

## PAEDIATRIC LUNG DISEASE

# Low birth weight for gestation and airway function in infancy: exploring the fetal origins hypothesis

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**Background:** Poor fetal growth has been associated with impaired airway function in adult life, but evidence linking birth weight and airway function in early childhood is sparse. We examined the hypothesis that low birth weight for gestation is associated with impaired airway function shortly after birth and that this is independent of impaired postnatal somatic growth.

**Methods:** Airway function was measured using the raised volume technique in healthy white infants of low ( $\leq 10$ th centile) or appropriate ( $\geq 20$ th centile) birth weight for gestation and was expressed as forced expiratory volume in 0.4 s ( $FEV_{0.4}$ ), forced vital capacity (FVC), and the maximal expired flow at 25% of forced vital capacity ( $MEF_{25}$ ). Infant length and weight, maternal height and weight, maternal report of smoking prenatally and postnatally, and parental occupation were recorded.

**Results:** Mothers of low birth weight for gestation infants ( $n=98$ ) were lighter, shorter, and more likely to smoke and have partners in manual occupations. At 6 weeks their infants remained lighter and shorter than those of appropriate birth weight ( $n=136$ ).  $FEV_{0.4}$ , FVC, and  $MEF_{25}$  were reduced in infants of low birth weight for gestation, in those whose mothers smoked in pregnancy, or who were in manual occupations. After adjusting for relevant maternal and infant characteristics, infants in the low birth weight for gestation group experienced a mean reduction of 11 ml in  $FEV_{0.4}$  (95% CI 4 to 18;  $p=0.002$ ), of 12 ml in FVC (95% CI 4 to 19;  $p=0.004$ ), and of 28 ml/s in  $MEF_{25}$  (95% CI 7 to 48;  $p=0.03$ ).

**Conclusions:** Airway function is diminished in early postnatal life as a consequence of a complex causal pathway which includes social disadvantage as indicated by maternal social class, smoking and height, birth weight as a proximal and related consequence of these factors, and genetic predisposition to asthma. Further work is needed to establish the relevance of these findings to subsequent airway growth and development in later infancy and early childhood.

Low rates of fetal growth have been associated with impaired airway function in adult life.<sup>1</sup> While the link between fetal growth and adult airway function has been investigated in a number of studies,<sup>2–3</sup> evidence linking birth weight and airway function in early childhood is sparse.<sup>4–5</sup> The association between fetal development and airway function is likely to be complex, involving causal pathways that include both genetic and prenatal and postnatal environmental factors.<sup>6</sup> The potential for confounding, particularly by socioeconomic status, in studies examining the fetal origins of adult disease has been discussed by Kramer<sup>7</sup> who, with others, has highlighted the need to develop study designs which provide a more robust and explicit test of the fetal origins hypothesis.<sup>8–9</sup>

We report here the findings of a prospective epidemiological study comparing airway function in early infancy in full term infants considered to be of low and appropriate birth weight for gestational age. We aimed to test the hypothesis that low birth weight for gestation was associated with impaired airway function shortly after birth, and that this association was independent of impaired postnatal somatic growth, maternal socioeconomic status, and fetal exposure to maternal smoking.

## METHODS

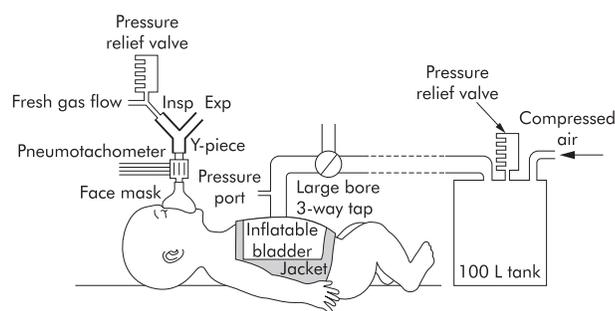
Parents of infants delivered in the maternity units at the Homerton University Hospital and University College London Hospital, London were contacted by post. Healthy infants ( $>35$  weeks gestation) of white mothers and with no congenital abnormalities, neuromuscular or cardiorespiratory disorders were eligible for inclusion, while those who needed ventilatory assistance during the neonatal period, had

