Spirometric Lung Function in School-Age Children

Effect of Intrauterine Growth Retardation and Catch-up Growth

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Rationale: Few studies have investigated childhood respiratory outcomes of intrauterine growth retardation (IUGR), and it is unclear if catch-up growth in these children influences lung function.

Objectives: We determined if lung function differed in 8- to 9-year-old children born at term with or without growth retardation, and, in the growth-retarded group, if lung function differed between those who did and those who did not show weight catch up.

Methods: Caucasian singleton births of 37 weeks or longer gestation from the Avon Longitudinal Study of Parents and Children ($n = 14,062$) who had lung spirometry at 8–9 years of age were included ($n = 5,770$).

Measurements and Main Results: Infants with gestation-appropriate birthweight ($n = 3,462$) had significantly better lung function at 8–9 years of age than those with IUGR (i.e., birthweight < 10th centile [$n = 576$] [SD differences and confidence intervals adjusted for sex, gestation, maternal smoking during pregnancy, and social class: FEV₁, -0.198 (-0.294 to -0.102), FVC, -0.131 (-0.227 to -0.036), forced midexpiratory flow between 25 and 75% of vital capacity -0.149 (-0.246 to -0.053)). Both groups had similar respiratory symptoms. All spirometry measurements were higher in children with IUGR who had weight catch-up growth ($n = 430$) than in those without ($n = 146$), although the differences were not statistically significant. Both groups remained significantly lower than control subjects. Growth-retarded asymmetric and symmetric children had similar lung function.

Conclusions: IUGR is associated with poorer lung function at 8–9 years of age compared with control children. Although the differences were not statistically significant, spirometry was higher in children who showed weight catch-up growth, but remained significantly lower than the control children.

Keywords: nutrition; somatic growth; somatic catch-up growth; Avon Longitudinal Study of Parents and Children; fetal development

Increasing evidence suggests that low birthweight (LBW) is associated with long-term morbidity, including adverse cardiovascular, endocrine, and respiratory outcomes (1–3). Intrauterine growth retardation (IUGR) represents a significant worldwide problem (4). The relationship between LBW and lung function has been studied in adults, a meta-analysis of eight such studies reporting an increase of 48 ml in FEV₁ for each kilogram increase in birthweight after adjustments for

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Some evidence suggests that intrauterine growth retardation (IUGR) is associated with poor lung function in infancy and beyond. Furthermore, weight catch-up early in infancy in term babies may be associated with less than optimal lung function in infancy.

What This Study Adds to the Field

This study provides evidence that term infants born without IUGR defined by weight have better lung spirometry at 8 to 9 years of age than term infants born with IUGR. All measures of lung function at age 8 to 9 were better in the children with weight catch-up than in those without, but the differences were not statistically significant.

age, smoking, and height (5). Associations between IUGR and lung function in childhood have been studied less extensively. Interpretation is often complicated by combining LBW and prematurity (6), which affect lung function abnormalities by different mechanisms. The literature is further complicated by different definitions of IUGR; the most commonly used definition is based on birthweight alone, as stated by the World Health Organization (4), but length is only rarely accounted for. Lower lung function has been reported in LBW infants compared with normal-birthweight infants (7–9). Rona and colleagues studied children aged 5–11 years and reported that lung function measurements, except forced midexpiratory flow between 25 and 75% of vital capacity (FEF_{25–75%}), were positively associated with birthweight, but respiratory symptoms were associated with prematurity (10). Wjst and colleagues (11) reported decreased total lung capacity and peak expiratory flow rates, but increased bronchial reactivity and asthma in 5–14 year olds who were born with LBW.

IUGR represents fetal growth restraint due to an adverse intrauterine environment, or may be due to genetic factors. Catch-up growth may represent “release” from adversity, such as maternal smoking, which may lead to improved lung function later in life. Those not showing catch-up growth may represent healthy infants who have reached their growth potential, and thus should have normal lung function later in life when adjusted for height. Weight catch-up in childhood is associated with improved respiratory outcomes in adulthood (12, 13). However, Lucas and colleagues (8) reported that gaining weight quickly in the first few weeks of life is linked to suboptimal lung development in 5- to 14-week-old infants born at term. Another study of term infants reported that lung function assessed at 1 and 12 months was inversely related to weight gain in infancy (14).

