Lung Function and Respiratory Symptoms at 11 Years in Children Born Extremely Preterm

The EPICure Study

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***Rationale*: The long-term respiratory sequelae of infants born extremely preterm (EP) and now graduating from neonatal intensive care remains uncertain.**

***Objectives*: To assess the degree of respiratory morbidity and functional impairment at 11 years in children born EP (i.e., at or less than 25 completed weeks of gestation) in relation to neonatal determinants and current clinical status.**

***Methods*: Pre- and postbronchodilator spirometry were undertaken at school in children born EP and classroom control subjects. Physical examination and respiratory health questionnaires were completed. Multivariable regression was used to estimate the predictive power of potential determinants of lung function.**

***Measurements and Main Results*: Spirometry was obtained in 182 of 219 children born EP (129 with prior bronchopulmonary dysplasia [BPD]) and 161 of 169 classmates, matched for age, sex, and ethnic group. Children born EP had significantly more chest deformities and respiratory symptoms than classmates, with twice as many (25 vs. 13%; $P < 0.01$) having a current diagnosis of asthma. Baseline spirometry was significantly reduced ($P < 0.001$) and bronchodilator responsiveness was increased in those born EP, the changes being most marked in those with prior BPD. EP birth, BPD, current symptoms, and treatment with β-agonists are each associated independently with lung function z-scores (adjusted for age, sex, and height) at 11 years. Fifty-six percent of children born EP had abnormal baseline spirometry and 27% had a positive bronchodilator response, but less than half of those with impaired lung function were receiving any medication.**

***Conclusions*: After extremely preterm birth, impaired lung function and increased respiratory morbidity persist into middle childhood, especially among those with BPD. Many of these children may not be receiving appropriate treatment.**

Keywords: prematurity; lung function; bronchopulmonary dysplasia; long-term follow-up

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Preterm birth may be associated with persistent respiratory morbidity, but less is known regarding long-term respiratory sequelae of more recent graduates from neonatal intensive care, who are generally more immature than their predecessors, but have been exposed to less aggressive ventilatory support.

What This Study Adds to the Field

At 11 years of age, 56% of children born before 25^{+6} weeks of gestation had abnormal baseline spirometry, 27% had a positive bronchodilator response, and 25% had a diagnosis of asthma (twice that observed in classmates). Among the 65% of extremely preterm children who had been asymptomatic over the previous 12 months, 48% had abnormal baseline spirometry, of whom 81% had prior bronchopulmonary dysplasia, emphasizing the need for continued monitoring of these children.

Rates of preterm birth are rising (1, 2) and survival after extremely preterm birth are improving (3), but morbidity among survivors, including that relating to long-term respiratory outcomes, remains high (4, 5). Increased respiratory morbidity is of concern as poor lung function tracks throughout life (6). Adults born preterm before 1990 have both structural (7) and functional lung impairments (8–10). Less is known about long-term sequelae of more recent graduates of neonatal intensive care, in whom bronchopulmonary dysplasia (BPD) is largely confined to the most immature infants who have been treated with antenatal steroids and surfactant, but less aggressive ventilatory support than in the past (11, 12).

We have previously studied respiratory outcomes at 6 years in an entire population of children born extremely preterm (EP) (i.e., at or less than 25 completed weeks [$\leq 25^{+6}$ wk] of gestation) and shown high rates of respiratory symptoms and medication use, with reduced peak expiratory flows compared with classmates (13). Reevaluation of the health status of this cohort at 11 years provided the opportunity for more detailed respiratory assessment, which is the focus of this article. The aim of this study was to assess the degree of respiratory morbidity and functional impairment at 11 years in children born EP in relation to neonatal determinants and current clinical status. We hypothesized that, compared with classmates, EP birth would be associated with reduced lung function and ongoing respiratory morbidity in middle childhood and that this would be worse for those children born EP with prior BPD,

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defined pragmatically as receiving supplemental oxygen at 36 weeks postmenstrual age (PMA; where PMA = gestational age + postnatal age) (11). Some of the results of this study have been previously reported in the form of an abstract (14).

METHODS

EPICure is a geographically based national cohort study, involving all babies born at or less than 25 completed weeks gestation in the United Kingdom and Ireland between March and December 1995 (15). This cohort has been assessed at 2.5, 6, and 11 years (13, 16, 17). The study was approved by the Southampton and South West Hampshire Research Ethics Committee (Reading, UK). Informed written consent was obtained from parents, and assent from the children who participated.

Children born EP were seen at school together with a classmate as part of a comprehensive assessment (17, 18). Schools were asked to identify up to three potential comparison children matched for age (within 3 mo), sex, and ethnic origin, one of whom was randomly selected as a comparison child. No comparison was sought for children born EP and attending special school. Classmates were ineligible if there was a prior history of preterm delivery, tuberculosis, whooping cough, pneumonia, or hospitalization for respiratory illness; however, asthma and atopy were not exclusion criteria. All children were evaluated by one of three pediatricians according to the study protocol (Figure 1).

Parents received a preassessment telephone call to check respiratory medication use and any intercurrent illness. Children were asked not to take short-acting bronchodilators or leukotriene antagonists on the day of assessment. Parents completed a questionnaire about their child's respiratory health (19) and relevant family information. Our operational definition of "current asthma" was use of asthma medication or wheeze in the past 12 months by children with a doctor diagnosis of asthma *or* use of asthma medication *and* wheeze in the past 12 months even if no prior diagnosis of asthma.