experienced any lower respiratory illness prior to testing, or were more than 12 weeks postnatal age at test were ineligible. Infants were classified according to birth weight and gestational age using the sex specific Child Growth Foundation (CGF) algorithms<sup>10</sup> as well as the Gestation Related Optimal Weight or "GROW" program.<sup>11</sup> The latter takes into account maternal characteristics such as height, booking weight, ethnic group, and parity as well as infant birth weight, gestation, and sex. Gestational age was based on ultrasound assessment before 20 weeks. Infants were eligible for inclusion if their birth weight fell at or below the 10th centile (low birth weight for gestation group) or between the 20th and 95th centile (appropriate birth weight for gestation group) on either algorithm. Infants of intermediate birth weight ( $>10$ th and  $<20$ th centile) were excluded.

The local research ethics committees approved the study and informed written consent was obtained from parents.

Respiratory function was measured between 4 and 12 weeks postnatally when infants had been well and free from upper respiratory tract infections for at least 3 weeks. Measurements were made following sedation with chloral hydrate syrup (60 mg/kg) and during quiet sleep as determined by the presence of regular respiration, relaxed and stable posture, and the absence of eye movements or grimaces.<sup>12–13</sup> Body weight, crown-heel length, chest and mid arm circumference were measured<sup>14</sup> and weight and length expressed as sex specific SD scores.<sup>10</sup>

Airway function was assessed from the forced expiratory volume at 0.4 s ( $FEV_{0.4}$ ), forced vital capacity (FVC), and the maximal expired flow at 25% of forced vital capacity ( $MEF_{25}$ ) during the raised volume technique as described pre-



**Figure 1** A schematic illustration of equipment used for raised lung volume manoeuvre.

vously.<sup>15 16</sup> In brief, forced expiratory flow-volume curves were obtained by wrapping an inflatable jacket around the infant's chest and abdomen and allowing the infant to breathe through a face mask and pneumotachometer (Hans Rudolph, Kansas City, MO, USA) as shown in fig 1. The respiratory muscles were relaxed by administering four or five augmented breaths to a pressure of 3 kPa before inflating the jacket at the end of an augmented breath to force expiration from raised lung volume. This manoeuvre was repeated until a minimum of three acceptable and reproducible flow-volume curves were obtained. These parameters were calculated according to previously described quality control criteria from the best of at least three acceptable and reproducible flow-volume curves obtained from raised volume techniques, where "best" is defined as the technically acceptable loop with the highest sum of FVC and FEV<sub>0.4</sub>.<sup>15 16</sup> The study design and further details of physiological methods have been published and preliminary data in infants born to non-smoking mothers have been described previously.<sup>17</sup>

At the time of lung function testing, mothers were asked about their own smoking prenatally and postnatally, their age at leaving full time education, maternal and paternal occupational status, and family history of asthma in the infant's first degree relatives. Maternal height and weight were measured and infant urine and maternal saliva obtained for cotinine assay.<sup>18</sup> Maternal salivary cotinine concentrations ranged from 21 to 435 ng/ml in five of the 139 mothers who reported themselves as non-smokers. As these values are consistent with values obtained from active smokers (>15 ng/ml), these five mothers were considered as smokers in subsequent analyses.<sup>19 20</sup>

### Sample size and statistical analysis

The study was designed to provide 90% power at the 5% significance level to detect a difference of one standard deviation (SD) in estimates of forced expiratory flows and volumes between the two birth weight status groups after adjustment for potential confounding factors. Comparisons of group characteristics and respiratory function between the groups were performed using *t* tests,  $\chi^2$ , or exact tests as appropriate (StatXact version 4.01). The extent to which low birth weight for gestation is associated with forced expiratory flow and volumes was examined using multiple linear regression (SPSS for Windows, Release 10.1.3) after adjustment for sex and current body size and after examining for the effects of other potential confounding factors. Analyses were also conducted using birth weight SDS.

