



## ORIGINAL ARTICLE

# Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents

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## ABSTRACT

**Background** Rates of preterm birth have increased in most industrialised countries but data on later lung function of late preterm births are limited. A study was undertaken to compare lung function at 8–9 and 14–17 years in children born late preterm (33–34 and 35–36 weeks gestation) with children of similar age born at term ( $\geq 37$  weeks gestation). Children born at 25–32 weeks gestation were also compared with children born at term.

**Methods** All births from the Avon Longitudinal Study of Parents and Children ( $n=14\,049$ ) who had lung spirometry at 8–9 years of age ( $n=6705$ ) and/or 14–17 years of age ( $n=4508$ ) were divided into four gestation groups.

**Results** At 8–9 years of age, all spirometry measures were lower in the 33–34-week gestation group than in controls born at term but were similar to the spirometry decrements observed in the 25–32-week gestation group. The 35–36-week gestation group and term group had similar values. In the late preterm group, at 14–17 years of age forced expiratory volume in 1 s ( $FEV_1$ ) and forced vital capacity (FVC) were not significantly different from the term group but  $FEV_1/FVC$  and forced expiratory flow at 25–75% FVC ( $FEF_{25-75\%}$ ) remained significantly lower than term controls. Children requiring mechanical ventilation in infancy at 25–32 and 33–34 weeks gestation had in general lower airway function ( $FEV_1$  and  $FEF_{25-75\%}$ ) at both ages than those not ventilated in infancy.

**Conclusions** Children born at 33–34 weeks gestation have significantly lower lung function values at 8–9 years of age, similar to decrements observed in the 25–32-week group, although some improvements were noted by 14–17 years of age.

## INTRODUCTION

In most industrialised countries the rate of preterm birth has risen markedly in recent years and late preterm births form a substantial proportion of these. In the USA the rate has increased from 9.5% in 1981 to 12.7% in 2005, with 20% of the preterm births occurring at 32–33 weeks gestation and 60–70% at 34–36 weeks gestation.<sup>1</sup> Therefore, even a small increased risk of later respiratory morbidity in infants born beyond 32 weeks gestation will contribute substantially to the number of individuals affected by respiratory disease associated with preterm birth. A workshop convened by the National Institute of Child Health and Human Development recognised the importance of infants

## Key messages

### What is the key question?

► We sought to compare lung function at 8–9 and 14–17 years in children born late preterm (33–34 and 35–36 weeks gestation) with children of similar age born at term ( $\geq 37$  weeks gestation). We also compared children born at 25–32 weeks gestation with children born at term.

### What is the bottom line?

► Children born at 33–34 weeks gestation have significantly lower lung function values at 8–9 years of age, similar to decrements observed in the 25–32-week group, although most of these differences were reduced by 14–17 years of age.

### Why read on?

► The findings from this longitudinal population-based observational cohort study suggest that children born at 33–34 weeks gestation may be at risk of decreased lung function at 8–9 years of age. By 14–17 years of age there were improvements in  $FEV_1$ .

born beyond 32 weeks gestation but identified the lack of outcome data for this population.<sup>2</sup> It is, however, increasingly recognised that late preterm infants have increased respiratory morbidity in the neonatal period, especially neonatal respiratory distress syndrome, transient tachypnoea of the newborn and pneumonia.<sup>3</sup> Few studies have reported later respiratory outcomes in children born late preterm,<sup>4,5</sup> with most studies on lung function outcomes following preterm birth focusing on extremely preterm infants of 32 weeks gestation or less, especially as they are at risk of developing chronic lung disease of prematurity (CLD).<sup>6</sup>

Prematurity is associated with delivery of an infant at early stages of lung development with the focus traditionally having been on those born at 32 weeks gestation or less.<sup>7</sup> As these infants are born at the late canalicular and early saccular stages of lung development, they often require intervention especially to support their respiratory system. However, those born ‘late’ preterm (ie, 33–34 weeks gestation) are also at a vulnerable stage of lung development (the late saccular stage),<sup>8</sup> and it is unknown if normal lung growth and

development continues normally in the extrauterine environment after preterm birth. Infants born at 35–36 weeks gestation are often termed ‘near term’ infants (eg, in the ECMO and Nitric Oxide clinical trials<sup>9–11</sup>) and are often assumed to behave like term infants, but it is unclear if being born at an early stage of alveolar development also results in adverse longer term respiratory outcomes.

In this study we sought to compare lung function at 8–9 and 14–17 years in a population-based cohort of children born late preterm at 33–34 weeks gestation and near term at 35–36 weeks gestation with children of similar age born at term ( $\geq 37$  weeks gestation). We also compared the results for these two gestation groups with children of similar age born extremely preterm at 25–32 weeks gestation. The longitudinal change in lung function between 8–9 and 14–17 years of age is also reported.

## METHODS

### Avon Longitudinal Study of Parents and Children (ALSPAC)

The study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) which has been described previously.<sup>12</sup> Additional detail is provided in the online supplement.

