

Small Size at Birth and Greater Postnatal Weight Gain Relationships to Diminished Infant Lung Function

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Recent evidence suggests that impaired lung development is linked with diminished lung function and an increased risk of chronic obstructive airway disease in adulthood. To examine environmental influences on early lung development, we measured lung function in 131 normal-term infants aged 5–14 weeks. Adjusting for age at measurement, FEV at 0.4 seconds fell by 4.4% for each standard deviation decrease in birth weight ($p = 0.047$); when adjusted for FVC, FEV at 0.4 seconds was not related to birth weight but fell by 3.2% per standard deviation increase in infant weight gain ($p = 0.001$). Age- and sex-adjusted total respiratory system compliance fell by 7.0% per standard deviation decrease in birth weight ($p < 0.001$) but was not related to infant weight gain. In univariate analyses, age-adjusted forced expiratory flow at functional residual capacity was not related to birth weight, but decreased by 11.0% per standard deviation increase in infant weight gain ($p = 0.007$). The respiratory rate rose by 5.1% per standard deviation increase in infant weight gain ($p = 0.001$). Lung function measurements were not related to infant feeding. The observations suggest that lower rates of fetal growth and higher rates of early infancy weight gain are associated with impaired lung development.

Keywords: infant; FEV; forced expiratory flow rates; lung function; weight gain

The normal physiologic growth and development patterns of the airways and parenchyma remain poorly understood, but epidemiologic studies measuring premorbid lung function in infancy indicate the importance of genetic and environmental factors during fetal and early postnatal life (1–8). Children and adults who were small at birth tend to have reduced lung function (9–11) and an increased risk of respiratory morbidity and mortality (12, 13). Although the mechanisms linking early lung development with lung function in later life are unknown, impaired airway and alveolar growth may be important. Airway branching is complete by 16-weeks gestation, and alveolar formation begins before birth. Between birth and 18 months of age there is a rapid increase in alveolar number and size, while airway diameter continues to grow. Environmental influences during both prenatal and early postnatal life therefore have the potential to affect lung development. Maternal smoking before and after birth has been associated with impaired lung function of the offspring in some, but not all, studies (6, 14–17).

Fetal growth and postnatal growth have been associated with later atopy and asthma. Links between a large neonatal head circumference and a raised total serum IgE in childhood (18, 19) and adulthood (20) led to the hypothesis that factors influencing fetal growth may program the developing respiratory or immune systems (21). Birth length and weight have been associated with later asthma (19), but this was not replicated in another study (13). The conflicting results may reflect the age at which the relationship is examined and whether persistent wheezing associated with atopy is considered separately from transient wheezing in children with small airways who are predisposed to wheeze with viral infections (3–5).

The rapid thoracoabdominal compression (RTC) technique to measure forced expiratory flow at functional residual capacity ($\dot{V}_{\max_{\text{FRC}}}$) is widely used for assessing peripheral airways function in infancy. Recently, measurement of forced expiratory flows in infants has been extended to include maneuvers initiated near total lung capacity (22, 23), eliminating the need for a volume landmark and improving intrasubject and intersubject variability. FEV in time t can be derived from this raised volume RTC. In many young infants, their rapid respiratory rate precludes reporting of FEV₁ and FEV_{0.75}; the current recommendation for infants under 3 months is to measure FEV_{0.4} (24).

We have examined the hypothesis that fetal and early postnatal growth, because of their effects on lung growth and development, will predict premorbid lung function, with implications for the general hypothesis that impaired early lung development impairs subsequent respiratory health. Here we report analyses of size at birth and weight gain in early infancy in relationship to lung function measured by FEV_{0.4}, total respiratory system compliance (Cr_s), $\dot{V}_{\max_{\text{FRC}}}$, and respiratory rate at 5–14 weeks of age.

METHODS

Additional details on the study population, methods, and statistical analysis are provided in an online supplement. In brief, white infants, born at 37 weeks or more of gestation (calculated using menstrual and ultrasound data) and without major congenital anomalies, were recruited from babies born to healthy pregnant women in the Southampton Women's Survey. We used questionnaires to ascertain maternal cigarette smoking (before conception and at infant testing) and infant feeding.

We approached 362 women about the study; 219 (60%) declined, and 12 (3%) agreed but were excluded because of recent upper respiratory tract infection or other illness, leaving 131 (36%) who took part. None had previously had a lower respiratory tract illness or had evidence of infection at testing. The Southampton and South West Hants Joint Research Ethics Committee approved the study, and we obtained parental informed written consent.