### RESULTS

We traced 1086 of 1669 potentially eligible infants born over a 4.5 year period (1998-May 2002) at Homerton University and the University College London hospitals. Parental consent was given for 368 infants (34%) to take part, 53 of

whom became subsequently ineligible either because they developed a lower respiratory illness (*n* = 12) or because cancellations due to upper respiratory infections meant they no longer met the age eligibility criterion (*n* = 41). A further 63 infants did not attend because their parents withdrew from the study (*n* = 30) or did not have time to attend the laboratory (*n* = 33). Thus, 252 infants attended for respiratory function testing and measurements were successfully obtained in 234 infants, 98 from the low birth weight for gestation group and 136 from the appropriate birth weight for gestation group. Recruitment and attendance rates were comparable between the different birth weight groups (data not shown).

Infants in the low birth weight for gestation group were of similar gestation but shorter and of smaller head circumference at birth than those of appropriate birth weight for gestation (table 1). Although the groups did not differ with respect to maternal age at delivery or maternal social class, maternal age and the percentage of fathers in non-manual occupations were higher in the study population overall than expected from national data.<sup>21</sup> Mothers of low birth weight infants were significantly lighter and shorter and were more likely to smoke. Maternal social class, stature, and smoking status were interrelated, with more mothers from manual occupations being below average height (163.7 cm) for the group ( $\chi^2 = 16.12$ ; *p* < 0.001) or smokers ( $\chi^2 = 24.32$ ; *p* < 0.001). Mothers who smoked were more likely to be below average height than those who did not ( $\chi^2 = 4.66$ ; *p* = 0.031).

When tested at about 6 weeks of age, infants of low birth weight remained significantly lighter and shorter, with smaller head, chest and mid arm circumferences than those of appropriate birth weight (table 1). At this age, urinary cotinine levels were significantly higher in infants whose mothers reported smoking (geometric mean (interquartile range) 12.2 (5.3–31.8) ng/ml) than in those whose mothers did not (1.3 (0.8–2.6) ng/ml; 95% CI of the ratio smokers: non-smokers: 6.6 to 13.5; *p* < 0.001).

In univariate analyses, flow and volume parameters were diminished in infants of low birth weight for gestational age and in those with mothers who smoked in pregnancy or who were in manual occupations (table 2). FEV<sub>0.4</sub>/FVC did not, however, differ according to birth weight status, maternal smoking, or social class. There was a marked difference in the pattern of associations with maternal, biological, and environmental factors for the flow and volume parameters, which were also related to the infant's age, weight, and length at test. FEV<sub>0.4</sub> and FVC were reduced in infants whose mothers were shorter, smoked, and were in a manual occupation (tables 3 and 4). By contrast, MEF<sub>25</sub> was lower in boys and in those with a family history of asthma (table 5).

In multivariate analyses, FEV<sub>0.4</sub> was a mean 11 ml (95% CI 4 to 18; *p* = 0.002) lower in the low birth weight for gestation group (table 3). It was also significantly lower in boys, and positively associated with length and postnatal age, with a tendency for a weak negative association with body weight at test (*p* < 0.06). With the exception of weight at test, a similar pattern was observed for FVC (table 4). This represents a reduction of about 8% at this age in FEV<sub>0.4</sub> and FVC among those of low birth weight for gestational age. MEF<sub>25</sub> was a mean 28 ml/s (95% CI 7 to 48; *p* = 0.008) lower in the low birth weight group (table 5). It was also significantly lower in boys and in those with a family history of asthma, and was positively associated with length and postnatal age but negatively with weight at test. This represents a 13% reduction at this age in MEF<sub>25</sub> among those of low birth weight and compares with an adjusted mean reduction in MEF<sub>25</sub> of 23 ml/s (95% CI 5 to 40) in boys relative to girls and 30 ml/s (95% CI 12 to 48) in infants with a family history of