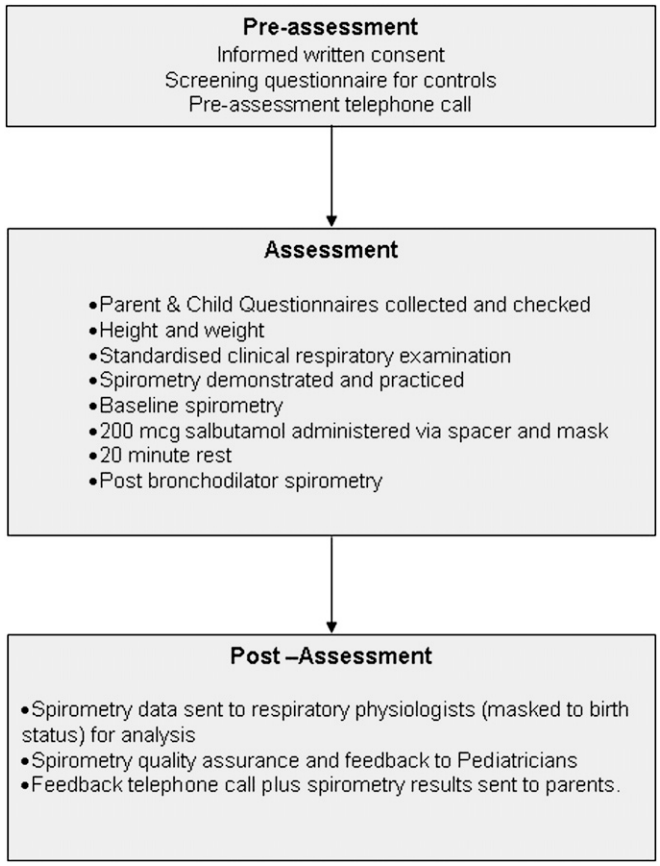

Figure 1. Study protocol.

Anthropometry and Physical Examination

Height and weight were measured according to established protocols (20). Height, weight, and body mass index were expressed as z-scores, that is, adjusted for sex and age (21). All children underwent a standardized clinical examination.

Spirometry

A portable spirometer (Jaeger Masterscope, Lab Manager, V4.65; CareFusion, Hoechberg, Germany) was used to measure FEV_1, forced expiratory flow over the middle half of the FVC ($FEF_{25–75}$), and FVC as described previously (20). The three pediatricians undertook an intensive 3-day spirometry training course at a pediatric respiratory laboratory (UCL, Institute of Child Health [ICH], London, UK). This included assessing technical acceptability at the time of data collection and opportunities to practice spirometry on local children. These pilot data were reviewed by respiratory physiologists and feedback was provided to ensure that repeatable measurements could be obtained before commencing assessments in school (20).

During school spirometry, attempts were made to achieve at least three acceptable and two repeatable forced expiratory maneuvers at baseline, before repeating measurements 20 minutes after administering a bronchodilator (two puffs of salbutamol, 100 μg, via a spacer). Each pediatrician received at least one visit from a physiologist, who observed school assessments in progress, with technical support being available throughout the study (20). Spirometric data were analyzed by respiratory physiologists at the ICH, masked to clinical and neonatal data.

Feedback regarding overall quality control was sent to pediatricians within 1 week of receiving data. Spirometry data were expressed as z-scores, to adjust for height, age, and sex (22, 23). A copy of the spirometry results, with a brief interpretation of findings, was sent to each family.

Data Management and Statistical Analysis

Spirometric data were automatically exported to a database to prevent transcription errors. Questionnaire data were double-entered and checked for outliers before importing into the main study database, which contained all prior medical and demographic history. Once lung function analysis had been completed and results were entered into the database, codes regarding birth status and whether the child had had BPD were released (15). Data were verified for accuracy and analyzed with SPSS (version 15.0; SPSS, Chicago, IL) and Stata (version 10.1; StataCorp, College Station, TX) (S.L. and E.H.). Differences between groups were analyzed by independent t tests with 95% confidence intervals (CIs) for continuous data and by χ^2 or Fisher exact test when appropriate for categorical outcomes. Paired t tests were used for within-subject comparisons. Multivariable regression analyses were performed to estimate the predictive power of independent variables such as sex, preterm birth, BPD, and birthweight-for-gestational age on lung function, and to estimate any potential interactions between group and asthma status. Significance levels were set at $P < 0.05$. Data management was undertaken with Re-Base software (J7IS Ltd. J7 Group, Rickmansworth, UK).

RESULTS

Study Population

Within the EPICure cohort, 219 of 307 survivors were evaluated at 11 years of age (range, 10.1 to 12.1 yr) (Figure 2). Those lost to follow-up were more likely to be of nonwhite ethnic origin, have unemployed parents, a lower IQ at 6 years, and higher rates of cognitive impairment (17, 18). The majority of assessments were undertaken in mainstream schools, but 29 children born EP were evaluated in special schools, 10 at home, and 2 in hospital outpatients. Satisfactory baseline spirometry was completed in 182 of 219 children born EP (Figure 2); results being obtained in 174 of 185 (94%)