Infant weights and crown–heel lengths were measured at birth and at lung function testing, and neonatal head circumference was recorded. Lung function was measured 5–14 weeks after birth during quiet sleep augmented by chloral hydrate 75–100 mg/kg. Data were collected using RASP software (Physiologic Ltd., Newbury, UK) and analyzed in SQUEEZE (Paul Dixon, London, UK). An inflatable jacket connected to a rapid inflation system was placed around the infant's chest and

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abdomen. A facemask attached to a Fleisch pneumotachograph (Dyna-science, Blue Bell, CA) measuring airway pressure and flow was placed over the nose and mouth. Flow and volume, calculated by digital integration of the flow signal, were displayed during RTC squeezes, passive inflations, and raised volume RTC.

Respiratory rate was measured during quiet tidal breathing. To record partial expiratory flow volume curves, a stable end expiratory level was established before performing an RTC at the lowest pressure to achieve the best $\dot{V}_{\text{maxFRC}}$, calculated from the partial expiratory flow volume curve. Passive, relaxed inflations were recorded using a resuscitator connected to the pneumotachograph. Crs (ml/cm) was calculated using SQUEEZE from the resultant passive flow-volume curves, and the airway opening pressure was measured during occlusion. Raised volume RTC curves were recorded at the optimal jacket pressure at the end of a passive inspiration using a technique adapted from Feher and colleagues (22), and FEV_{0.4} and FVC were measured from the forced expiratory flow-volume curve.

FEV_{0.4}, C_{rs}, $\dot{V}_{\text{maxFRC}}$, and respiratory rate were positively skewed, and logarithmic transformed values were analyzed by multivariate linear regression. FEV_{0.4} was also analyzed adjusting for FVC by including it as a covariate in the analyses. Because of the logarithmic transformation, results are presented as the percentage change in lung function parameter per unit change in the factor of interest and back-transformed means of the logged variables.

Neonatal weight, head circumference, and crown-heel length were adjusted for sex and weight and length at lung function testing adjusted for age/sex by conversion to SD scores compared with reference values for British neonates and infants (25). We derived SD scores for weight gain between birth and testing that are conditional on birth weight and take account of regression to the mean (26).

RESULTS

Lung function tests were performed on 131 infants (66 males). Their median (10th–90th percentile) weights and crown-heel lengths at birth and at lung function testing are shown in Table 1, together with their head circumference and duration of gestation at birth. Seven percent were less than the 10th percentile of birth weight for gestational age using standard Child Growth Foundation charts for the United Kingdom. The distributions of weight, crown-heel length, head circumference, and gestation at birth are graphically portrayed in the online supplement (Figure E1). Table 1 also shows the distributions of the infant's lung function measurements. Full lung function data were not col-

lected in all cases because of the infant waking before completion of the protocol or unacceptable data quality (*see* online supplement). Ten percent of subjects were tested during the same session by a second researcher; in all cases, the interoperator differences in FEV_{0.4} and $\dot{V}_{\text{maxFRC}}$ were within 10%.

Age at Test and Sex

Lung function was measured between 5 and 14 weeks after birth (Table 1); the median (10th–90th percentile) age at testing was 9.4 (7.0–12.4) weeks. FEV_{0.4}, Crs, and $\dot{V}_{\text{maxFRC}}$ increased with increasing infant age at testing; for each additional week of age, FEV_{0.4} rose by 4.2% (95% confidence interval [CI], 2.0 to 6.4, $p < 0.001$), Crs by 5.2% (95% CI, 3.3 to 7.1, $p < 0.001$) and $\dot{V}_{\text{maxFRC}}$ by 7.2% (95% CI, 3.0 to 11.4, $p = 0.001$). The increases in FEV_{0.4} and Crs with increasing age were similar in infants of different birth weight, but in infants of below-average, average, and above-average birth weight, $\dot{V}_{\text{maxFRC}}$ rose by 1.2% ($p = 0.8$), 5.9% ($p = 0.08$), and 14.0% ($p < 0.001$), respectively, for each additional week of age. This interaction of birth weight in relationship to the association between $\dot{V}_{\text{maxFRC}}$ and infant age was strongly significant ($p = 0.02$). FVC-adjusted FEV_{0.4} was not related to age at test. The respiratory rate fell by 0.8% with increasing infant age, but this relationship was not statistically significant ($p = 0.3$). Crs was lower in female infants (by 8.6%; 95% CI, 0.7% to 15.9%, $p = 0.03$), but FEV_{0.4}, FVC-adjusted FEV_{0.4}, $\dot{V}_{\text{maxFRC}}$, and respiratory rate were all similar in male and female infants. Table 2 shows the back-transformed geometric means of lung function parameters by thirds of age at testing and by infant sex. FEV_{0.4}, FVC-adjusted FEV_{0.4}, Crs, $\dot{V}_{\text{maxFRC}}$, and respiratory rate were not related to the infant's duration of gestation at birth. In all further analyses of FEV_{0.4} and $\dot{V}_{\text{maxFRC}}$, we adjusted for age at testing by including it as a covariate in the regression models; for Crs, we included both age at testing and infant sex in the regression models.