**Table 1** Characteristics of infants according to birth weight status

Birth weight group	Low for gestation (n = 98)	Appropriate for gestation (n = 136)	95% CI of difference: low – appropriate
Boys	47 (48%)	72 (53%)	–18 to 8
<i>Infant characteristics at birth</i>			
Gestational age (weeks)	40.0 (1.5)	39.8 (1.4)	–0.2 to 0.5
Birth weight (kg)	2.7 (0.3)	3.5 (0.4)	–0.8 to –0.7
Birth weight SD score	–1.7 (0.5)	0.04 (0.5)	–1.8 to –1.6
Crown–heel length (cm)‡	49.0 (3.0)	52.1 (2.7)	–3.9 to –2.3
Crown–heel length SD score‡	–0.8 (1.4)	0.9 (1.3)	–2.0 to –1.3
Head circumference (cm)*	33.0 (1.5)	34.5 (1.3)	–1.9 to –1.1
<i>Maternal and family characteristics</i>			
Maternal age at delivery (years)	32.0 (5.6)	32.9 (5.5)	–2.4 to 0.5
Primipara	65 (66%)	88 (65%)	–11% to 14%
Maternal smoking in pregnancy	44 (45%)	51 (38%)	–5% to 20%
Maternal weight at booking (kg)	59.4 (9.7)	63.4 (10.7)	–6.7 to –1.3**
Maternal height (cm)#	162.3 (6.4)	164.9 (6.5)	–4.3 to –0.9**
Mother in non-manual occupation	73 (74%)	110 (81%)	–17% to 4%
Father in non-manual occupation§	56 (57%)	98 (72%)	–27% to –3%**
<i>Infant characteristics at test</i>			
Age (weeks)†	6.6 (2.5)	6.2 (2.0)	–0.2 to 0.9
Weight (kg)	4.2 (0.8)	4.8 (0.7)	–0.8 to –0.4***
Weight SD score	–1.1 (0.9)	–0.02 (0.9)	–1.3 to –0.9***
Length (cm)	54.2 (2.8)	56.4 (2.6)	–2.9 to –1.5***
Length SD score	–0.8 (0.9)	0.4 (0.9)	–1.4 to –1.0***
Head circumference (cm)	38.0 (1.7)	38.9 (1.5)	–1.4 to –0.5***
Chest circumference (cm)	37.2 (2.7)	39.0 (2.2)	–2.5 to –1.2***
Mid arm circumference (cm)	11.8 (1.4)	12.4 (1.2)	–0.9 to –0.2**

Data shown as mean (SD) for continuous and n (%) for categorical variables. SD scores were calculated using CGF algorithms.<sup>10</sup>

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

†Age after expected date of delivery.

‡84 low birth weight for gestation, 128 appropriate birth weight for gestation.

¶86 low birth weight for gestation, 126 appropriate birth weight for gestation.

§97 low birth weight for gestation, 136 appropriate birth weight for gestation.

#96 low birth weight for gestation, 133 appropriate birth weight for gestation.

asthma. Similar findings were obtained when analyses were conducted using birth weight SDS as the outcome variable. For each unit decline in birth weight SDS there was a mean reduction of 8.6 ml (95% CI 4.4 to 12.7) in FEV<sub>0.4</sub>, of 10.1 ml (95% CI 5.3 to 14.8) in FVC, and of 12.0 ml/s (95% CI –0.7 to 24.8) in MEF<sub>25</sub> (p<0.001, p<0.001, and p = 0.065, respectively).