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We defined IUGR on the basis of birthweight and ponderal index (PI), which includes both weight and length at birth and tested two hypotheses: children aged 8–9 years, born at term with IUGR, have poorer lung function compared with infants born without IUGR; and, in the IUGR group, differences in lung function exist between those who did and those who did not show weight catch-up growth.

METHODS

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), which has been described previously (15). Additional detail is provided in the online supplement. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the local research ethics committees.

The best estimate of gestational age was based on maternal reporting and medical assessments (16). The recorded birthweight and PI ($\text{PI} = \text{birthweight}/\text{length}^3 [\text{kg}/\text{m}^3]$) were standardized and converted to z scores, adjusted for gestational age and gender in babies born at 37 weeks gestation or later. Details of the methods for standardization are provided in the online supplement. IUGR was defined by birthweight, and separately by PI at birth, including babies with a z score of less than -1.28 (i.e., <10th centile) (4); infants between the 20th and 80th centiles for each variable were selected as control subjects. This range was chosen to avoid emerging obesity or borderline IUGR influencing the results. The Child Growth Foundation growth charts (17) were not used, as the data on which they were based were acquired between 1978 and 1990, and the ALSPAC data showed a trend toward earlier maturity and growth (data not shown). Infants below the 10th centile for both birthweight and PI were classified as “asymmetric IUGR,” and those below the 10th centile for birthweight and at or above the 10th centile for PI were classified as “symmetric IUGR” (4). Weight at the time of lung function testing was converted to a z score (details are given in the online supplement). Catch-up growth for weight was defined as an increase in z score of at least 0.67 between birth and ages 8–9 years, as previously described (18).

Spirometry was performed at ages 8–9 years using identical equipment and protocol, and following American Thoracic Society

standards (19). FEV_1 , $\text{FEV}_{0.5}$, $\text{FEF}_{25-75\%}$, $\text{FEF}_{25\%}$, $\text{FEF}_{50\%}$, and $\text{FEF}_{75\%}$ were converted to SD scores and adjusted for age, sex, and also for height (20). Children, unselected for asthma status or wheezing, had a bronchial challenge test with methacholine following the method of Yan and colleagues (21). Additional details of the methods are given in the online supplement. Previous respiratory illnesses/symptoms were recorded. Current asthma, from a questionnaire study at 91 months, was based on reported doctor-diagnosed asthma ever with symptoms and/or treatment in previous 12 months.

Smoking during pregnancy, socioeconomic status (*see* online supplement for definitions) and exclusive breast feeding longer than 3 months were considered as potential confounders, but there was no evidence for breast feeding being a confounder. More details of confounders are provided in the online supplement.

Lung function comparisons between the IUGR and control groups were performed using *t* tests. Comparisons were adjusted for potential confounders using a general linear model (22). The modeling was adjusted simultaneously for all of the confounders. Similar methods were employed for the comparison within the IUGR group between those with and those without catch-up growth. One-way analysis of variance was used to compare both these groups with the control children. All statistical analysis was performed using SPSS 15 (SPSS Inc., Chicago, IL). A *P* value less than 0.05 was considered significant.

RESULTS

IUGR Defined by Birthweight

Participants' characteristics are shown in Table 1. From 14,049 live births, 7,394 had lung spirometry at 8–9 years of age. After exclusions of preterm births of less than 37 weeks, multiple births, deaths, and non-whites, 5,770 remained, with 576 classified as IUGR and 3,462 as control subjects. From the IUGR group, 430 showed catch-up growth and 146 did not, with 94 remaining below the 10th centile. Table E1 in the online supplement shows additional group characteristics, and Table E2 shows characteristics of those who did not attend lung spirometry (*see* online supplement). As expected in a longitudi-