### Gestation groups and perinatal data

Gestational age was based on maternal reporting and medical assessments.<sup>13</sup> All children who had spirometry results at either 8–9 or 14–17 years of age were divided into four groups based on gestational age: 25–32 weeks, 33–34 weeks, 35–36 weeks and  $\geq 37$ –43 weeks (term control). Perinatal data on respiratory management were extracted from hospital records. Additional detail is provided in the online supplement.

### Self-reported respiratory symptoms and tobacco smoke exposure

As part of ALSPAC studies, questionnaires at 7.6 years of age established if children ‘ever had asthma diagnosed by a doctor together with symptoms and/or treatment in the previous 12 months’. Questionnaires at 13.8 years of age established if the children ‘ever had asthma diagnosed by a doctor’. Regular smoking at age 14 was defined as the usual smoking of at least one cigarette per day or at least six cigarettes per week.

### Lung spirometry

Spirometry was performed at 8–9 and 14–17 years of age as previously reported.<sup>14</sup> The variables forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC) and forced expiratory flow at 25–75% of FVC (FEF<sub>25–75</sub>) were recorded and transformed to SD scores adjusted for age, sex and height according to the method of Chinn *et al* in the ALSPAC cohort independently at 8–9 and 14–17 years of age.<sup>15</sup> FEV<sub>1</sub>/FVC and FEF<sub>25–75</sub>/FVC were calculated as markers of airway obstruction and dysanapsis.<sup>16</sup>

### Bronchial challenge

At 8–9 years of age children, unselected for asthma or wheezing, had a bronchial challenge test with methacholine using the method of Yan *et al*,<sup>17</sup> as previously described.<sup>14</sup> Additional detail is given in the online supplement.

### Statistical analysis

Gestations of  $\geq 44$  weeks were considered implausible and thus excluded. The birth weight z-scores were calculated using the lms Growth program (Medical Research Council, UK) to take into account gestation, as the numbers in the earlier gestation groups were small and the birth weights of the ALSPAC cohort were

similar to published reference values (data not shown). Weight at the time of lung function testing was converted into a z-score within the ALSPAC cohort as the ALSPAC data showed a trend towards earlier growth (data not shown). Spirometry values are summarised using the mean with 95% CIs. For longitudinal changes in spirometry, only data from children who had spirometry at both time points were included in the analyses. To account for confounders the spirometry data, already adjusted for age, gender and height, were further adjusted using general linear modelling for smoking during pregnancy and social class status based on father’s occupation, which are well-described confounders of lung function and preterm delivery. Missing values of each confounder were coded into a separate missing category. Adjusted scores were calculated and used in subsequent analyses. Longitudinal changes were assessed using paired t tests on the adjusted spirometry values. Differences between different gestational age groups and the term group and between ventilated and non-ventilated infants were tested using independent samples t tests. The results for ventilated and non-ventilated infants are given unadjusted for social class and smoking during pregnancy but are adjusted for age, gender and height. Bronchial hyper-responsiveness was compared between gestation groups by one-way analysis of variance.  $\chi^2$  Tests were used to compare asthma rates between gestation groups at 7.6 and 13.8 years of age. p values  $< 0.05$  were considered statistically significant. All analyses were performed using SPSS V.16 (SPSS Inc).

## RESULTS

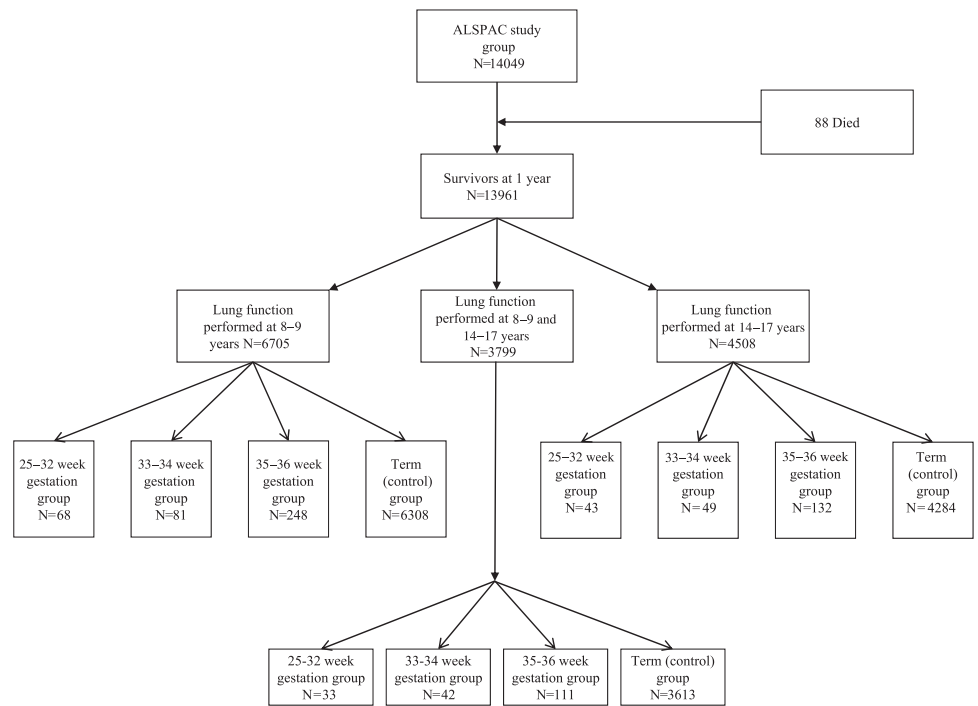
From 14 049 live births, spirometry data were available for 6705 (47.7%) children at 8–9 years of age and 4508 (32.1%) at 14–17 years of age, with measurements at both ages available for 3799 (27.0%) children (figure 1). Tables 1 and 2 show the characteristics of the children in each gestation group. A higher percentage of children in the 25–32-week gestation group were from lower social classes and had a higher prevalence of maternal smoking. A higher percentage of children who did not attend for spirometry were from a lower social class and had higher exposure to maternal smoking (table 3). 76% of the extremely preterm group and 17% of the late preterm group required mechanical ventilation but few ( $\leq 1\%$ ) did so in the more mature groups (table 2).