A model incorporating birth weight status, age, and body length accounted for 49% of the total variance in FEV<sub>0.4</sub> and 55% in FVC with birth weight status accounting for 2.5% and 1.7%, respectively. By contrast, the model for MEF<sub>25</sub> explained only 18% of the total variance in this parameter,

with birth weight status, sex and a family history of asthma accounting for 2.7%, 2.5% and 3.9%, respectively.

## DISCUSSION

In this population based study, low birth weight for gestation was associated with reduced airway function when measured in early infancy and before the onset of any lower respiratory illness. These findings were consistent whether assessed from forced expiratory flows or volumes, and were independent of postnatal body weight or length or their interaction with birth weight. These data therefore provide some support for the fetal origins hypothesis<sup>22</sup> in that they suggest that the

**Table 2** Respiratory function results according to birth weight status, maternal smoking, and maternal occupation

	N	FEV <sub>0.4</sub> (ml)	FVC (ml)	MEF <sub>25</sub> (ml/s)	FEV <sub>0.4</sub> /FVC
<i>Birth weight status</i>					
Low birth weight for gestation	98	106 (26)	121 (32)	169 (64)	0.87 (0.7)
Appropriate birth weight for gestation	136	126 (27)	145 (34)	196 (67)	0.87 (0.6)
Difference (low – appropriate)		–19	–24	–28	0
95% CI		–26 to –12***	–33 to –15***	–45 to –11**	–0.01 to 0.02
<i>Maternal smoking in pregnancy</i>					
Yes	95	112 (31)	131 (38)	176 (68)	0.87 (0.07)
No	139	121 (26)	139 (33)	191 (65)	0.87 (0.06)
Difference (smoking – non-smoking)		–9	–8	–15	0
95% CI		–16 to –1*	–17 to 1	–33 to 2	–0.02 to 0.01
<i>Maternal occupation</i>					
Manual	51	106 (29)	120 (36)	172 (60)†	0.88 (0.06)
Non-manual	182	121 (28)	140 (34)	188 (68)†	0.87 (0.06)
Difference (manual – non-manual)		–15	–20	–16	0.02
95% CI		–23 to –6**	–31 to –10***	–37 to 5	–0.003 to 0.04

FEV<sub>0.4</sub> = forced expired volume in 0.4 s; FVC = forced vital capacity; MEF<sub>25</sub> = maximal expired flow at 25% of forced vital capacity; FEV<sub>0.4</sub>/FVC (%) = forced expiratory volume in 0.4 s as a proportion of forced vital capacity; CI = confidence interval.

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

†n = 51 and n = 181 in manual and non-manual groups, respectively.

**Table 3** Association of FEV<sub>0.4</sub> with birth weight status and other factors

	Difference in FEV <sub>0.4</sub> (ml)	95% CI of difference	p value
<i>Univariate analyses</i>			
Birth weight status (baseline: appropriate birth weight for gestation)	-19.4	-26.5 to -12.3	<0.001
Sex (baseline: female)	-0.7	-8.1 to 6.7	0.85
Weight at test (per kg)	18.8	14.7 to 22.9	<0.001
Length at test (per cm)	6.5	5.5 to 7.5	<0.001
Postnatal age (per week)	6.6	5.1 to 8.1	<0.001
Maternal smoking (baseline: no maternal smoking)	-8.6	-16.1 to -1.2	0.02
Maternal social class (baseline: non-manual occupation)	-14.6	-23.4 to -5.8	0.001
Maternal height (per cm)	0.8	0.3 to 1.4	0.004
Family history of asthma (baseline: no history of asthma)	-7.3	-15.4 to 0.9	0.08
<i>Multivariate analysis*</i>			
Birth weight status (baseline: appropriate birth weight for gestation)	-11.2	-18.0 to -4.3	0.002
Sex (baseline: female)	-6.8	-12.6 to -1.1	0.02
Weight at test (per kg)	-6.6	-13.5 to 0.3	0.06
Length at test (per cm)	5.6	3.6 to 7.7	<0.001
Postnatal age (per week)	3.2	1.3 to 5.2	0.001
Maternal smoking (baseline: no maternal smoking)	-3.6	-9.5 to 2.2	0.22
Maternal social class (baseline: non-manual occupation)	-2.1	-9.3 to 5.1	0.65
Maternal height (per cm)	0.1	-0.4 to 0.5	0.70
Family history of asthma (baseline: no history of asthma)	-5.4	-11.5 to 0.6	0.08