Infant Anthropometry and Weight Gain

Age-adjusted FEV_{0.4} fell by 4.4% (95% CI, 0.1 to 8.9, $p = 0.047$) for each SD decrease in birth weight, by 3.7% (95% CI, –0.6 to 8.1%, $p = 0.09$) for each SD decrease in neonatal head circumference, and by 5.3% (95% CI, 0.8 to 10.0, $p = 0.02$) for each SD

TABLE 1. STUDY POPULATION CHARACTERISTICS AND LUNG FUNCTION MEASUREMENTS

	Median	10th–90th Percentiles	No. Subjects
Measurements at birth			
Weight, kg	3.6	3.0–4.2	131
Crown–heel length, cm	50.5	47.7–52.3	128
Head circumference, cm	35.3	33.6–36.6	131
Gestation, wk	40.4	38.9–41.9	131
Age at lung function testing, wk		%	
5–6		9	12
7–8		32	42
9–10		27	36
11–12		27	35
13–14		5	6
Measurements at lung function testing		10th–90th percentiles	
Crown–heel length, cm	58.6	55.5–62.5	130
Weight, kg	5.3	4.5–6.4	131
FEV _{0.4} , ml	136.0	106.6–183.4	87
Crs, ml/mm H ₂ O	47.7	37.1–61.0	97
$\dot{V}_{\text{maxFRC}}$, ml/s	133.0	61.9–238.7	129
Respiratory rate, per min	43.5	36.2–55.9	128

Definition of abbreviations: Crs = respiratory system compliance; $\dot{V}_{\text{maxFRC}}$ = forced expiratory flow at functional residual capacity.

Excluding infants below the 10th percentile for gestational age, median (10th–90th percentile) values were 137.6 (108.0 to 183.4) ml for FEV_{0.4}, 48.9 (37.9 to 62.0) ml/mm H₂O for Crs, 131.8 (66.1 to 241.1) ml/second for $\dot{V}_{\text{maxFRC}}$, and 43.3 (36.1 to 53.5) per minute for respiratory rate.

TABLE 2. GEOMETRIC MEANS OF LUNG FUNCTION PARAMETERS BY THIRDS OF AGE AT LUNG FUNCTION TESTING AND INFANT SEX

	FEV _{0.4} (ml)	Crs (ml/cm H ₂ O)	$\dot{V}$ max _{FRC} (ml/s)	Respiratory Rate (per min)
Age at testing				
Youngest third (≤ 8.5 wk)	121 (29)	43 (31)	105 (42)	45 (42)
Middle third (8.5–10.8 wk)	148 (30)	49 (34)	132 (42)	44 (40)
Oldest third (> 10.8 wk)	147 (28)	54 (32)	161 (45)	44 (46)
P _{trend}	< 0.001	< 0.001	0.001	0.3
Sex				
Males	137 (44)	50 (48)	127 (66)	45 (64)
Females	139 (43)	46 (49)	136 (63)	44 (64)
p Value for difference	0.8	0.03	0.4	0.6

For definition of abbreviations see Table 1.

Each cell contains the back-transformed geometric mean, with the number of observations contributing to the mean in parentheses.

