16%	6 (n=38)	24%	8 (n=34)
Weight-for-length at 1 y				
< 85 th percentile	31% *	67 (n=214)	36%	70 (n=197)
≥ 85 th percentile	16%	6 (n=38)	24%	8 (n=34)
Weight-for-length at 2 y				
< 85 th percentile	28%	58 (n=201)	33%	61 (n=187)
≥ 85 th percentile	27%	13 (n=48)	33%	14 (n=43)
BMI at 3 y				
< 85 th percentile	27%	53 (n=195)	33%	60 (n=181)
≥ 85 th percentile	28%	15 (n=54)	27%	13 (n=48)
BMI at 5 y				
< 85 th percentile	27%	54 (n=199)	32%	60 (n=186)
≥ 85 th percentile	32%	18 (n=56)	33%	16 (n=49)
Weight change between 1 and 5 y				
Never overweight	30%	52 (n=173)	35%	56 (n=160)
Overweight 1 y only	11%	2 (n=19)	21%	4 (n=19)
Overweight 5 y only	38% ^	14 (n=37)	35%	12 (n=34)
Overweight 1 & 5 y	21%	4 (n=19)	27%	4 (n=15)

* p-value < 0.05 from chi-square test.

^ p-value < 0.05 compared to overweight 1y only group.

TABLE III

Adjusted associations between asthma at age 6 and 8 y and weight status at different ages

	Asthma 6 y			Asthma 8 y		
	OR	95% CI	p-value	OR	95% CI	p-value
Birth weight *			0.73			0.84
< 15 th percentile	0.78	0.24, 2.51		1.01	0.32, 3.23	
15–85 th percentile	0.72	0.32, 1.63		0.82	0.36, 1.90	
≥ 85 th percentile	1.00			1.00		
Rapid weight gain 0–6 mo			0.78			0.71
≥ 0.67 z-score	1.11	0.50, 2.51		0.86	0.37, 1.96	
< 0.67 z-score	1.00			1.00		
Weight-for-length at 1 y			0.07			0.10
< 15 th percentile	3.42	0.97, 12.05		3.78	1.09, 13.13	
15–85 th percentile	3.36	1.19, 9.54		2.71	0.97, 7.62	
≥ 85 th percentile	1.00			1.00		
Weight-for-length at 1 y			0.02			0.04
< 85 th percentile	3.14	1.17, 8.44		2.85	1.07, 7.57	
≥ 85 th percentile	1.00			1.00		
Weight-for-length at 2 y			0.62			0.48
< 85 th percentile	1.23	0.55, 2.73		1.35	0.59, 3.10	
≥ 85 th percentile	1.00			1.00		
BMI at 3 y			0.92			0.30
< 85 th percentile	1.04	0.50, 2.15		1.51	0.69, 3.30	
≥ 85 th percentile	1.00			1.00		
BMI at 5 y			0.81			0.49
< 85 th percentile	0.91	0.45, 1.88		1.31	0.61, 2.82	
≥ 85 th percentile	1.00			1.00		
Weight change between 1 & 5 y			0.12			0.21
Normal	4.20	0.84, 20.96		3.40	0.79, 14.64	
Overweight 1 y only	1.00			1.00		

	Asthma 6 y			Asthma 8 y		
	OR	95% CI	p-value	OR	95% CI	p-value
Overweight 5 y only	5.78	1.03, 32.45		2.87	0.57, 14.42	
Overweight 1 & 5 y	1.80	0.25, 12.77		1.30	0.20, 8.39	

* Other variables included in the analysis were: gender, maternal asthma and environmental factors during 1st yr: breastfeeding, dog and cat ownership, smoke exposure, daycare attendance and having older children in the household, RV wheezing. Besides these variables, birth weight was included in other models.

TABLE IV

Pulmonary function tests by first year weight status

	Correlation ¹	Weight-for-length at age 1 y		
		<15 th %tile	15–85 th %tile	>85 th %tile
At age 6 y				
FVC%	0.13	103.88 (11.19)	106.86 (13.90)	108.44 (13.98)
FEV1%	0.12	102.50 (12.02)	105.55 (14.44)	105.50 (11.39)
FVC	0.25 [¶]	1.42 (0.20) ^{^*}	1.53 (0.24)	1.60 (0.28)
FEV1	0.22 [¶]	1.25 (0.18) ^{^*}	1.34 (0.22)	1.37 (0.20)
FEV0.5	0.21 [¶]	0.95 (0.17) [*]	1.01 (0.18)	1.04 (0.16)
At age 8 y				
FVC%	0.25 [¶]	103.74 (12.26) [*]	107.20 (12.60)	112.27 (11.74)
FEV1%	0.24 [¶]	96.42 (14.05) [*]	101.21 (13.63)	103.38 (11.19)
FVC	0.30 [¶]	1.84 (0.30) [*]	1.92 (0.30) [*]	2.08 (0.28)
FEV1	0.29 [¶]	1.50 (0.28) [*]	1.59 (0.26)	1.68 (0.20)
FEV0.5	0.25 [¶]	1.12 (0.22) ^{^*}	1.20 (0.22)	1.24 (0.18)

¹ Correlation coefficients between weight-for-height percentiles at age 1 y and lung function test scores.² Overall group comparisons from simple regression.[¶] p-value<0.05 for correlation coefficient test.[^] p<0.05 compared to weight-for-length 15–85th %tile group^{*} p<0.05 compared to weight-for-length >85th %tile group