\*Adjusted for birth weight status, sex, weight and length at test, postnatal age, maternal smoking, maternal social class, maternal height, and family history of asthma.

impaired airway function observed in infants of low birth weight for gestational age is not simply due to their smaller postnatal body size or poorer postnatal growth. Intrauterine stress is associated with altered patterns of lung and airway maturation<sup>23</sup> and we speculate that factors associated with low birth weight may also specifically impair fetal lung and airway development.

The fetal origins hypothesis suggests that organ function in later life is "programmed" by impaired fetal nutrition or

growth at a critical period of organ development.<sup>24</sup> We were unable to measure fetal growth during pregnancy, but investigated size at birth as a summary of fetal growth. Our observations confirm that the postnatal growth of infants of low birth weight for gestation is diminished relative to their appropriate birth weight counterparts. However, after adjusting for birth weight and later body size and their interaction as recommended by Lucas *et al.*,<sup>22</sup> we still found a significant association between low birth weight for gestation and

**Table 4** Association of FVC with birth weight status and other factors

	Difference in FVC (ml)	95% CI of difference	p value
<i>Univariate analyses</i>			
Birth weight status (baseline: appropriate birth weight for gestation)	-24.0	-32.7 to -15.3	<0.001
Sex (baseline: female)	1.3	-7.8 to 10.4	0.78
Weight at test (per kg)	26.8	22.2 to 31.4	<0.001
Length at test (per cm)	8.6	7.5 to 9.8	<0.001
Postnatal age (per week)	9.2	7.5 to 10.9	<0.001
Maternal smoking (baseline: no maternal smoking)	-8.2	-17.4 to 1.0	0.08
Maternal social class (baseline: non-manual occupation)	-20.2	-31.0 to -9.5	<0.001
Maternal height (per cm)	1.1	0.5 to 1.8	0.001
Family history of asthma (baseline: no history of asthma)	-5.5	-15.6 to 4.6	0.28
<i>Multivariate analysis*</i>			
Birth weight status (baseline: appropriate birth weight for gestation)	-11.6	-19.4 to -3.8	0.004
Sex (baseline: female)	-5.9	-12.5 to 0.7	0.08
Weight at test (per kg)	-2.3	-10.2 to 5.6	0.57
Length at test (per cm)	6.0	3.7 to 8.3	<0.001
Postnatal age (per week)	4.4	3.7 to 8.3	<0.001
Maternal smoking (baseline: no maternal smoking)	-2.0	-8.7 to 4.6	0.54
Maternal social class (baseline: non-manual occupation)	-3.1	-11.3 to 5.2	0.46
Maternal height (per cm)	0.2	-0.3 to 0.8	0.34
Family history of asthma (baseline: no history of asthma)	-2.7	-9.6 to 4.3	0.45

\*Adjusted for birth weight status, sex, weight and length at test, postnatal age, maternal smoking, maternal social class, maternal height, and family history of asthma.