The overall geometric means (and the SD of the logged values) for FEV_{0.4}, Crs, $\dot{V}$ max_{FRC}, and respiratory rate were 138 (0.21), 48 (0.21), 131 (0.49), and 44 (0.17), respectively.

decrease in neonatal crown–heel length. Although age-adjusted FEV_{0.4} had a positive association with crown–heel length SD score at the time of lung function testing ($p = 0.047$), it was not related to the infant's weight SD score at this time ($p = 0.96$). A weak trend for FEV_{0.4} to fall with increasing weight gain SD score was not statistically significant ($p = 0.1$). Table 3 presents geometric mean age-adjusted FEV_{0.4} according to thirds of the infants' birth weight; within each birth-weight grouping, results are also shown according to thirds of weight gain between birth and lung function testing.

When adjusted for FVC, FEV_{0.4} fell by 0.5% (95% CI, -1.6% to 2.6% , $p = 0.6$) for each SD increase in birth weight and by 3.1% (95% CI, 1.2% to 4.9% , $p = 0.002$) for each SD increase in weight at lung function testing. FVC-adjusted FEV_{0.4} therefore had a strong relationship with infant weight gain, falling by 3.2% (95% CI, 1.4 to 4.9% , $p = 0.001$) for each SD increase in weight gain (Figure 1). The relationship between FVC-adjusted FEV_{0.4} and weight gain was strengthened by further adjustment for age at test ($p < 0.001$). FVC-adjusted FEV_{0.4} was not associated with respiratory rate ($r = -0.12$, $p = 0.3$) and adjustment for respiratory rate did not alter the relationship between infant weight gain and FVC-adjusted FEV_{0.4}.

In a similar pattern to that found for FEV_{0.4}, age- and sex-adjusted Crs fell by 7.0% for each SD decrease in birth weight (95% CI, 3.6 to 10.6 , $p < 0.001$), by 5.8% (95% CI, 2.2 to 9.5 , $p = 0.002$) for each SD decrease in neonatal head circumference, and by 7.1% (95% CI, 3.5 to 10.9 , $p < 0.001$) for each SD decrease in neonatal crown–heel length. Age- and sex-adjusted Crs fell by 4.6% for each SD decrease in infant weight at lung function testing (95% CI, 0.8 to 8.6 , $p = 0.02$) and by 7.5%

(95% CI, 3.9 to 11.3 , $p < 0.001$) for each SD decrease in infant crown–heel length but was not related to infant weight gain ($p = 0.8$). Table 4 presents mean age- and sex-adjusted Crs according to thirds of the infants' birth weight and infant weight gain.

Age-adjusted $\dot{V}$ max_{FRC} was not related to birth weight ($p = 0.7$) or to neonatal head circumference ($p = 0.8$) and crown–heel length ($p = 0.4$). Age-adjusted $\dot{V}$ max_{FRC} was also not related to crown–heel length SD score at the time of lung function testing ($p = 0.7$) but did, however, decrease by 8.6% for each SD increase in weight at this time (95% CI, 0.3 to 16.2 , $p = 0.04$) and by 11.0% for each SD increase in infant weight gain (95% CI, 3.2 to 18.2 , $p = 0.007$). Table 5 presents mean age-adjusted $\dot{V}$ max_{FRC} according to thirds of the infants' birth weight and infant weight gain. Although the effect of higher infant weight gain on lower $\dot{V}$ max_{FRC} was strongest in the lowest birth-weight grouping, there was no statistically significant interaction between the effects of birth weight and infant weight gain (data not shown).

Respiratory rate rose by 2.9% (95% CI, -0.1 to 5.8 , $p = 0.06$) for each SD decrease in birth weight, by 2.7% (95% CI, -0.3 to 5.6 , $p = 0.08$) for each SD decrease in neonatal head circumference, and by 3.2% (95% CI, 0.2 to 6.1 , $p = 0.04$) for each SD decrease in neonatal crown–heel length. Respiratory rate tended to rise with increasing weight and crown–heel length at lung function testing, but these associations were not significant ($p = 0.2$ and $p = 0.5$, respectively); each SD increase in infant weight gain was, however, associated with a 5.1% (95% CI, 2.1 to 8.2 , $p = 0.001$) rise in respiratory rate. Table 6 presents mean respiratory rate according to thirds of the infants' birth weight and infant weight gain. Although there was no statistically significant interaction between the effects of birth weight and

TABLE 3. GEOMETRIC MEAN FEV_{0.4} (ml), ADJUSTED FOR AGE AT TESTING, ACCORDING TO THIRDS OF BIRTH-WEIGHT SD SCORE AND WEIGHT-GAIN SD SCORE

Birth-weight SD Score	Weight-gain SD Score			Total
	Lowest Third ≤ -0.54 SD	Middle Third -0.54 to 0.21 SD	Highest Third > 0.21 SD	
Lowest third, ≤ -0.2 SD	124 (6)	129 (12)	116 (6)	125 (24)
Middle third, -0.2 to 0.58 SD	141 (11)	144 (10)	129 (12)	137 (33)
Highest third, > 0.58 SD	148 (13)	128 (8)	143 (9)	141 (30)
Total	140 (30)	134 (30)	130 (27)	135 (87)

Each cell contains the back-transformed geometric mean, with the number of observations contributing to the mean in parentheses.