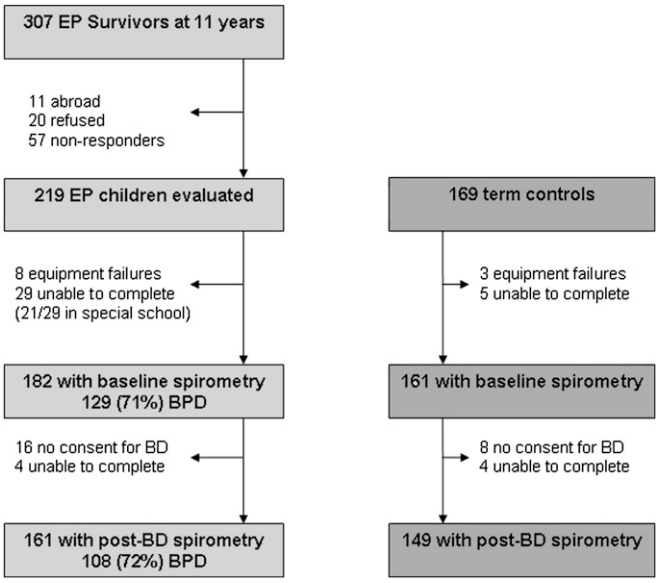

Figure 2. Study population at 11 years follow-up. BD = bronchodilator; BPD = bronchopulmonary dysplasia; EP = extremely premature.

children born EP and evaluated in mainstream schools and in 8 of 29 (28%) in special schools.

No potential classmates required exclusion from the study on the basis of the exclusion criteria for control subjects. Among classmates, 161 of 169 (95%) completed baseline spirometry, two assessments being performed at home. Technically acceptable postbronchodilator data were obtained in 161 children born EP and 149 classmates, dropout being due primarily to lack of parental consent for salbutamol (9% EP, 5% classmates; Figure 2).

Perinatal characteristics of children born EP with spirometry data are summarized in Table 1. Those with prior BPD were significantly more likely to have received surfactant, postnatal steroids, longer courses of postnatal steroids, be discharged home with supplemental oxygen, and were more immature. With the exception of a higher proportion of white mothers (83 vs. 65%) and a slightly lower proportion of children being discharged home on supplemental oxygen (28 vs. 41%), there were no significant differences in perinatal characteristics between those in whom spirometry was measured at 11 years and those lost to follow-up (n = 88; *see* Table E1 in the online supplement). Among those assessed at 11 years, children in whom spirometry could not be obtained had a stormier antenatal and neonatal course, as indicated by lower maturity (GA: −0.4 wk; $P < 0.01$), increased frequency of antepartum hemorrhage (41 vs. 19%; $P < 0.01$), greater exposure to postnatal steroids (89 vs. 69%; $P < 0.05$), and more frequent discharge home on supplemental oxygen (47 vs. 28%; $P < 0.05$); these children were also more likely to be in special school (57 vs. 4%; Table E2).

Anthropometry and Respiratory Morbidity

Among those with successful spirometry, questionnaire data were available for 168 (92%) children born EP and 148 (92%) classmates (Table 2). The three groups (classmates and EP ± BPD) were well matched for age, sex, and ethnic group and a similar proportion had reached puberty (Tanner stage 3; Table 2). Children born EP were significantly shorter and lighter than

TABLE 1. PERINATAL DATA FOR CHILDREN BORN EXTREMELY PRETERM AND FROM WHOM SPIROMETRIC DATA WERE OBTAINED

	All EP [*mean* (*SD*)]	BPD [*mean* (*SD*)]	No BPD [*mean* (*SD*)]	BPD – No BPD Δ (95% CI)
n	182	129	53	
Gestational age, wk	25.0 (0.7)	24.9 (0.8)	25.1 (0.6)	**−0.22 (−0.5; 0.0)***
Birthweight, kg	0.75 (0.12)	0.74 (0.12)	0.78 (0.12)	−0.04 (−0.1; −0.0)
Birthweight z-score†	−0.15 (0.76)	−0.18 (0.71)	−0.05 (0.87)	−0.13 (−0.37; 0.11)
Maternal age, yr	29.0 (5.4)	29.1 (5.5)	28.5 (5.2)	0.6 (−1.2; 2.3)
	n (%)	n (%)	n (%)	Δ (95% CI)
Gestational age < 25 wk	68 (37%)	53 (41%)	15 (28%)	13% (−2; 28%)
Male	79 (43%)	59 (46%)	20 (38%)	8% (−8; 24%)
White mother	151 (83%)	108 (84%)	43 (81%)	3% (−9; 16%)
Multiple births	52 (29%)	39 (30%)	13 (24%)	6% (−8; 24%)
Antenatal steroids	148 (82%)	106 (83%)	42 (81%)	2% (−11; 15%)
Maternal smoking‡	63 (35%)	49 (39%)	14 (27%)	12% (−3; 26%)
Maternal PET	5 (3%)	4 (3%)	1 (2%)	1% (−4; 6%)
Maternal APH	34 (19%)	23 (18%)	11 (22%)	−4% (−17; 10%)
Chorioamnionitis	41 (23%)	30 (23%)	11 (22%)	1 (−12; 15)%
PROM (>24 h)	47 (26%)	32 (25%)	15 (29%)	−4% (−19; 10)%
Received surfactant	153 (85%)	114 (89%)	39 (74%)	**15% (2; 29%)**§
Postnatal steroids	125 (69%)	101 (79%)	24 (45%)	**34% (18; 49%)**‖
Duration of postnatal steroids, d¶	14 (0–171)	18 (0–171)	0 (0–49)	***P* < 0.001**
O_2 at discharge	50 (28%)	49 (39%)	1 (2%)	**37% (28; 46%)**‖

Definition of abbreviations: Δ (95% CI) = difference in mean or proportion between groups, with 95% confidence interval; APH = antepartum hemorrhage; BPD = bronchopulmonary dysplasia; EP = extremely preterm; PET = preeclamptic toxemia; PROM = premature rupture of membranes more than 24 hours before delivery.