TABLE 1. PARTICIPANT CHARACTERISTICS

Characteristics	IUGR			Control	Whole Cohort
	Whole Group	Catch Up	No Catch Up		
Number	576	430	146	3,462	5,770
Mean birthweight, g	2,745.4	2,711.4	2,845.5	3,491.2	3,499.4
SD	253.9	269.6	164.7	250.1	463.8
Range	1,120–3,100	1,120–3,100	2,350–3,100	2,750–4,040	1,120–5,300
% Male	50	48.7	52.8	49.2	50.0
Mean gestation, wk	39.7	39.7	39.7	39.8	39.8
SD	1.2	1.2	1.2	1.3	1.3
Range	37–42	37–42	37–42	37–44	37–44
Maternal smoking, %	28.8	32.3	18.5	18	18.8
Manual workers, %	41.1	39.7	44.8	37.8	37.9
Exclusively breast fed for at least 3 mo, %	8.4	7.7	10.3	12.4	12.0
Mean height at 8–9 yr, cm	129.9	131.5	125.4	132.4	132.5
SD	5.5	5.0	4.2	5.6	5.7
Range	114.9–146.3	114.9–146.3	115.4–139.1	112.7–157.4	112.7–157.4
Mean standardized height at 8–9 yr	−0.443	−0.169	−1.263	−0.012	0.000
SD	0.950	0.853	0.728	0.984	0.999
Range	−3.03–2.59	−2.98–2.59	−3.03–0.73	−3.43–4.33	−3.43–4.33
Mean weight at 8–9 yr, kg	28.1	29.7	23.4	30.2	30.2
SD	5.1	4.9	1.8	5.6	5.7
Range	18.1–65.8	21.0–65.8	18.1–27.3	19.0–62.7	18.1–65.8
Mean standardized weight at 8–9 yr	−0.369	−0.091	−1.20	−0.0135	−0.001
SD	0.891	0.848	0.315	0.978	0.999
Range	−2.18–6.55	−1.61–6.55	−2.18 to −0.64	−0.190–5.35	−2.18–6.55
Mean age 8–9 yr	8.7	8.7	8.7	8.7	8.7
SD	0.3	0.3	0.2	0.3	0.3
Range	8.3–10.3	8.3–10.3	8.3–9.9	7.9–10.4	7.9–10.4
Current Asthma at 91 mo, %	14.9	14.8	15.4	13.6	14

Definition of abbreviation: IUGR = intrauterine growth retardation.

TABLE 2. MEAN OF Z SCORES OF LUNG FUNCTION MEASURES AT AGES 8–9 YEARS, WITH CONFIDENCE INTERVALS FOR THE DIFFERENCE OF MEANS (INTRAUTERINE GROWTH RETARDATION–CONTROL), UNADJUSTED AND ADJUSTED FOR MATERNAL SMOKING IN PREGNANCY AND SOCIAL STATUS, WHEN INTRAUTERINE GROWTH RETARDATION AND CONTROL GROUPS ARE DEFINED BY BIRTHWEIGHT

	IUGR (<i>n</i> = 576) Mean (SD)	Control (<i>n</i> = 3,462) Mean (SD)	Unadjusted Difference (95% CI)	Adjusted Difference (95% CI)	<i>P</i> Value for Adjusted Analysis
FEV _{0.5}	−0.146 (1.062)	0.038 (0.987)	−0.184 (−0.274 to −0.093)	−0.176 (−0.272 to −0.079)	<0.01
FEV ₁	−0.159 (1.012)	0.045 (0.990)	−0.204 (−0.295 to −0.114)	−0.198 (−0.294 to −0.102)	<0.01
FVC	−0.106 (0.962)	0.031 (0.993)	−0.137 (−0.227 to −0.048)	−0.131 (−0.227 to −0.036)	<0.01
FEF _{25–75%}	−0.129 (1.094)	0.028 (0.981)	−0.156 (−0.247 to −0.066)	−0.149 (−0.246 to −0.053)	<0.01
FEF _{25%}	−0.066 (1.089)	0.018 (0.973)	−0.084 (−0.174 to 0.006)	−0.079 (−0.175 to 0.017)	0.105
FEF _{50%}	−0.120 (1.091)	0.027 (0.980)	−0.147 (−0.238 to −0.057)	−0.135 (−0.231 to −0.038)	<0.01
FEF _{75%}	−0.109 (1.059)	0.030 (0.996)	−0.139 (−0.231 to −0.048)	−0.133 (−0.230 to −0.037)	<0.01

Definition of abbreviations: CI = confidence interval; FEF = forced expiratory flow; IUGR = intrauterine growth retardation.

nal study, loss to follow up was associated with lower social class; thus, the prevalence of maternal smoking in those who attended for lung spirometry was lower. The difference in proportions for maternal smoking between those attending and those not attending for lung spirometry was 14.2% (95% confidence interval [CI], 12.6–15.8%). The difference in proportions for manual social class between those attending and those not attending for lung spirometry was 14% (95% CI, 12.1–15.9%). Maternal smoking in pregnancy was reported for 18% of the control group and 29% of the IUGR group, and was associated with both IUGR and catch-up status (Tables E3 and E4); 32 and 19% of mothers smoked during pregnancy in the catch-up growth and no catch-up groups, respectively.