The geometric mean (SD of the logged values) for age-adjusted FEV_{0.4} was 135 (0.20) ml.

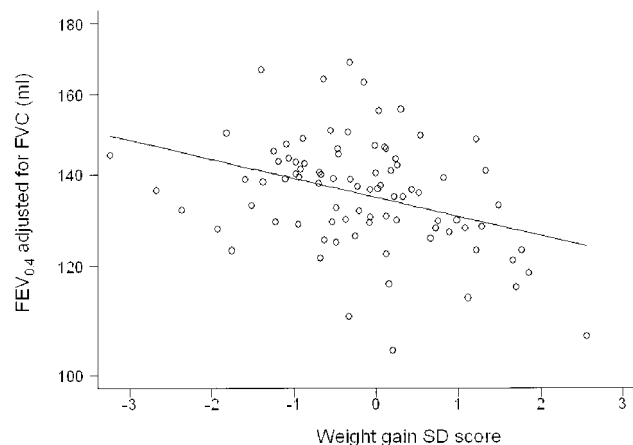


Figure 1. Scatterplot of FVC-adjusted $FEV_{0.4}$ against weight gain SD score, including regression line for the association.

infant weight gain (data not shown), in a simultaneous analysis, respiratory rate was inversely related to weight at birth ($p = 0.001$) and positively related to weight at lung function testing ($p = 0.003$).

Confirmatory analyses omitting the infant's age from the analyses of $FEV_{0.4}$ and $\dot{V}_{maxFRC}$ and age and sex from the analyses of Crs showed little change in the associations between lower birth size and lower $FEV_{0.4}$ and Crs; $\dot{V}_{maxFRC}$ remained not associated with size at birth. Omitting age as a co-variate in the analyses of weight gain SD score marginally strengthened the inverse associations with $FEV_{0.4}$ ($p = 0.03$) and $\dot{V}_{maxFRC}$ ($p = 0.001$); Crs remained not associated with weight gain ($p = 0.4$). Back-transformed mean values of $FEV_{0.4}$, Crs, $\dot{V}_{maxFRC}$, and respiratory rate according to thirds of birth weight and infant weight gain are graphically portrayed in the online supplement (see Figure E2 in the online supplement).

Maternal Smoking and Infant Feeding

Of the 131 mothers, 21% reported smoking at the time of lung function testing. Compared with the infants of mothers who did not smoke, the infants of smokers were lighter by 0.281 kg ($p = 0.005$) and shorter by 1.2 cm ($p = 0.003$) at birth. Maternal smoking lowered $FEV_{0.4}$ by 7% (95% CI, -3% to 16%), FVC-adjusted $FEV_{0.4}$ by 1% (95% CI, -4% to 6%), C_{rs} by 8% (95% CI, -1% to 16%), and $\dot{V}_{maxFRC}$ by 11% (95% CI, -10% to 27%), but none of these associations was significant ($p = 0.2$, 0.7, 0.07, and 0.3, respectively); respiratory rate was similar in infants born to smokers and nonsmokers ($p = 0.9$). Findings were similar for smoking status before conception (data not

shown). Of the 131 infants, 56% were breast-fed at the time of lung function testing; all lung function variables were similar in those breast-fed and bottle-fed (data not shown). Further analyses showed that the associations of infant anthropometry and weight gain with lung function were changed little by taking account of maternal smoking and infant feeding.