Not more than four case subjects with missing data for each variable. Boldface entries indicate significance.

* $P < 0.05$.

† Child Growth Foundation Standards (21).

‡ Maternal smoking in pregnancy.

§ $P < 0.01$.

‖ $P < 0.001$.

¶ Data presented as median (range); *P* value calculated from nonparametric test for trend.

TABLE 2. GROUP CHARACTERISTICS AND RESPIRATORY MORBIDITY IN THOSE WITH SPIROMETRY RESULTS

	All EP	Classmates (C)	EP – C Δ (95% CI)	EP: BPD	EP: No BPD	BPD – No BPD Δ (95% CI)
n	182	161		129	53	
Boys, %	43%	43%	1% (−10; 11%)	59 (46%)	20 (38%)	8% (−7; 24%)
Age, yr	10.9 (0.38)	10.9 (0.55)	0.0 (−0.1; 0.1)	11.0 (0.4)	10.9 (0.4)	−0.1 (−0.2; 0.0)
Height, z-score	−0.48 (0.99)	0.11 (0.96)	**−0.58 (−0.8; −0.4)***	−0.47 (0.99)	−0.48 (0.98)	−0.00 (−0.3; 0.3)
Weight, z-score	−0.41 (1.29)	0.17 (1.15)	**−0.57 (−0.8; −0.3)***	−0.37 (1.31)	−0.49 (1.25)	0.13 (−0.3; 0.5)
BMI, z-score	−0.27 (1.4)	0.13 (1.3)	**−0.39 (−0.7; −0.1)†**	−0.22 (1.4)	−0.39 (1.4)	0.17 (−0.28, 0.62)
Puberty (Tanner stage 3), %	30%	26%	3% (−7; 13%)	29%	31%	−2% (−18; 12%)
White mother, %	179 (82%)	135 (88%)	−6% (−13; 1%)	108 (84%)	43 (81%)	3% (−8%; 17%)
Passive smoke exposure	38%	30%	8% (−3; 18%)	41%	31%	10% (−6; 24%)
Physical examination‡						
Chest asymmetry	6 (3.3%)	1 (0.6%)	3% (0; 5.6%)	6 (4.7%)	0 (0%)	5% (0; 8%)
Harrison's sulci	16 (9%)	0 (0%)	**9% (5; 13%)***	15 (12%)	1 (2%)	**10% (3; 17%)§**
Pectus excavatum	29 (17%)	3 (2%)	**15% (10; 20%)***	23 (19%)	6 (12%)	7% (−4; 18%)
Pectus carinatum	2 (1%)	0 (0%)	1% (−0; 3.0%)	2 (2%)	0 (0%)	2% (−0; 4%)
Respiratory morbidity in past 12 mo‖						
Current asthma¶	42 (25%)	20 (13%)	**12% (4; 21%)†**	32 (28%)	10 (19%)	9% (−5; 22%)
Asthma medication	41 (25%)	16 (11%)	**14% (6; 22%)†**	31 (27%)	10 (19%)	8% (−6; 21%)
Seen by respiratory specialist	14 (8%)	4 (3%)	**6% (1; 11%)§**	7 (6%)	7 (14%)	−8% (−20; 3%)
Wheeze	35 (21%)	21 (14%)	7% (−2; 15%)	29 (25%)	6 (12%)	**13% (2; 25%)§**
Number of wheeze attacks over past 12 mo						
1–3	19 (11%)	14 (9%)	***P* = 0.039****	17 (15%)	2 (4%)	*P* = 0.061**
4–12	12 (7%)	5 (3%)		8 (7%)	4 (8%)	
>12	4 (2%)	0 (0%)		4 (3%)	0 (0%)	
Sleep disturbed by wheeze						
<1 night/wk	11 (7%)	7 (5%)	*P* = 0.073**	9 (8%)	2 (4%)	*P* = 0.43**
⩾1 night/wk	7 (4%)	1 (1%)		5 (4%)	2 (4%)	
Speech limited by wheezing	8 (5%)	2 (1%)	3% (−0; 7%)	6 (5%)	2 (4%)	1% (−5; 8%)
Exercise-induced wheeze	34 (21%)	13 (9%)	**12% (4; 19%)†**	27 (24%)	7 (13%)	10% (−2; 23%)
Nocturnal cough	33 (20%)	16 (11%)	**9% (1; 17%)§**	25 (22%)	8 (15%)	6% (−6; 19%)
Maternal education > 16 yr, %	121 (67%)	119 (77%)	**−10% (−19; 0%)§**	83 (65%)	38 (72%)	−7% (−20; 9%)

Definition of abbreviations: Δ (95% CI) = difference in mean or proportion between groups, with 95% confidence interval; BMI = body mass index; BPD = bronchopulmonary dysplasia; EP = extremely preterm.

Results are presented as mean (SD) or n (%). Boldface entries indicate significance.

* $P < 0.001$.

† $P < 0.01$.

‡ Physical examination in 181 children born EP and 160 classmates.

§ $P < 0.05$.

‖ Among those with successful spirometry, the respiratory questionnaire was returned by 168 children born EP (116 with BPD, 52 without BPD) and 148 classmates.