Asthma in the previous year at 7.6 years of age was reported by more than 20% in the 25–32-week and 33–34-week gestation groups but by  $< 15\%$  in the 35–36-week gestation and term groups, although these differences were not statistically significant. The rates of asthma ever at 13.8 years of age were similar (23–30%) in all groups. No differences were noted for smoking at 14 years of age between the gestational groups. Of the children who had any lung spirometry, 104 children reported regular smoking at 14 years of age (3 in the 35–36-week gestation group, 101 in the term group and none in those born at  $< 35$  weeks gestation).

### Association of preterm birth with lung function in later childhood

Spirometry data by gestation group at 8–9 and 14–17 years of age are shown in tables 4 and 5, respectively. At 8–9 years of age, all spirometry measures were significantly lower in the 33–34-week gestation group compared with the term group whereas values in the 35–36-week gestation group were similar to term infants. In the 25–32-week gestation group, all spirometry measures except FVC were significantly lower compared with the term group. The decrements of lung function were similar (table 4) between the 25–32-week and the 33–34-week

**Figure 1** Study profile: number of children excluded from group analysed. ALSPAC, Avon Longitudinal Study of Parent and Children.



gestation groups. The approximate differences compared with term infants after adjustment for age, gender and height were  $-143$  ml for  $FEV_1$ ,  $-98$  ml for FVC and  $-253$  ml/s for  $FEF_{25-75}$  in the 33–34-week gestation group and  $-121$  ml for  $FEV_1$ ,  $-65$  ml for FVC and  $-297$  ml/s for  $FEF_{25-75}$  in the 25–32-week gestation group.

At 14–17 years of age,  $FEF_{25-75}$ ,  $FEF_{25-75}/FVC$  and  $FEV_1/FVC$  remained significantly lower in the late preterm group than in the term group but  $FEV_1$  and FVC were not significantly different. The approximate differences from those born at term after adjustment for age, gender and height were  $-20$  ml for  $FEV_1$ ,  $156$  ml for FVC and  $-382$  ml/s for  $FEF_{25-75}$ , in the 33–34-

**Table 1** Characteristics of gestation groups

	25–32 weeks gestation	33–34 weeks gestation	35–36 weeks gestation	Term
Total liveborn	185	169	522	13148
Survivors at 1 year	160	165	519	13117
Had spirometry at 8–9 years	68 (43%)	81 (49%)	248 (48%)	6308 (48%)
Had spirometry at 14–17 years	43 (27%)	49 (30%)	132 (25%)	4284 (33%)
Had spirometry at 8–9 years and 14–17 years	33 (21%)	42 (25%)	111 (21%)	3613 (28%)
Total number in group who had any spirometry	78	88	269	6979
Male (%)	48 (62%)	54 (61%)	144 (54%)	3446 (49%)
Maternal smoking (%)	21/74 (28%)	20/84 (24%)	49/264 (19%)	1282/6826 (19%)
Manual workers (%)	27/54 (50%)	32/77 (42%)	108/255 (42%)	2439/6431 (38%)
Exclusively breast fed for at least 3 months (%)	6/75 (8%)	12/84 (14%)	25/266 (9%)	819/6834 (12%)
At spirometry at 8–9 years of age				
Mean (SD) age (years)	8.7 (0.4)	8.6 (0.3)	8.7 (0.3)	8.6 (0.3)
Mean (SD) height (cm)	130.9 (6.8)	130.9 (5.3)	132.8 (5.1)	132.4 (5.8)
Mean (SD) height (z-score)	-0.336 (1.225)	-0.252 (0.945)	0.036 (0.883)	0.011 (1.002)
Mean (SD) weight (kg)	28.1 (6.4)	28.3 (4.2)	30.4 (6.0)	30.3 (5.8)
Mean (SD) weight (z-score)	-0.439 (1.107)	-0.363 (0.738)	-0.046 (0.988)	-0.033 (0.990)
At spirometry at 14–17 years of age				
Mean (SD) age (years)	15.5 (0.2)	15.5 (0.4)	15.5 (0.3)	15.5 (0.3)
Mean (SD) height (cm)	166.7 (9.0)	168.2 (7.6)	170.0 (8.0)	169.2 (8.4)
Mean (SD) height (z-score)	-0.505 (1.237)	-0.202 (0.972)	0.028 (0.933)	0.007 (0.998)
Mean (SD) weight (kg)	56.3 (9.4)	60.6 (10.3)	60.6 (11.8)	61.6 (12.0)
Mean weight (z-score, SD)	-0.468 (0.898)	-0.090 (0.840)	-0.101 (1.006)	0.011 (1.001)
For children who had any spirometry				
Current asthma at 7.6 years of age based on reported doctor-diagnosed asthma ever with symptoms and/or treatment in previous 12 months (%)	11/52 (21%)	13/58 (22%)	22/182 (12%)	738/5221 (14%)
Current asthma at 13.8 years of age based on doctor-diagnosed asthma ever (%)	13/50 (26%)	17/57 (30%)	48/186 (26%)	1197/5227 (23%)

Some of the variables reported had missing data but the denominators are given.