DISCUSSION

Age at Test

This is one of the largest studies measuring raised volume RTC in healthy infants of this age range and, therefore, contributes to the limited population-based data that have been published. Our study had a narrow age window for testing, but we found that age at test nonetheless had a major influence on $FEV_{0.4}$, Crs, and $\dot{V}_{maxFRC}$. This has important implications for accurate reporting of age at test in future studies. Other studies over much larger age ranges have also found a correlation between age and lung function (27, 28), but our data highlight that even an additional week can lead to a significant change in $FEV_{0.4}$, Crs, and $\dot{V}_{maxFRC}$. However, we found that among infants of below-average birth weight there was no increase in $\dot{V}_{maxFRC}$ with age. As our data are cross-sectional, further work is required to confirm and explain this observation. Nonetheless, if a high proportion of normal infants of below-average birth weight are essentially increasing their lung size over the first two months of life (greater $FEV_{0.4}$ and Crs) but failing to increase their maximal forced expiratory flows at FRC, this is a potentially important finding that could have major implications for respiratory health. Confirmation of how lung development evolves over the first months of life is needed, but using currently available techniques, the practical and ethical issues of conducting longitudinal studies to investigate lung function in infancy are considerable.

Maternal Smoking and Sex

Although the detrimental effects of tobacco smoke exposure in childhood are well established, the influence of smoking during pregnancy on lung development is less clear. A recent systematic review concluded that although most studies have produced evidence of reduced lung and airway function during the first year of life in infants whose mothers smoked during pregnancy, this is by no means true of all such studies (17). We found that the infants of smoking mothers tended to have reduced $FEV_{0.4}$, Crs and $\dot{V}_{maxFRC}$, but these trends were not statistically significant. This could partly reflect insufficient statistical power, and the upper bound of the 95% confidence limits of the reduction in $FEV_{0.4}$ that we found (16%) is close to the "approximate 20%" average reduction in infant expiratory flows reported in preliminary meta-analysis of the effect of maternal smoking (17). As we did not verify smoking data by measurement of urinary

TABLE 4. GEOMETRIC MEAN C_{rs} (ml/cm H₂O) ADJUSTED FOR SEX AND AGE AT TESTING ACCORDING TO THIRDS OF BIRTH-WEIGHT SD SCORE AND WEIGHT-GAIN SD SCORE

Birth-weight SD Score	Weight-gain SD Score			Total
	Lowest Third ≤ -0.54 SD	Middle Third 0.54 to 0.21 SD	Highest Third > 0.21 SD	
Lowest third, ≤ -0.2 SD	42 (8)	45 (15)	45 (8)	44 (31)
Middle third, -0.2 to 0.58 SD	48 (11)	51 (11)	50 (14)	50 (36)
Highest third, > 0.58 SD	55 (12)	51 (8)	49 (10)	52 (30)
Total	49 (31)	48 (34)	49 (32)	49 (97)

Each cell contains the back-transformed geometric mean, with the number of observations contributing to the mean in parentheses.

Geometric mean (SD of the logged values) for age/sex-adjusted respiratory system compliance was 49 (0.18) ml/cm H₂O.

TABLE 5. GEOMETRIC MEAN $\dot{V}_{\text{maxFRC}}$ (ml/s) ADJUSTED FOR AGE AT TESTING ACCORDING TO THIRDS OF BIRTH-WEIGHT SD SCORE AND WEIGHT-GAIN SD SCORE

Birth-weight SD Score	Weight-gain SD Score			Total
	Lowest Third ≤ −0.54 SD	Middle Third −0.54 to 0.21 SD	Highest Third > 0.21 SD	
Lowest third, ≤ −0.2 SD	140 (12)	116 (18)	107 (11)	120 (41)
Middle third, −0.2 to 0.58 SD	146 (16)	128 (14)	131 (14)	135 (44)
Highest third, > 0.58 SD	137 (15)	131 (10)	110 (19)	123 (44)
Total	141 (43)	123 (42)	115 (44)	126 (129)

Each cell contains the back-transformed geometric mean, with the number of observations contributing to the mean in parentheses.

The geometric mean (SD of the logged values) for age-adjusted $\dot{V}_{\text{maxFRC}}$ was 126 (0.47) ml/s.

cotinine, we cannot exclude misclassification of maternal smoking. However, we found a significant effect of maternal smoking on birth weight (mean reduction in birth weight 281 g) that is similar to the around 150 g reduction reported in a meta-analysis of maternal smoking (29). Moreover, we ascertained maternal smoking using an administered questionnaire both at the time of lung function testing and prospectively at home before conception; the associations that we found between infant birth weight and weight gain and the lung function parameters were changed little by taking account of maternal smoking at either time point.