Effect of IUGR Defined by Birthweight on Childhood Lung Function

For spirometry, Table 2 shows the mean and SD in each group, the difference in means between subjects with IUGR and control subjects, with a 95% CI, both unadjusted and after adjustment for confounders of maternal smoking and social status, and a *P* value for the adjusted comparison. More details of confounders are shown in Tables E3–E8. There were clear differences between the IUGR and control populations for all spirometry measures, except FEF_{25%}. Approximate means of these differences were −35 ml for FEV_{0.5}, −50 ml for FEV₁, −40 ml for FVC, and −80 ml for FEF_{25–75%}, adjusted for height, age, and sex. No significant differences between the groups were noted for previous respiratory illnesses, including current asthma at 91 months (Table 1), self-reported wheezing, and any respiratory infections or symptoms.

Effect of Catch-up Growth Defined by Weight on Lung Function in Childhood

Although all lung function measures were greater in the catch-up IUGR group compared with the no catch-up group, the differences were not statistically significant, but remained significantly lower than the control group (Table 3). The results remained essentially unchanged when we regressed the lung function measurements on the actual change in weight z scores, increasing our confidence that the conclusions are robust (data not shown). Approximate mean differences, adjusted for height, age, and sex, were −35 ml for FEV_{0.5}, −30 ml for FEV₁, −25 ml for FVC, and −50 ml for FEF_{25–75%}. No differences were noted between the groups for previous respiratory illnesses, including asthma, self-reported wheezing, or for reported respiratory infections or symptoms.

Effect of Symmetric or Asymmetric IUGR, Defined by PI in the IUGR Group Defined by Birthweight, on Childhood Lung Function

Infants with IUGR who had both weight and length at birth were divided into 335 (73%) symmetrical and 126 (27%) asymmetrical infants based on their birth PI, with catch up occurring in 241 (72%) of the former and 106 (84%) of the latter group. The symmetrical and asymmetrical groups had similar lung function measurements at 8–9 years of age (Table 4). The catch-up infants in the symmetrical group appeared to have slightly higher values for spirometry than those who did not show catch-up. However, these differences were not statistically significant.

TABLE 3. MEAN OF Z SCORES OF LUNG FUNCTION MEASURES AT AGE 8–9 YEARS, WITH CONFIDENCE INTERVALS FOR THE DIFFERENCE OF MEANS (BETWEEN GROUPS), UNADJUSTED AND ADJUSTED FOR MATERNAL SMOKING IN PREGNANCY AND SOCIAL STATUS, WHEN INTRAUTERINE GROWTH RETARDATION GROUP, CONTROL GROUP, AND CATCH-UP GROWTH WERE DEFINED BY BIRTHWEIGHT

Control (<i>n</i> = 3,462)	IUGR			Unadjusted Difference between No Catch Up and Catch Up (95% CI)	Adjusted Difference between No Catch Up and Catch Up (95% CI)	<i>P</i> Value	
	No Catch-Up (<i>n</i> = 146)	Catch-Up (<i>n</i> = 430)	Mean (<i>SD</i>)			Difference between No Catch Up and Catch Up	Difference between No Catch Up, Catch Up, and Control
	Mean (<i>SD</i>)	Mean (<i>SD</i>)					
FEV _{0.5}	0.038 (0.987)	−0.279 (1.041)	−0.102 (1.067)	−0.177 (−0.385 to 0.031)	−0.182 (−0.406 to 0.042)	0.110	<0.01
FEV ₁	0.045 (0.990)	−0.260 (1.026)	−0.127 (1.007)	−0.133 (−0.333 to 0.067)	−0.133 (−0.347 to 0.080)	0.221	<0.01
FVC	0.031 (0.993)	−0.189 (1.015)	−0.079 (0.944)	−0.111 (−0.299 to 0.078)	−0.078 (−0.279 to 0.123)	0.446	<0.01
FEF _{25–75%}	0.028 (0.981)	−0.189 (1.055)	−0.109 (1.107)	−0.080 (−0.295 to 0.134)	−0.107 (−0.337 to 0.123)	0.362	<0.01
FEF _{25%}	0.018 (0.973)	−0.221 (1.121)	−0.016 (1.075)	−0.206 (−0.419 to 0.007)	−0.211 (−0.440 to 0.018)	0.071	0.021
FEF _{50%}	0.027 (0.980)	−0.196 (1.088)	−0.095 (1.092)	−0.101 (−0.314 to 0.113)	−0.122 (−0.352 to 0.109)	0.300	<0.01
FEF _{75%}	0.030 (0.996)	−0.137 (1.026)	−0.100 (1.071)	−0.037 (−0.244 to 0.171)	−0.089 (−0.310 to 0.131)	0.425	0.011