**Table 2** Neonatal characteristics of gestation groups

	25–32 weeks gestation	33–34 weeks gestation	35–36 weeks gestation	Term
Total liveborn	185	169	522	13148
Survivors at 1 year	160	165	519	13117
Total number in group who had any spirometry	78	88	269	6979
Mean (SD) birth weight of those who had any spirometry (g)	1437 (439.5)	2449 (416.8)	2634 (424.7)	3478 (476.6)
Mean (SD) birth weight of those who had any spirometry (z-score)	0.051 (1.297)	0.396 (1.267)	0.180 (1.066)	0.117 (0.976)
Mean (SD) gestation of those who had any spirometry (weeks)	29.7 (2.0)	33.6 (0.5)	35.7 (0.5)	39.7 (1.3)
Ventilated, n/N (%)*	59/78 (76)	15/88 (17)	2/269 (1)	12/6979 (0.2)
Mean (range) length of time of ventilation (h)	245 (1–1416)	77 (9–168)	15 (8–22)	107 (1–576)
Type of ventilation, n/N (%)† *				
CPAP	43/78 (55.1)	6/88 (6.8)	2/269 (0.7)	3/6979 (0.0)
Ventilated via ETT	41/78 (52.6)	7/88 (8.0)	0/269 (0)	11/6979 (0.2)
Other	21/78 (26.9)	6/88 (6.8)	1/269 (0.4)	5/6979 (0.1)
Surfactant treatment, n/N (%)*	35/78 (44.9)	6/88 (6.8)	0/269 (0)	1/6979 (0.01)
Received oxygen at any time, n/N (%)*	66/78 (85)	31/88 (35)	16/269 (6)	45/6979 (0.6)
Number (%) receiving oxygen treatment for:*				
<1 day	17/78 (21.8)	13/88 (14.8)	8/269 (3.0)	31/6986 (0.4)
2–4 days	11/78 (14.1)	8/88 (9.1)	7/269 (2.6)	9/6986 (0.1)
≥5 days	38/78 (48.7)	10/88 (11.4)	0/269 (0)	4/6986 (0.1)

Some of the variables reported had missing data.

\*It was assumed the answer was no for children who did not have a neonatal admissions questionnaire completed, hence percentages are calculated based on the total number in the group who had any spirometry, not the number who had neonatal admissions questionnaires completed.

†Some children may have received more than one mode of ventilation.

CPAP, continuous positive airway pressure; ETT, endotracheal tube.

week gestation group and  $-114$  ml for FEV<sub>1</sub>,  $-120$  ml for FVC and  $-428$  ml/s for FEF<sub>25–75</sub> in the 25–32-week gestation group.

### Changes in spirometry between 8–9 years and 14–17 years of age

Table 6 shows changes in spirometry for children with measurements at both time points. For the 33–34-week gestation group, significant increases were observed for FEV<sub>1</sub>. In contrast, no significant changes were noted between the time periods for the 25–32-week, 35–36-week and term groups.

### Effect of ventilation in the newborn period on later lung function

Table E1 (in the online supplement) shows spirometry for the extremely and late preterm children according to ventilation requirements in the newborn period. In general, children who

were ventilated in infancy had lower airway function (FEV<sub>1</sub> and FEF<sub>25–75</sub>) at both ages compared with those not ventilated in infancy. More results are shown in the online supplement.

### Bronchial responsiveness

No significant differences were found between the different gestation groups for the geometric mean provocative dose of methacholine causing a fall in FEV<sub>1</sub> of 20% or more (PD<sub>20</sub>) in either responders or the whole study population (table 7).

### DISCUSSION

This study shows that most lung function variables measured by spirometry at 8–9 years of age were significantly lower in infants born at 33–34 weeks gestation compared with term infants, with the effect sizes being very similar to those in the 25–32-week gestation group. By 14–17 years of age the differences in FEV<sub>1</sub> and FVC attenuated but differences with term controls persisted for FEF<sub>25–75%</sub>, FEV<sub>1</sub>/FVC and FEF<sub>25–75%</sub>/FVC in the 33–34-week gestation group. In contrast, children born at 35–36 weeks had comparable lung function with children born at term at both follow-ups. While the numbers were small, the indications were that those in the 33–34-week gestation group who required mechanical ventilation fared worse than those who did not.