Our data suggest that male infants have more compliant lungs, but we found no sex difference in $\dot{V}_{\text{maxFRC}}$ or $\text{FEV}_{0.4}$. Some studies measuring $\dot{V}_{\text{maxFRC}}$ suggest that girls demonstrate higher flows than boys (2, 8, 18, 19), although other studies, like ours, have found no difference (27, 30, 31). Studying forced expiratory flows from raised volumes, Jones and colleagues found that sex was only significant for FEF_{75} , girls having higher flows than boys after accounting for body length and smoking during pregnancy (28). The same study found no difference in FVC between girls and boys aged 3–149 weeks.

Size at Birth in Relationship to $\text{FEV}_{0.4}$ and Crs

Independent of the infant's age and weight at the time of testing, we found that infants who had a lower birth weight and shorter neonatal crown–heel length had a lower $\text{FEV}_{0.4}$. This effect was not apparent for FVC-adjusted $\text{FEV}_{0.4}$, presumably because this correction will normalize for lung size. We have not studied severely compromised infants of low birth weight, but in a study of infants who were either small for gestational age or appropriately sized, Lum and colleagues reported diminished airway function in the low birth-weight infants (32). Our study excluded infants with major congenital abnormalities or neonatal problems and was designed to recruit healthy, term infants represen-

tative of the local population; 7% of those we studied had a birth weight less than the 10th percentile for gestational age of unknown etiology, but the associations we found were graded across the range of size at birth. Our data suggest that restricted fetal growth is associated with particular impairment of lung and airway development, which are adversely affected more than one might expect for the infant's size. Moreover, our data indicate that the reduced adult lung function of individuals of below-average birth weight (11, 12) at least in part originates from impaired lung and airway development in the prenatal and immediate postnatal period and not simply from increased susceptibility to respiratory illness after birth.

We found that Crs was highly correlated with birth weight and length, with larger babies having more compliant respiratory systems. Crs is influenced by chest wall compliance as well as lung compliance and interpretation of these data needs caution. Joyce and colleagues found that Crs was lower in term growth-restricted lambs than in control animals (33) and that the lung component was significantly lower in the growth-restricted group. If restricted fetal growth is associated with less compliant lungs, it has important implications for future respiratory health; if smaller infants have decreased elastic tissue laid down *in utero*, they are likely to have an increased rate of respiratory decline with aging.

There is increasing evidence from animal studies that fetal growth restriction influences lung development (34, 35) and function (33) and that some of these effects persist (36). A number of mechanisms are likely to contribute to diminished lung function in infants of below-average birth weight, including reduced fetal nutrient supply and an altered endocrine milieu. Impaired prenatal nutrition in animal models is associated with reduced surfactant (37, 38) or surfactant activity (39), a reduction in lung DNA or protein content (38), loss of respiratory drive (40), decreased alveolarization (38), and decreased lung cellularity

TABLE 6. GEOMETRIC MEAN RESPIRATORY RATE (/min) ACCORDING TO THIRDS OF BIRTH-WEIGHT SD SCORE AND WEIGHT-GAIN SD SCORE

Birth-weight SD Score	Weight-gain SD Score			Total
	Lowest Third ≤ −0.54 SD	Middle Third 0.54 to 0.21 SD	Highest Third > 0.21 SD	
Lowest third, ≤ −0.2 SD	48 (12)	44 (20)	50 (11)	47 (43)
Middle third, −0.2 to 0.58 SD	41 (16)	43 (13)	45 (13)	43 (42)
Highest third, > 0.58 SD	40 (15)	47 (9)	45 (19)	44 (43)
Total	42 (43)	44 (42)	47 (43)	44 (128)

Each cell contains the back-transformed geometric mean, with the number of observations contributing to the mean in parentheses.

The geometric mean (SD of the logged values) for respiratory rate was 44 (0.17).

(38, 39). Some of these abnormalities of lung development may be direct consequences of nutrient deficiencies. However, the nutritional stress may also induce fetal endocrine responses that themselves affect lung development (41).

Our data cannot definitively identify the timing of the intra-uterine effect on lung development and infant lung function. However, lower infant FEV_{0.4} and Crs and faster respiratory rate had similar relationships with lower birth weight, neonatal head circumference, and crown–heel length, suggesting symmetrical growth restriction. Symmetrical restriction of fetal growth is thought to originate in early pregnancy, whereas asymmetrical growth restriction reflects impaired soft tissue accretion in late pregnancy. Our data provide weak evidence for an early pregnancy effect on infant FEV_{0.4}, Crs, and respiratory rate, perhaps mediated by impaired development of the bronchial tree, which is complete by 16-weeks gestation. Alveolar development does not begin until airway growth is complete but continues through both prenatal and postnatal life until 8–10 years of age; alveolar number at birth has been reported as being anything between 8% and 50% of the eventual adult number (42, 43).