For definition of abbreviations see Table 2.

TABLE 4. MEAN SCORES OF LUNG FUNCTION MEASURES AT 8–9 YEARS OF AGE, WHEN INFANTS BELOW THE 10TH CENTILE FOR BOTH BIRTHWEIGHT AND PONDERAL INDEX WERE CLASSIFIED AS “ASYMMETRIC INTRAUTERINE GROWTH RETARDATION” AND THOSE BELOW THE 10TH CENTILE FOR BIRTHWEIGHT, BUT NOT PONDERAL INDEX, WERE CLASSIFIED AS “SYMMETRIC INTRAUTERINE GROWTH RETARDATION”

	Symmetric-IUGR				Asymmetric-IUGR			
	Overall (n = 335) Mean (SD)	Catch Up (n = 241) Mean (SD)	No Catch Up (n = 94) Mean (SD)	Difference between Catch Up and No Catch Up P Value	Overall (n = 126) Mean (SD)	Catch Up (n = 106) Mean (SD)	No Catch Up (n = 20) Mean (SD)	Difference between Catch Up and No Catch Up P Value
FEV _{0.5}	−0.143 (1.095)	−0.077 (1.107)	−0.314 (1.052)	0.075	−0.115 (0.940)	−0.097 (0.966)	−0.209 (0.805)	0.628
FEV ₁	−0.144 (1.053)	−0.101 (1.047)	−0.255 (1.065)	0.236	−0.122 (0.842)	−0.119 (0.859)	−0.140 (0.765)	0.919
FVC	−0.092 (0.995)	−0.069 (0.993)	−0.149 (1.006)	0.511	−0.091 (0.864)	−0.089 (0.841)	−0.101 (1.002)	0.952
FEF _{25–75%}	−0.115 (1.114)	−0.061 (1.149)	−0.255 (1.012)	0.152	−0.144 (0.951)	−0.126 (0.989)	−0.243 (0.731)	0.616
FEF _{25%}	−0.071 (1.136)	0.023 (1.133)	−0.312 (1.114)	0.015	−0.017 (1.016)	−0.002 (1.016)	−0.093 (1.037)	0.716
FEF _{50%}	−0.114 (1.098)	−0.053 (1.132)	−0.270 (0.996)	0.105	−0.133 (0.971)	−0.110 (0.991)	−0.250 (0.867)	0.556
FEF _{75%}	−0.082 (1.077)	−0.049 (1.088)	−0.168 (1.052)	0.362	−0.138 (0.958)	−0.124 (1.005)	−0.214 (0.668)	0.701

Definition of abbreviations: FEF = forced expiratory flow; IUGR = intrauterine growth retardation.

Bronchial Responsiveness

A total of 356 (61.8%) in the IUGR group and 2,229 (64.4%) of control children underwent methacholine challenge; 7.3% and 5.9%, respectively, were excluded, as their FEV₁ was less than 70% predicted. Of those who did not start a methacholine challenge, the prevalence of current asthma was similar (16 and 17.7% in IUGR and control groups, respectively), being similar to the study groups (Table 1). Similar percentages of children who completed the methacholine challenge (14.3 and 11.4% for the IUGR and control groups, respectively) had current asthma at 91 months. Response to methacholine challenge ($\geq 20\%$ fall in FEV₁ at less than maximal cumulative dose) occurred in 15.7 and 14.4% of the IUGR and control groups, respectively; the remainder were classed as nonresponders. Bronchial responsiveness in responders was similar between the IUGR and control groups (geometric mean PD₂₀, 2.12 and 1.68 μmol , respectively). For the whole group undergoing bronchial challenge, the PD₂₀ geometric means were also similar (IUGR, 9.24 μmol ; controls, 9.14 μmol —with maximum methacholine dose allocated to nonresponders). Furthermore, the PD₂₀ and rates of asthma for the catch-up and no catch-up groups were similar to each other and to the control groups.