Late preterm infants of 33–34 weeks gestation are a growing population which is increasingly recognised to be at risk of morbidity in the neonatal period from respiratory diseases including respiratory distress syndrome,<sup>18</sup> and in infancy from

**Table 3** Characteristics of attenders and non-attenders

	Children who had any spirometry	Children who had no spirometry and were alive at 1 year
Number	7414	6547
Mean (SD) birth weight (g)	3412 (554)	3369 (565)
Mean (SD) gestation (weeks)	39.4 (1.9)	39.4 (1.9)
Male, N (%)	3692 (49.8)	3520 (53.8)
Maternal smoking, N (%)	1372/7248 (18.9)	2033/5896 (34.5)
Manual workers, N (%)	2606/6817 (38.2)	2407/4681 (51.4)
Exclusively breast fed for at least 3 months, N (%)	862/7259 (11.9)	470/5408 (8.7)

**Table 4** Mean and SD of z-score of lung function measures adjusted for age, gender and height at age 8–9 years, with CIs for the difference of means (premature – term), unadjusted and adjusted for maternal smoking in pregnancy and social status

	25–32 weeks (n=65)		Term (n=6144)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.461	0.876	0.011	1.000	-0.472 (-0.716 to -0.228)	-0.487 (-0.791 to -0.184)	0.002
FVC	-0.204	0.950	0.005	1.001	-0.209 (-0.453 to 0.035)	-0.151 (-0.454 to 0.152)	0.329
FEF <sub>25–75</sub>	-0.573	0.928	0.013	1.001	-0.586 (-0.829 to -0.342)	-0.627 (-0.930 to -0.325)	< 0.001
FEV <sub>1</sub> /FVC	-0.362	1.183	0.009	0.997	-0.371 (-0.617 to -0.125)	-0.488 (-0.793 to -0.182)	0.002
FEF <sub>25–75</sub> /FVC	-0.457	0.963	0.010	1.001	-0.467 (-0.713 to -0.221)	-0.512 (-0.818 to -0.207)	0.001
	33–34 weeks (n=79)		Term (n=6144)		Difference and 95% CI (unadjusted)	Difference and 95% CI (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.498	1.094	0.011	1.000	-0.509 (-0.733 to -0.285)	-0.485 (-0.724 to -0.246)	<0.001
FVC	-0.313	1.036	0.005	1.001	-0.318 (-0.540 to -0.096)	-0.352 (-0.589 to -0.115)	0.004
FEF <sub>25–75</sub>	-0.425	1.095	0.013	1.001	-0.438 (-0.659 to -0.217)	-0.434 (-0.670 to -0.197)	< 0.001
FEV <sub>1</sub> /FVC	-0.312	1.169	0.009	0.997	-0.320 (-0.545 to -0.096)	-0.239 (-0.477 to -0.001)	0.049
FEF <sub>25–75</sub> /FVC	-0.271	1.059	0.010	1.001	-0.281 (-0.503 to -0.060)	-0.267 (-0.503 to -0.031)	0.027
	35–36 weeks (n=238)		Term (n=6144)		Difference and 95% CI (unadjusted)	Difference and 95% CI (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	0.008	0.908	0.011	1.000	-0.003 (-0.133 to 0.127)	-0.012 (-0.147 to 0.123)	0.867
FVC	0.015	0.950	0.005	1.001	0.010 (-0.120 to 0.139)	0.009 (-0.125 to 0.143)	0.893
FEF <sub>25–75</sub>	-0.010	0.879	0.013	1.001	-0.023 (-0.152 to 0.106)	-0.034 (-0.168 to 0.099)	0.616
FEV <sub>1</sub> /FVC	0.004	0.906	0.009	0.997	-0.005 (-0.135 to 0.125)	-0.017 (-0.151 to 0.117)	0.805
FEF <sub>25–75</sub> /FVC	-0.022	0.925	0.010	1.001	-0.033 (-0.162 to 0.097)	-0.037 (-0.171 to 0.096)	0.582

FEF<sub>25–75</sub>, forced expiratory volume at 25–75% of FVC; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

respiratory viruses such as respiratory syncytial virus.<sup>19</sup> A large study of over 150 000 singleton births at 34–41 weeks gestation showed rates of severe respiratory disorders in neonates decreased with increasing gestational age (from 19.8% at 34 weeks to 0.28%

at 39–41 weeks).<sup>20</sup> Using the raised volume rapid thoracic compression technique, Friedrich *et al* reported decreased airway flows despite normal FVC at 4 and 16 months of age in healthy late preterm infants. However, it is unclear if decreased lung

**Table 5** Mean and SD of z-scores of lung function measures adjusted for age, gender and height at age 14–17 years, with CIs for the difference of means (premature – term), unadjusted and adjusted for maternal smoking in pregnancy and social status