Postnatal Weight Gain in Relationship to $\dot{V}_{\text{maxFRC}}$ and FVC-adjusted FEV_{0.4}

In contrast to our observations for FEV_{0.4} and Crs, we found that $\dot{V}_{\text{maxFRC}}$ was not related to the infant's weight and crown–heel length at birth but was lower in those who gained more weight between birth and testing. In consequence, $\dot{V}_{\text{maxFRC}}$ was lower in those with a greater weight at testing; there was, however, no association between $\dot{V}_{\text{maxFRC}}$ and crown–heel length in infancy. Postnatal weight gain was not related to Crs and only weakly related to FEV_{0.4}. Although both $\dot{V}_{\text{maxFRC}}$ and FEV in time *t* are influenced by lung size, FEV in time *t* is thought principally to reflect the size and function of larger airways, whereas $\dot{V}_{\text{maxFRC}}$ is influenced more by the function of the peripheral airways (24). Our observations raise the possibility that particular aspects of growth may have differing effects on these components of lung development. This is supported by our observation that when we normalized FEV_{0.4} for FVC we found a strong inverse relationship with postnatal weight gain. Previous studies of infants and young children of widely varying ages with respiratory disorders have reported that interpretation of FEV in time *t*/FVC is complicated by inverse associations with age and respiratory rate (24), but in the normal infants that we studied over a narrow age range, FEV in time *t*/FVC was not related to age or respiratory rate.

We found that the lowest $\dot{V}_{\text{maxFRC}}$ was in infants of below-average birth weight with above-average postnatal weight gain (Table 5). One explanation for these findings is that above-average postnatal weight gain may serve to identify fetuses that had followed a rapid trajectory of prenatal growth, which faltered in late pregnancy, impairing lung growth and development. Fetuses subject to such growth faltering in late gestation have increased postnatal weight gain unless they are exposed to severe or prolonged restriction in nutrient supply *in utero*.

An alternative explanation for the association between increased postnatal weight gain and diminished lung function is that above-average weight gain is itself impairing lung development. There has been considerable interest in the relationship between asthma and obesity in recent years (44–47), but this is the first study to suggest that increased weight gain in early infancy is associated with worse lung function. It is unlikely that different feeding modes are responsible for this finding, as infants who were breast-fed and bottle-fed had similar lung function. As children who have high weight gain in early infancy tend to have a higher body mass index and a more central fat distribution

in childhood, our data offer a possible explanation for the association of asthma and obesity.

Respiratory Rate

We studied infants during quiet sleep augmented by chloral hydrate; respiratory rate measured in these circumstances provides no more than a crude summary measure of lung function. Nonetheless, we found that infants that were of below-average birth weight and who had above-average postnatal weight gain had a faster respiratory rate. This observation again points to impaired lung development in these infants and complements our findings relating to the detailed measures of lung function.

In conclusion, we describe associations of birth anthropometry and early postnatal weight gain with lung function measured in the first few months of life. We have shown that even a 1-week increase in age is significant when reporting these infant lung function parameters. The absence of serial measurements in our study precludes definitive conclusions, but the observations suggest that lower rates of fetal growth and higher rates of early infancy weight gain are associated with impaired lung development. The association with higher infant weight gain appears paradoxical but could reflect catch-up in infants whose fetal growth faltered in late gestation. This may result in some infants having relatively small lungs, which have not grown at the same rate as the “infant.” These findings may have implications for respiratory health in childhood and later life.

Conflict of Interest Statement: J.S.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; H.M.I. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; K.M.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.T.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.O.W. is chairman of a scientific advisory board overseeing the conduct of two studies (ETAC and EPAAC) investigating the early life origins of allergy and the effect of cetirizine and levocetirizine for UCB Pharma and has given lectures for a number of pharmaceutical companies, including UCB Pharma, Novartis, SHS International, Merck Sharpe & Dohme, Glaxo-SmithKline, and AstraZeneca and over the last three years has received small grants from UCB Pharma for investigator-led research studies; R.K.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.B.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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