¶ Current asthma defined as either (*1*) a doctor diagnosis of asthma (at any time) and *either* respiratory symptoms *or* asthma medication in the last 12 months, or (*2*) asthma medication *and* respiratory symptoms in the past 12 months even if no recall of prior doctor diagnosis.

** *P* value calculated from nonparametric test for trend.

classmates, but there were no significant differences in body size between children born EP with and without prior BPD. Compared with children born EP with acceptable data, those unable to complete spirometry were significantly shorter at 11 years but did not differ with respect to respiratory morbidity (Table E2).

Findings on clinical examination are summarized in Table 2. The resting respiratory rate was significantly higher (Table 3), and both pectus excavatum and Harrison's sulci were more common, in children born EP than in classmates. Among children born EP, Harrison's sulci were more common in those with prior BPD, but there were no other significant physical differences between the subgroups. Mild coryzal symptoms within the past week were reported by 22 of 182 (12%) children born EP and by 20 of 161 (12%) classmates, but no child was tested when unwell.

When compared with classmates, children born EP were more likely to have a current diagnosis of asthma (25 vs. 13%; $P < 0.01$), recent respiratory symptoms and medication, as well as a tendency for increased asthma-associated sleep disturbance during the past 12 months. Among members of the EP group, significantly more with prior BPD reported wheeze in the past 12 months (Table 2).

Spirometry: Baseline and Post–bronchodilator Response

After adjustment for age, sex, and body size by using z-scores, children born EP had significantly lower baseline spirometry than classmates ($P < 0.0001$), values being reduced by up to 1.5 z-scores for both FEV_1 and $FEF_{25–75}$ (equivalent to reductions of 17 and 28% predicted, respectively; Table 3 and Figure 3A). The most marked reductions were seen in children born EP with prior BPD, in whom lung function was significantly lower than in either classroom control subjects or those born EP but without BPD. Abnormally low baseline lung function (i.e., FEV_1, FEV_1/FVC, or $FEF_{25–75} \leqslant -1.96$ z-scores) was observed in 14 of 161 (9%) classmates, 17 of 53 (32%) children born EP but no prior BPD, and 85 of 129 (66%) children with prior BPD. Among the children born EP with abnormal lung function who returned questionnaire data, only 5 of 16 (31%) of those without BPD and 24 of 75 (32%) with BPD were receiving any respiratory medication.

After administration of a bronchodilator, statistically significant increases in FEV_1 occurred in all groups, these changes being most marked in children born EP, especially if with prior BPD (Table 3 and Figure 3B). Nevertheless, postbronchodilator lung function remained significantly lower in children born EP than in their classmates, suggesting that airway obstruction was

TABLE 3. COMPARISON OF PRE- AND POSTBRONCHODILATOR RESULTS

	EP: No BPD	EP: BPD	All EP	Classmates (C)	EP – C Δ (95% CI)	EP Only BPD – No BPD Δ (95% CI)	EP No BPD – C *P* Value*
Baseline, n	53	129	182	161			
Respiratory rate, breaths/min	20 (3)	20 (3)	20 (3)	18 (3)	**2 (1; 3)**†	0.0 (−1; 1)	**<0.001**
$zFEV_1$‡	−0.8 (1.3)	−1.7 (1.1)	−1.4 (1.2)	0.0 (1.0)	**−1.5 (−1.7; −1.2)**†	**– 0.9 (−1.2; −0.5)**†	**<0.001**
FEV_1, %pred	90 (15)%	80 (13)%	83 (14)%	100 (12)%	**−17 (−20; −14)%**†	**−10 (−14; −6)%**†	**<0.001**
zFVC‡	−0.3 (1.2)	−0.8 (1.2)	−0.7 (1.2)	0.1 (1.1)	**−0.8 (−1.0; −0.6)**†	**−0.6 (−1.0; −0.2)**§	0.094
FVC, %pred	97 (13)%	91 (13)%	93 (14)%	102 (12)%	**−9 (−12; −6)%**†	**−6 (−11; −2)%**§	0.087
FEV_1/FVC	0.81 (0.09)	0.78 (0.10)	0.79 (0.10)	0.86 (0.07)	**−0.07 (−0.09; −0.06)**†	**−0.04 (−0.07; −0.01)**‖	**<0.001**
$zFEV_1$/FVC‡	−0.9 (1.3)	−1.4 (1.3)	−1.3 (1.3)	−0.2 (1.0)	**−1.0 (−1.3; −0.8)**†	**−0.4 (−0.9; −0.03)**‖	**<0.001**
FEV_1/FVC, %pred	92 (11)%	88 (11)%	89 (11)%	98 (8)%	**−9 (−11; −7)%**†	**−4.0 (−7.6; −0.4)%**‖	**<0.001**
$zFEF_{25–75}$§	−1.5 (1.4)	−2.2 (1.2)	−2.0 (1.3)	−0.5 (1.1)	**−1.5 (−1.8; −1.2)**†	**– 0.7 (−1.1; −0.3)**†	**<0.001**
$FEF_{25–75}$, %pred	71 (25)%	58 (21)%	61 (23)%	90 (23)%	**28 (−33; −24)%**†	**−13 (−20; −6)%**†	**<0.001**
Post BD, n	45	117	162	149			
$zFEV_1$ post BD‡	−0.4 (1.2)	−1.0 (1.0)	−0.8 (1.1)	0.3 (1.0)	**−1.2 (−1.4; −0.9)**†	**−0.6 (−1.0; −0.3)**†	**<0.001**
Percent change in FEV_1	5.5 (7.3)%	10.7 (10.0)%	9.3 (9.6)%	4.0 (5.0)%	**5.3 (3.5; 7.0)%**†	**5.2 (2.0; 8.5)%**§	0.58
Change in FEV_1 > 12%	7 [16%]	37 [32%]	44 [27%]	12 [8%]	**19 (11; 27)%**†	**16 (3; 30)%**‖	0.55