**Table 5** Association of MEF<sub>25</sub> with birth weight status and other factors

	Difference in MEF <sub>25</sub> (ml/s)	95% CI of difference	p value
<i>Univariate analyses</i>			
Birth weight status (baseline: appropriate birth weight for gestation)	-27.8	-44.9 to -10.6	0.002
Sex (baseline: female)	-19.7	-36.8 to -2.6	0.02
Weight at test (per kg)	7.8	-3.1 to 18.7	0.16
Length at test (per cm)	5.4	2.5 to 8.3	<0.001
Postnatal age (per week)	4.8	0.9 to 8.7	0.015
Maternal smoking (baseline: no maternal smoking)	-15.2	-32.7 to 2.3	0.09
Maternal social class (baseline: non-manual occupation)	-16.2	-37.0 to 4.5	0.13
Maternal height (per cm)	0.8	-0.5 to 2.1	0.22
Family history of asthma (baseline: no history of asthma)	-24.7	-43.6 to -5.8	0.01
<i>Multivariate analysis*</i>			
Birth weight status (baseline: appropriate birth weight for gestation)	-27.8	-48.2 to -7.4	0.008
Sex (baseline: female)	-22.5	-39.7 to -5.4	0.01
Weight at test (per kg)	-34.1	-54.6 to -13.5	0.001
Length at test (per cm)	9.8	3.7 to 15.8	0.002
Postnatal age (per week)	3.4	-2.3 to 9.2	0.24
Maternal smoking (baseline: no maternal smoking)	-13.4	-30.7 to 3.9	0.13
Maternal social class (baseline: non-manual occupation)	-2.5	-23.9 to 18.9	0.82
Maternal height (per cm)	-0.45	-1.8 to 0.9	0.50
Family history of asthma (baseline: no history of asthma)	-29.6	-47.6 to -11.6	0.001

\*Data adjusted for those variables found to be significant in univariate analyses—that is, birth weight status, infant sex, length at test, postnatal age, and family history of asthma.

impaired airway function, providing further support for the fetal origins hypothesis.

Routine neonatal anthropometric measurements of body length were not available to us so we could not compare length and weight SD scores at birth in our study population. However, despite earlier suggestions that infants of low birth weight for gestation might be dichotomised into those with symmetrical and asymmetrical growth retardation, in practice these phenotypes have not been confirmed. Kramer *et al* found no evidence of bimodality in body proportions that would characterise infants into these subtypes.<sup>25, 26</sup>

In older children and adults, FEV<sub>1</sub> and MEF<sub>25</sub> are traditionally considered to reflect primarily large and peripheral airway function respectively, but such relationships are less clear when these measures are obtained during infancy. During early childhood measurement of FEV<sub>1</sub> is rarely feasible due to the rapidity of lung emptying during a forced expiration. Hence, FEV<sub>0.4</sub> or FEV<sub>0.5</sub> are usually reported.<sup>16</sup> As these timed expired volumes still encompass the majority of the forced expiration, they probably reflect the integrated output from both central and peripheral airways. Despite this, different patterns of associations with maternal, biological, and environmental factors were evident for the various flow and volume parameters. Thus, FEV<sub>0.4</sub> was associated with maternal height, smoking and social class, which were interrelated as well as being associated with low birth weight for gestation. By contrast, MEF<sub>25</sub> was inversely related to infant characteristics such as male sex and a family history of asthma with a weaker association with maternal smoking. We did not, however, find any significant associations with FEV<sub>0.4</sub> when expressed as a proportion of FVC, perhaps reflecting the marked variability of this parameter in healthy infants during the first months of life, with a strong negative age dependency.<sup>16</sup>

We have previously reported that the reduction in airway function associated with low birth weight for gestation was largely mediated through reduced body size in infants not exposed to maternal smoking.<sup>17</sup> However, more complex associations are evident in the full cohort, reflecting larger sample size as well as the more complex causal pathways associated with maternal smoking. Thus, in the full cohort,

low birth weight for gestation accounted for approximately 2–3% of the total variation in airway function, as assessed from forced flow or volume parameters. These novel observations help to shed some light on the biological pathways linking size at birth, postnatal growth, and airway development.