	25–32 weeks (n=42)		Term (n=4105)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.186	0.850	0.001	1.004	-0.186 (-0.494 to 0.121)	-0.145 (-0.534 to 0.244)	0.464
FVC	-0.151	1.034	-0.004	1.002	-0.148 (-0.452 to 0.156)	-0.041 (-0.427 to 0.346)	0.836
FEF <sub>25–75</sub>	-0.438	0.899	0.011	1.001	-0.449 (-0.753 to -0.145)	-0.382 (-0.768 to 0.005)	0.053
FEV <sub>1</sub> /FVC	-0.195	1.117	0.010	0.995	-0.205 (-0.517 to 0.106)	-0.150 (-0.535 to 0.236)	0.446
FEF <sub>25–75</sub> /FVC	-0.260	1.006	0.013	1.000	-0.274 (-0.581 to 0.034)	-0.338 (-0.723 to 0.046)	0.084
	33–34 weeks (n=49)		Term (n=4105)		Difference and 95% CI (unadjusted)	Difference and 95% CI (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.022	1.135	0.001	1.004	-0.023 (-0.304 to 0.259)	-0.059 (-0.348 to 0.231)	0.691
FVC	0.169	0.905	-0.004	1.002	0.173 (-0.109 to 0.454)	0.127 (-0.161 to 0.415)	0.386
FEF <sub>25–75</sub>	-0.279	1.143	0.011	1.001	-0.290 (-0.572 to -0.009)	-0.289 (-0.577 to -0.001)	0.049
FEV <sub>1</sub> /FVC	-0.401	1.104	0.010	0.995	-0.411 (-0.693 to -0.130)	-0.379 (-0.666 to -0.092)	0.010
FEF <sub>25–75</sub> /FVC	-0.415	0.984	0.013	1.000	-0.428 (-0.709 to -0.147)	-0.397 (-0.683 to -0.110)	0.007
	35–36 weeks (n=129)		Term (n=4105)		Difference and 95% CI (unadjusted)	Difference and 95% CI (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	0.057	0.859	0.001	1.004	0.057 (-0.120 to 0.234)	0.094 (-0.089 to 0.276)	0.315
FVC	0.095	0.956	-0.004	1.002	0.099 (-0.077 to 0.274)	0.119 (-0.060 to 0.299)	0.191
FEF <sub>25–75</sub>	-0.077	0.877	0.011	1.001	-0.088 (-0.263 to 0.087)	-0.056 (-0.235 to 0.124)	0.543
FEV <sub>1</sub> /FVC	-0.079	1.047	0.010	0.995	-0.089 (-0.267 to 0.088)	-0.062 (-0.243 to 0.119)	0.502
FEF <sub>25–75</sub> /FVC	-0.137	0.957	0.013	1.000	-0.151 (-0.326 to 0.024)	-0.133 (-0.311 to 0.045)	0.143

FEF<sub>25–75</sub>, forced expiratory volume at 25–75% of FVC; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

**Table 6** Mean and SD of z-scores of lung function measures adjusted for age, gender and height at age 8–9 and 14–17 years, with CIs for the difference of means (14–17 – 8–9 years of age), unadjusted and adjusted for maternal smoking in pregnancy and social status

	25–32 weeks: age 8–9 (n=30)		25–32 weeks: age 14–17 (n=30)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.441	0.946	-0.318	0.932	0.123 (-0.258 to 0.504)	0.013 (-0.471 to 0.497)	0.958
FVC	-0.032	1.050	-0.052	0.918	-0.021 (-0.408 to 0.367)	-0.275 (-0.764 to 0.214)	0.271
FEF <sub>25–75</sub>	-0.717	0.944	-0.572	0.909	0.145 (-0.202 to 0.491)	0.227 (-0.214 to 0.688)	0.313
FEV <sub>1</sub> /FVC	-0.605	1.294	-0.438	1.132	0.167 (-0.211 to 0.546)	0.397 (-0.082 to 0.877)	0.104
FEF <sub>25–75</sub> /FVC	-0.665	0.941	-0.509	0.949	0.156 (-0.184 to 0.496)	0.296 (-0.134 to 0.727)	0.177
	33–34 weeks: age 8–9 (n=42)		33–34 weeks: age 14–17 (n=42)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.483	1.039	-0.079	1.191	0.404 (0.082 to 0.726)	0.347 (0.015 to 0.680)	0.041
FVC	-0.090	0.938	0.130	0.960	0.220 (-0.108 to 0.547)	0.226 (-0.562 to 0.111)	0.188
FEF <sub>25–75</sub>	-0.622	1.127	-0.336	1.173	0.287 (-0.006 to 0.580)	0.241 (-0.062 to 0.544)	0.119
FEV <sub>1</sub> /FVC	-0.621	1.272	-0.432	1.156	0.190 (-0.130 to 0.510)	0.143 (-0.187 to 0.473)	0.395
FEF <sub>25–75</sub> /FVC	-0.566	1.052	-0.445	1.017	0.121 (-0.166 to 0.408)	0.112 (-0.183 to 0.408)	0.456
	35–36 weeks: age 8–9 (n=107)		35–36 weeks: age 14–17 (n=107)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	0.148	0.863	0.021	0.860	-0.127 (-0.332 to 0.079)	-0.130 (-0.343 to 0.084)	0.234
FVC	0.115	0.941	0.045	0.955	-0.070 (-0.275 to 0.135)	-0.097 (-0.308 to 0.115)	0.370
FEF <sub>25–75</sub>	0.086	0.900	-0.076	0.888	-0.161 (-0.345 to 0.022)	-0.132 (-0.322 to 0.059)	0.175
FEV <sub>1</sub> /FVC	0.006	0.911	-0.048	1.076	-0.054 (-0.258 to 0.150)	-0.007 (-0.218 to 0.205)	0.951
FEF <sub>25–75</sub> /FVC	0.027	0.970	-0.104	0.992	-0.131 (-0.311 to 0.049)	-0.095 (-0.281 to 0.091)	0.318
	Term weeks: age 8–9 (n=3431)		Term weeks: age 14–17 (n=3431)		Difference (95% CI) (unadjusted)	Difference (95% CI) (adjusted)	p Value for adjusted analysis
	Mean	SD	Mean	SD			
FEV <sub>1</sub>	-0.004	1.006	0.010	1.002	0.014 (-0.021 to 0.051)	-0.013 (-0.060 to 0.034)	0.582
FVC	-0.019	1.003	0.005	1.001	0.025 (-0.012 to 0.061)	0.007 (-0.054 to 0.040)	0.774
FEF <sub>25–75</sub>	0.014	0.997	0.010	1.001	-0.005 (-0.037 to 0.028)	-0.016 (-0.058 to 0.027)	0.468
FEV <sub>1</sub> /FVC	0.016	1.003	0.003	0.982	-0.013 (0.049 to 0.023)	-0.006 (-0.053 to 0.041)	0.801
FEF <sub>25–75</sub> /FVC	0.023	1.005	0.005	0.989	-0.017 (-0.049 to -0.014)	-0.011 (-0.052 to -0.031)	0.616