Definition of abbreviations: Δ (95% CI) = difference in mean or proportion between groups, with 95% confidence interval; BD = bronchodilator; BPD = bronchopulmonary dysplasia; EP = extremely preterm; $zFEV_1$ = FEV_1 z-score; $FEF_{25–75}$ = forced expiratory flow over the middle half of the FVC; $zFEF_{25–75}$ = $FEF_{25–75}$ (z-score); $zFEV_1$/FVC = FEV_1/FVC (z-score); zFVC = FVC (z-score).

Results are expressed as mean (SD) or n [%]. Boldface entries indicate significance.

* Sidak's *P* value: adjusted for the three comparisons. When BPD versus no BPD in the children born EP were adjusted for the three comparisons, the *P* values remained in the same categories with the exception of FEV_1/FVC (z-score), which had a *P* value of 0.053. Given the large numbers and greater magnitude of difference in all lung function parameters between BPD and Classmates, these differences were all highly significant but, because of space constraints, are not displayed .

† $P < 0.001$.

‡ Results are expressed as z-scores (23), which adjust for sex, height, and age. %pred = percentage of predicted value, based on Stanojevic and colleagues (23).

§ $P < 0.01$.

‖ $P < 0.05$.

only partially reversible (Table 3). A positive bronchodilator response (BDR), as indicated by a within-subject increase in FEV_1 by more than 12% compared with baseline (24), occurred more frequently in children born EP (27%) than in classmates (8%), and in children born EP with prior BPD (32%) than in those without (16%) (Figures 3C and E1). Among those born EP with prior BPD, both baseline and postbronchodilator spirometry outcomes were significantly lower in those with current asthma whereas there were no differences in lung function according to asthma status in either classroom control subjects or those born EP but without BPD. Among those with complete data, only 17 of 37 (46%) of children born EP with both abnormal lung function and increased BDR had received any respiratory medication over the past 12 months (Table E4 and Figure E2).

Determinants of Lung Function in Children Born EP: Univariable Analysis

Ethnicity and sex. FEV_1 was lower among children of nonwhite mothers (n = 31) by, on average, 0.7 (95% CI: 0.2, 1.2; $P = 0.003$) z-scores. By contrast, ethnic origin was not associated with either FEF% or FEV_1/FVC. The magnitude of differences in lung function between children born EP and classmates or between those with or without BPD was similar whether based on the entire cohort or limited to children of white mothers (data not shown). After adjusting for sex by using z-scores (23), there was no further impact of sex on lung function results in either classmates or children born EP.

Maternal and perinatal factors. Associations between lung function at 11 years and the factors summarized in Table 1 were investigated. With the exception of BPD, which had a detrimental impact on all spirometry outcomes, and "duration of postnatal steroids," which was associated with a mean reduction of 0.07 z-score per week of treatment (95% CI: −0.13, –0.02; $P = 0.01$; Table E3), none of the perinatal or maternal factors was associated with spirometric lung function at 11 years.

Respiratory morbidity and current exposures. Associations between lung function at 11 years and characteristics at time of testing (Table 2) were also investigated. On univariate analysis, current asthma and recent asthma medication were negatively associated with all baseline spirometry outcomes (Table E3) but not with postbronchodilator lung function (data not shown). The effect of having asthma on z-score FEV_1 ($zFEV_1$) was, however, significant only in those with BPD, deficits in $zFEV_1$ on univariate analysis being −0.21 (−0.69, 0.27), −0.35 (−1.25, 0.56), and −0.74 (−1.19, –0.30) for classmates, children born EP without BPD, and children born EP with BPD, respectively (*see* Table E3 for details of univariable analysis). The impact of EP delivery on lung function at 11 years was similar when analysis was restricted to those without prior asthma, $zFEV_1$ being −0.9 (−1.3, −0.4) ($P < 0.001$) lower in children born EP without BPD and –1.5 (−1.8; −1.2) ($P < 0.001$) lower in children born EP with BPD when compared with nonasthmatic classroom control subjects. A similar pattern was found with $FEF_{25–75}$ z-score ($zFEF_{25–75}$) results.

"Wheeze after exercise" and "nocturnal wheeze affecting sleep" were negatively associated with FEV_1 but not with FEF% or FEV_1/FVC. Lung function was not associated with any child's growth centiles, current smoke exposure, family history of atopy, socioeconomic status, or maternal education (Table E3).