During fetal development all airway branches are formed by the 16th week of gestation, with subsequent prenatal and postnatal growth of the airways resulting from an increase in size rather than number.<sup>27</sup> By contrast, there is a rapid increase in alveolar number during the first 2 years of life, resulting in a greater increase in lung volume than airway size during this period, a phenomenon known as dysanaptic growth. Age, sex, and body length are important determinants of infant airway function during this critical period of growth and development.<sup>28</sup> We chose to measure infants as soon as possible after birth at an age when the pattern of breathing had stabilised and infants were able to tolerate sedation, but before they had experienced a lower respiratory illness. Those whose mothers smoked during pregnancy were therefore also exposed to environmental tobacco smoke postnatally, albeit for relatively few weeks.

These findings are generalisable to healthy white infants of low and appropriate birth weight for gestation. Our study population was biased towards those with milder impairment of growth in utero as we excluded preterm infants delivered before 35 weeks gestation as well as those with respiratory problems at birth requiring neonatal ventilation, both factors associated with alterations in airway function.<sup>29</sup> The proportion of parents consenting to take part in the study among those contacted was comparable to that reported from other population based studies.<sup>30–32</sup> The study population was, however, biased towards the more educated and older mother and, overall, the prevalence of maternal smoking was higher than the national average<sup>33</sup> but comparable to other studies of antenatal populations in this part of London.<sup>30</sup> There was no evidence of bias in participation rates according to birth weight status.

The parameters used to assess airway function are sensitive to impaired airway function<sup>34</sup> and all results were checked to ensure adherence to quality control criteria by an independent observer masked to the birth weight status and smoking

exposure of the infants. We therefore consider that these observations are unlikely to be biased or due to chance.

These findings were independent of maternal smoking, which is known to be related to low birth weight and impaired airway function in infancy.<sup>30 35 36</sup> Associations of infant airway function with maternal height and social class have not been reported previously, and indicate the complexity of the causal chain linking socioeconomic disadvantage to low birth weight for gestation. Both forced expiratory volume and flow were positively associated with age and body length and negatively with birth weight status. However, forced expiratory flows were also significantly reduced in boys and in infants with a family history of asthma.

These findings are in accord with the findings from studies of airway function and birth weight in school aged children. Rona *et al* reported a significant association between birth weight and lung function in primary school aged children which was independent of parental smoking and social factors.<sup>4</sup> Similarly, Chan *et al* reported that low birth weight (<2000 g) was closely associated with poor airway function at 7 years of age and noted that male sex and exposure to maternal smoking were also important factors.<sup>5</sup> Earlier studies of adult airway function have taken birth weight as a measure of intrauterine growth but should more correctly be adjusted for gestational age to ensure that the effects of prematurity can be separated from those of poor fetal growth.<sup>1-3</sup> Boezen *et al* have recently reported a significant independent relation between low birth weight and FEV<sub>1</sub> in young adults which was independent of current height, gestational age, maternal smoking, and family history of asthma.<sup>37</sup>

Impaired airway function in adult life is an important and independent indicator of mortality risk.<sup>38</sup> Evidence to suggest that reduced size at birth is associated with impaired airway function in adult life is accumulating, but the biological and social pathways that mediate these associations remain unclear.<sup>3 39 40</sup> Our study provides evidence to support the fetal origins hypothesis by the finding of a link between impaired fetal growth, as assessed by low birth weight for gestation, and airway function in early infancy that is independent of current size. However, it also demonstrates that, in early postnatal life, airway function is diminished as a consequence of a complex causal pathway which includes social disadvantage as indicated by maternal social class, smoking and height, birth weight as a proximal and related consequence of these factors, and genetic predisposition to asthma. Further follow up will be needed to establish the relevance of these early findings to subsequent airway growth and development in later infancy and early childhood.

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CD and JS conceived the study and, with KC, were responsible for the study design; JH and KC assisted with recruitment; SL and AFH recruited

and measured infants and, together with JS, calculated airway function parameters; CD and SL were responsible for statistical analyses and drafted the manuscript. All authors contributed to interpretation and commented on the manuscript.

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