FEF<sub>25–75</sub>, forced expiratory volume at 25–75% of FVC; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

function persists into childhood and beyond. Our data show that the preterm group of 33–34 weeks gestation have lower spirometry measurements than those born at term at 8–9 years of age; however, improvement was observed for FEV<sub>1</sub> by 14–17 years of age but not for other measurements. The extremely preterm group had similar effect sizes but, in contrast, the 35–36-week gestation group had similar lung function to the term control group at both ages. Infants at 33–34 weeks gestation are born at the stage of sacular development<sup>8</sup> and early delivery may alter their subsequent alveolar development, as has been suggested for extremely preterm infants.<sup>21</sup> Interventions such as mechanical ventilation and oxygen therapy are well

known to promote pulmonary inflammation in infancy leading to abnormal growth and development.<sup>6</sup> Although the numbers are small, especially as only 17% of the 33–34-week gestation group required mechanical ventilation in infancy, the data appear to support the notion that intervention is associated with worse spirometry at 8–9 years, which did not appear to improve to the same degree as for the non-ventilated group between the two ages (table E1 in online supplement). The interpretation is further complicated by the fact that mechanical ventilation was likely to be instituted in infants with underlying lung disease which may already identify them as candidates for future lung abnormalities. Other possible explanations for the poorer lung function in the

**Table 7** Bronchial responsiveness at 8–9 years of age

	25–32 weeks	33–34 weeks	35–36 weeks	Term
Number who had lung function at 8–9 years	68	81	248	6308
Number (%) who were excluded or did not complete the challenge for the reasons listed below*	35 (51.5%)	34 (42.0%)	90 (36.3%)	2185 (34.6%)
Number (%) who underwent challenge	33 (48.5%)	47 (58.0%)	158 (63.7%)	4123 (65.4%)
Number (%) who responded to methacholine challenge	9 (27.3%)	9 (19.1%)	22 (13.9%)	646 (15.7%)
Geometric mean PD <sub>20</sub> in responders (μmol)	1.20 (0.43, 3.35)	2.25 (1.08, 4.70)	2.27 (1.50, 3.42)	1.71 (1.57, 1.87)
Geometric mean PD <sub>20</sub> for the whole population who underwent the challenge (μmol)	6.46 (4.15, 10.04)	8.86 (7.08, 11.09)	9.62 (8.65, 10.69)	8.96 (8.73, 9.19)

\*Children did not start or complete the challenge for a number of reasons: the child refused whole/part of session, parent refused, parents did not attend, staff illness/difficulties, need doctor, child ill or taking medications, time restraint, equipment error/failure, staff error (general), child started coughing, child problems/difficulties with task, couldn't get reproducible FEV<sub>1</sub> <70% predicted.

33–34-week gestation group are an adverse prenatal environment associated with preterm delivery (eg, chorioamnionitis may affect later lung function)<sup>22–25</sup> or dysregulated lung growth associated with premature cessation of late gestational development. The loss of late intrauterine lung maturation in the 33–34-week gestational group suggests that lung growth may be dysregulated after birth resulting in physiological differences compared with those completing term gestation.