Of the 124 children born EP with prior BPD who returned questionnaire data, 33 (27%) had both abnormal baseline spirometry and a positive BDR, of whom only 19 (58%) had received any medication in the past 12 months, despite a high prevalence of symptoms (Figures E2 and E3, and Table E4). By contrast, only 4 of 52 children born EP without prior BPD who returned the questionnaire had abnormal spirometry *and* a pos-

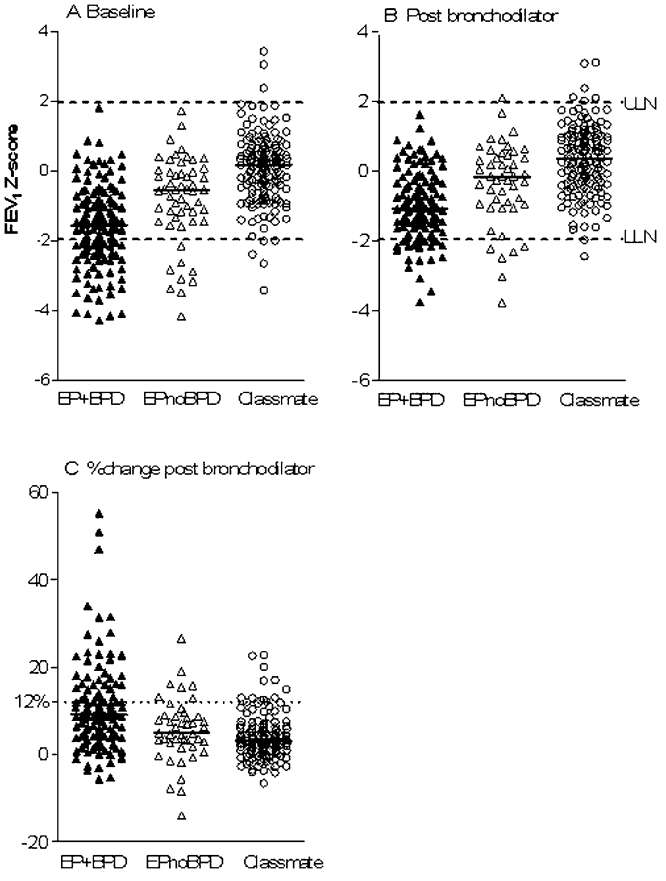

Figure 3. Pre- and postbronchodilator responsiveness according to diagnostic group. Similar changes were observed for forced expiratory flows. BPD = bronchopulmonary dysplasia; EP = extremely premature.

itive BDR, and all but one of these was being treated. Of the 15 children born EP with a diagnosis of asthma plus medication in the past 12 months *and* a positive BDR, 12 (80%) were symptomatic. By contrast, although 15 of 18 (83%) children born EP without a previous diagnosis of asthma but with a positive BDR had abnormal baseline spirometry, only 2 (11%) were symptomatic.

Determinants of Lung Function in Children Born EP: Multivariable Analysis

On multivariable analysis, after adjusting for all significant variables shown in Table 4, being born EP was associated with significant reductions of 0.8 z-score for FEV_1, 0.9 z-score for $FEF_{25–75}$, and 0.7 z-score for FEV_1/FVC (Table 4). For those with prior BPD, there was a further significant reduction of 0.7 z-score for FEV_1, 0.6 z-score for $FEF_{25–75}$, and 0.5 z-score for FEV_1/FVC. Additional reductions of 0.9 z-score for FEV_1 and 0.7 z-score for $FEF_{25–75}$ were observed in those with prior BPD who had received β-agonists within the last 12 months (Table 4). Thus, in a child born EP with prior BPD who was currently receiving β-agonists for asthma, FEV_1 was reduced on average by 2.4 z-scores and $FEF_{25–75}$ by 2.2 z-scores when compared with classmate control subjects, which equates to reductions of 28 and 47%, respectively, if expressed as a percentage of the predicted value (23). "Asthma ever" was associated with a further mean reduction of 0.4 z-score for FEV_1/FVC (Table 4). No other birth, neonatal, or 11-year factors were associated with baseline or postbronchodilator spirometric outcomes. z-scores for peak expiratory flow at 6 years were strongly and independently associated with all these spirometry outcomes ($P < 0.001$ for each). The association with FEV_1 can be seen in Figure E4.

DISCUSSION

When compared with classmates, persistent respiratory morbidity, deficits in baseline lung function, and increased bronchodilator response were observed at 11 years of age in a geographically based cohort of children born before 25^{+6} weeks of gestation. These changes were most marked among extremely preterm children with prior BPD (71% of entire cohort), particularly those receiving current asthma medication, whereas respiratory outcome of survivors of EP birth who do not develop BPD is encouraging. Evidence of increased respiratory morbidity and airflow obstruction has been reported at 6 years of age in surviving EPICure study members (13), and the current study demonstrates that such changes persist into middle childhood. Despite being symptomatic and/or having both diminished lung function and increased bronchial responsiveness, a significant proportion of the children with prior BPD were not receiving any respiratory medication. These results indicate that despite improvements in obstetric and neonatal care that have resulted in increased survival of extremely preterm infants, airway obstruction remains a common long-term outcome.

Although the magnitude of changes observed in this study is somewhat greater than that reported by others, reflecting the extreme prematurity of this cohort, our findings are in keeping with reports regarding long-term respiratory follow-up of graduates of modern neonatal intensive care, whereby persistent functional and structural alterations of the respiratory system have been observed throughout childhood (25–29). Indeed, preterm children born in different eras of neonatology appear to have similar long-term decrements in lung function (12, 30). The availability of improved pediatric reference equations for spirometry (22, 23) enabled us to extend our analyses beyond the group comparisons commonly reported in previous studies, to investigate the extent to which abnormal lung function in individual children relates to current symptoms and treatment.

Although the duration of postnatal steroids was significantly associated with FEV_1 on univariate analysis (Table E3), postnatal steroid therapy is more likely to have been used in infants with persistent neonatal respiratory problems (and hence a diagnosis of BPD). Once adjusted for BPD in multivariate analysis, neither steroid treatment nor its duration remained significantly associated with any lung function indices at 11 years, and therefore no causal association can be implied.