Effect of IUGR Defined by PI on Lung Function in Childhood

After using similar criteria, definitions, and exclusions as for the IUGR defined by birthweight, 445 children had standardized PI at or below the 10th centile, and 2,684 between the 20th and 80th centile. Lung function at 8–9 years did not differ significantly between those with and those without IUGR by this definition (Table 5).

DISCUSSION

In this, the largest study to our knowledge of accurately defined IUGR, we have shown that term infants with IUGR had significantly reduced lung function at 8–9 years of age compared with term infants of normal birthweight. Differences were noted for both small and large airway function, but did not translate into increased clinical symptoms. Although the differences were not statistically significant, all measures of lung function at ages 8–9 years appeared to be higher in children showing catch-up growth compared with those without catch-up growth. These measures, however, remained significantly lower than the control group. Furthermore, asymmetric and symmetric children with IUGR had similar lung function. Symmetric infants with IUGR with catch up appeared to show better spirometry than those without, although overall differences were small and not statistically significant.

Like most other similar studies, we defined IUGR by birthweight, but included length in defining PI (which indicates proportionality) and symmetry/asymmetry. However, by including length or PI, the population defined as IUGR changed considerably compared with the population identified by the commonly used birthweight definition (4). For example, a low PI may indicate a “normal” birthweight on the 25th centile, but a length on the 90th centile, which is very different to a child born below the 10th centile for birthweight although the former may represent relative fetal growth restraint. We chose to use as our primary exposure a definition of IUGR based on birthweight. Haggarty and colleagues (23) reported that body weight alone was a better predictor than PI of factors thought to be associated with IUGR. Furthermore, birthweight is more fre-

TABLE 5. MEAN OF Z SCORES OF LUNG FUNCTION MEASURES AT AGES 8–9 YEARS, WITH CONFIDENCE INTERVALS FOR THE DIFFERENCE OF MEANS (INTRAUTERINE GROWTH RETARDATION–CONTROL), UNADJUSTED, AND ADJUSTED FOR MATERNAL SMOKING IN PREGNANCY AND SOCIAL STATUS, WHEN INTRAUTERINE GROWTH RETARDATION AND CONTROL GROUP WERE DEFINED BY PONDERAL INDEX

	IUGR (n = 445)		Control (n = 2,684)		Unadjusted Difference (95% CI)	Adjusted Difference (95% CI)	P Value for Adjusted Analysis
	Mean	SD	Mean	SD			
FEV _{0.5}	0.021	0.980	0.033	0.993	−0.012 (−0.112 to 0.087)	0.003 (−0.101 to 0.106)	0.960
FEV ₁	0.007	0.971	0.043	0.982	−0.036 (−0.135 to 0.063)	−0.030 (−0.132 to 0.073)	0.572
FVC	0.006	0.976	0.018	0.981	−0.012 (−0.111 to 0.086)	−0.024 (−0.126 to 0.078)	0.640
FEF _{25–75%}	0.000	1.001	0.039	0.995	−0.039 (−0.139 to 0.061)	−0.015 (−0.119 to 0.088)	0.770
FEF _{25%}	0.036	0.982	0.019	1.011	0.017 (−0.084 to 0.118)	0.033 (−0.072 to 0.138)	0.536
FEF _{50%}	−0.002	0.992	0.037	0.989	−0.039 (−0.139 to 0.060)	−0.015 (−0.118 to 0.088)	0.770
FEF _{75%}	0.000	0.996	0.045	1.001	−0.044 (−0.145 to 0.056)	−0.026 (−0.130 to 0.078)	0.625

For definition of abbreviations see Table 4.

quently and more accurately measured than length at birth. Height at the time of spirometry was taken into account, as lung function values were standardized for height, in addition to sex and age. Nevertheless, we subdivided the infants with IUGR into symmetrical and asymmetrical infants to include birth length via PI in order to assess the influence of birth length on later lung function.