We noted poorer lung function in childhood in the late preterm children which was similar to the extremely preterm group, but did not note significant differences in rates of asthma between the gestation groups. It would be interesting to investigate if the decreased FEV<sub>1</sub> can be reversed by bronchodilators as was recently shown for children who were born extremely preterm.<sup>26</sup> Furthermore, if there is plasticity of the airways, bronchodilators may be effective in this group of children, but whether they improve longer term airway function needs further investigation. Few studies have reported longitudinal lung function in preterm infants with most focusing on severe long-term respiratory consequences—that is, those who develop CLD. In a small number of children with CLD, often also called bronchopulmonary dysplasia, Filippone *et al* reported that airflow limitation tracked between 2 and 8.8 years of age did not show improvements between the two time points.<sup>27</sup> In contrast, Doyle and colleagues reported significant improvements in predicted values of lung function between 8 and 14 years of age in children with a birth weight <1501 g.<sup>28</sup> When we compared the preterm children who had spirometry at both time periods, our data support potential improvements in lung function in children born at 33–34 weeks gestation from 7–8 years of age to 14–17 years, especially for the larger airways. For the 25–32-week gestation group, relative improvements were noted in the z-scores for lung spirometry but these were not statistically significant. While tracking appears to be an attractive concept, our longitudinal data question the concept of tracking as lung function improved between 7–8 and 14–17 years of age. More recent imaging modalities such as the use of hyperpolarised helium may assist in investigating lung growth and development beyond infancy<sup>29</sup> to clarify if, indeed, continued growth and development occurs beyond infancy.

While we acknowledge that the data were not specifically collected to address the current hypothesis, the strength of this study is that it uses data from a large unselected population-based cohort with comprehensive longitudinal data with reasonable numbers of preterm-born children and a large number in the term control group. A further strength is that spirometry was measured using the same methods at the two time points and is an objective outcome. As with all cohort studies, a major weakness is the loss to follow-up and the resulting potential attrition bias. Fewer children who had mothers who smoked during pregnancy and a from lower social class attended for lung spirometry compared with the attenders. Since lower social class is associated with more preterm births, more maternal smoking and decreased attendance for spirometry, it is possible that a higher rate of attendance in these children would have increased the observed differences. In addition, ALSPAC did not measure the lung function of severely disabled children and, as these represent the severe end of morbidity associated with preterm delivery, the differences may have been attenuated by their exclusion. We included children from ethnic minorities in our analysis as there were very few of them (in the whole ALSPAC cohort only 5% of the children who reported their ethnic background reported being non-white), and the ALSPAC cohort is broadly representative of the population of the UK.<sup>12</sup>

In summary, our data show that, at 8–9 years of age, measures of airway function are reduced in children born at 33–34 weeks gestation compared with children born at term, and are of similar magnitude to those in the extremely preterm group who received a much higher proportion of respiratory intervention during the neonatal period. However, by 14–17 years of age, there was no significant difference in FEV<sub>1</sub> and FVC in the late preterm group compared with children born at term, although FEV<sub>1</sub>/FVC and FEF<sub>25–75%</sub> remained significantly lower than term controls. This raises the question about what occurs from a lung development point of view between 33–34 and 35–36 weeks of gestation. Now that there is a strong suspicion of respiratory physiological abnormalities in late preterm-born children, it will be interesting to study in more detail whether they are at greater risk of respiratory infections in infancy, have increased respiratory symptoms or indeed have limitation of exercise with or without exercise-induced bronchoconstriction.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the ALSPAC Law and Ethics Committee and the local research ethics committees.

**Contributors** All authors led by SK were involved in study design including hypothesis generation and execution. AJH is co-director of ALSPAC and was involved in collection of the data. FD and WJW were primarily responsible for statistical analyses. SJK and SK wrote the initial drafts of the paper which was contributed to by all authors. SK is the guarantor.

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**Data Sharing Statement** Data generated by the ALSPAC study are held as a national resource. Data are anonymised at entry and held separately from administrative data; therefore, identification of individual subjects' data is concealed from researchers. Access to data items is provided on application to the ALSPAC Executive Committee. The full ALSPAC collaboration policy, including details of data sharing arrangements, is published online at: <http://www.bris.ac.uk/alspac/sci-com/collab-policy/>.

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## Journal club

### Differentiation of malignant pleural mesothelioma from other pleural diseases

In this study, pleural effusion samples from 101 patients with suspected or newly diagnosed malignant pleural mesothelioma (MPM) or metastatic adenocarcinoma (ADCA) were collected between 1998 and 2010. Of the 101 patients, 65 were diagnosed with MPM, 25 with ADCA and 15 with benign pleural effusion. Cancer cells isolated from pleural effusion samples were subjected to genome-wide gene expression analysis, done with the help of microarrays and real-time PCR.

The study found 74 genes coding for markers that were overexpressed in MPM and 9 genes that were overexpressed in ADCA. The highest expression in MPM cells was the gene COL3A1, coding for type III collagen. Immunohistochemistry demonstrated 100% staining of MPM biopsy samples with antibodies specific for COL3A1 and no staining in ADCA.

Soluble markers such as CCL2 and galectin-3 were identified as useful markers for diagnosing MPM. CCL2 concentration was significantly higher in patients with MPM than in patients with ADCA or benign pleural effusion whereas galectin-3 was significantly lower in MPM compared with ADCA. CCL2 and COL3A1 can be used as positive markers, whereas galectin-3 can be used as a negative marker. Statistical analysis using receiver operating characteristic curve and sensitivity suggested that both these markers performed better than existing markers in differentiating MPM from other pleural diseases.

Although type III collagen, CCL2 and galectin-3 markers have been shown to be valuable diagnostic aids, a large multicentre study is required to validate these results and investigate other potential markers.

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