Our study focused entirely on infants born at term, and thus avoided combining LBW term and premature infants in an IUGR group. This distinction is important, as mechanisms leading to abnormal lung development are possibly different in these two groups, with little known about the former, but evidence suggesting dysregulation of alveolar development in the latter (24).

Our results are in agreement with a recent meta-analysis in adults reporting a positive association between FEV₁ and birthweight (5), and also with three studies that reported that infants born at or near term with LBW had lower lung function than normal-birthweight infants (7–9). Rona and colleagues (10) reported that most lung spirometry parameters in school-aged children were associated with birthweight, but respiratory symptoms were associated more with prematurity. We also noted an association of lower lung function with LBW, but reported respiratory symptoms were not.

Studies of adults generally conclude that catch-up growth, or gaining weight faster in early childhood, is associated with improved pulmonary function outcomes (12, 13), but it has been suggested that catch-up growth in infancy may be detrimental to lung function (8, 14). Our data demonstrate that spirometry at age 8–9 years was nonsignificantly higher in IUGR children who showed catch-up growth than those who did not, although their lung function was significantly lower than in control infants. Despite ours being one of the largest studies of term infants with IUGR, the numbers in this category are relatively small, reducing the power for these comparisons. It is important to confirm or refute this finding, given the importance of lung function tracking during childhood and into adulthood. Stern and colleagues (25) suggested, “poor airway function shortly after birth should be recognized as a risk factor for airflow obstruction in young adults.”

An explanation for lung function differences in childhood between infants with and those without catch-up growth is that they were different soon after birth due to intrauterine development. Infants of maternal smokers were smaller at birth compared with infants of nonsmokers, as previously reported in ALSPAC (26). The incidence of catch-up growth in infants with IUGR was greater if the mothers had smoked during pregnancy than if they had not, suggesting that the effects on growth of an adverse intrauterine environment may be compensated by rapid postnatal growth. However, developmental changes associated with fetal growth restraint may persist in spite of catch-up somatic growth. Infants with genetic or other constitutional determinants of IUGR may have programmed reduced airway and lung development during fetal life, with little opportunity to improve after birth. We found asymmetric and symmetric children with IUGR defined by PI at birth had similar lung function at 8–9 years of age; although there was limited evidence of differences between catch-up and no catch-up children in the symmetric group. If this was demonstrated in larger studies, it would be consistent with generalized growth restraint in the symmetrically IUGR group being compensated in part by postnatal growth.

The magnitudes of lung function differences between the IUGR and control groups were similar for markers of both large and small airway function, with only FEF_{25%} not showing significant differences between the two groups. The population that attended for spirometry was represented by fewer maternal

smokers and lower social class. This is unlikely to affect the results, as greater attendance of manual socioeconomic class is most likely to enhance the differences. A meta-analysis of adult lung function in relation to birth weight (5) suggested an increase of 48 ml in FEV₁ for each kilogram increase in birthweight after adjustments. Our data suggest a difference of approximately 50 ml for FEV₁ that is already established at 8–9 years of age in children with IUGR (mean birthweight, 2,745 g) compared with control subjects (mean birthweight, 3,491 g). These data suggest that IUGR at term may have a greater effect on lung function than previously reported. In addition, children born with IUGR at term who did not have catch-up growth have a decrement in FEV₁ of approximately 30 ml compared with those who had catch-up growth, suggesting that there may be different life-course implications for different mechanisms of IUGR as currently defined.

Differences observed in lung function did not translate into clinical symptoms, perhaps unsurprisingly given the respiratory reserve in childhood and the relatively small effect sizes. Our data did not show that the children born with IUGR had greater airway reactivity, nor did they report an increased incidence of asthma or other respiratory illnesses. Identifying decreased lung function is important, as public health measures, such as improved nutrition, may potentially improve lung development, and future prevention of smoking may prevent or retard the development of later chronic obstructive pulmonary disease.

In summary, our data show a clear difference for all spirometric measures of lung function between children born at term with IUGR and control term infants, but without associated increased clinical symptoms. Catch-up growth was associated with a nonsignificantly higher lung function, suggesting that nutritional improvement after fetal growth restraint may modify postnatal lung function development. Studies of larger numbers of IUGR infants with early life lung function measurements are required to confirm these findings.

Conflict of Interest Statement: S.J.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; W.J.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J. Heron does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J. Henderson received up to \$1,000 from MSD in advisory board fees; F.D.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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