The magnitude of reduction in lung function among nonwhite participants in the current study is in keeping with well-recognized ethnic differences in spirometric outcomes, which appear to be largely associated with differences in body proportions (31). In contrast to the increased vulnerability of boys to developing BPD and reduced lung function during infancy and early childhood (32, 33), we found no sex differences in either lung function z-scores or respiratory morbidity at 11 years of age. This probably reflects the fact that the male disadvantage in respiratory function decreases with growth and is ultimately reversed, with females tending to be more at risk for respiratory illnesses such as asthma post-puberty (34, 35). Neither maternal smoking in pregnancy nor current exposure to environmental tobacco smoke was associated with any of the lung function measurements. Similar findings had been previously reported in respiratory follow-up of very low birthweight children in mid-childhood (36–38). This may suggest that susceptibility to pulmonary injury from

TABLE 4. INDEPENDENT ASSOCIATIONS BETWEEN LUNG FUNCTION OUTCOMES WITH EXTREMELY PRETERM BIRTH AND OTHER FACTORS

	$zFEV_1$*	$zFEF_{25-75}$*	$zFEV_1/FVC$*	$zFEV_1$ Change Post-BDR*
n (adjusted R^2%)	**296 (40.5%)**	**312 (33.6%)**	**314 (20.8%)**	**285 (11.5%)**
Constant	−0.51 (−0.86; −0.15)	−0.50 (−0.69; −0.32)	−0.09 (−0.28; 0.11)	0.30 (0.22; 0.38)
EP†	**−0.81 (−1.15; −0.47)**‡	**−0.88 (−1.26; −0.50)**‡	**−0.70 (−1.06; −0.33)**‡	NA
BPD†	**−0.67 (−1.03; −0.31)**‡	**−0.58 (−0.99; −0.18)**§	**−0.45 (−0.82; −0.07)**‖	**0.30 (0.19; 0.42)**‡
White mother	**0.66 (0.31; 1.00)**‡	NA	NA	NA
Height (z-score)	NA	**0.14 (0.02; 0.27)**‖	NA	NA
Ever diagnosed with asthma (by 11 yr)¶	NA	NA	**−0.38 (−0.66; −0.11)**§	**0.12 (0.01; 0.24)**‖
BPD + β-agonist (int)†	**−0.90 (−1.34; −0.45)**‡	**−0.73 (−1.22; −0.23)**§	NA	NA
Other variables of interest (respiratory symptoms and medication in last 12 mo) not significantly associated with lung function outcomes after adjusting for previous variables				
Wheeze	−0.08 (−0.43; 0.26)	0.06 (−0.32; 0.44)	0.04 (−0.34; 0.41)	−0.01 (−0.17; 0.15)
Wheeze after exercise	−0.24 (−0.61; 0.14)	−0.14 (−0.55; 0.28)	0.05 (−0.37; 0.47)	−0.05 (−0.23; 0.12)
Night cough	−0.02 (−0.37; 0.32)	−0.12 (−0.50; 0.26)	−0.11 (−0.49; 0.26)	−0.02 (−0.18; 0.14)
Steroid medication	0.04 (−0.37; 0.46)	0.01 (−0.46; 0.47)	−0.15 (−0.58; 0.28)	−0.06 (−0.24; 0.13)

Definition of abbreviations: BDR = bronchodilator; BPD = bronchopulmonary dysplasia; EP = extremely preterm; int = interaction arm; NA = not applicable (factor not included in the model as it was not significantly associated with the lung function variable); $zFEF_{25-75}$ = forced expiratory flow over the middle half of the FVC (z-score); $zFEV_1$ = FEV_1 (z-score).

Data are presented as coefficients (95% CI). Boldface entries indicate significance.

* Results are expressed as z-scores (23), which adjust for sex, height, and age.

† Interpretation of EP and BPD coefficients in these multiple regressions where all children with BPD are EP (extremely preterm). The coefficients for EP are the mean effect for children born EP without BPD compared with control children assuming other significant factors are similar. Where BPD and the interaction term of BPD and β-agonists are independently significant, the coefficient for BPD children is the effect of being BPD without β-agonists compared with children born EP without BPD, and the coefficient of BPD and β-agonist is the effect of BPD children taking β-agonist compared with the other BPD children. Where the interaction of BPD and β-agonist is not in the model, the BPD coefficient is the additional effect of being BPD compared with children born EP without BPD. Hence the BPD children taking β-agonists have a mean FEV_1 z-score (0.81 + 0.67 + 0.90) = 2.38 SD lower than control children assuming the same ethnicity of their mothers.

‡ $P < 0.001$.

§ $P < 0.01$.

‖ $P < 0.05$.

¶ Similar associations on all spirometric indices were found when "Current asthma or symptomatic in the last 12 months" was used instead.

cigarette smoke exposure may have different etiologies in those surviving EP birth compared with term control subjects. However, within our study, after adjustment for BPD, both maternal smoking in pregnancy and current environmental tobacco smoke exposure were marginally associated with wheeze in the past 12 months (odds ratio, 1.90 [1.00; 3.61]; $P = 0.050$ and odds ratio, 1.68 [0.93; 3.07]; $P = 0.090$, respectively).

The strengths of this study include the geographical basis of the population and the fact that those assessed at 11 years were representative of the entire cohort. Those in whom spirometry could not be successfully obtained at the 11-year assessment tended to be more severely disabled and to have had a stormier neonatal course suggesting that, if anything, our results may slightly underestimate the true degree of respiratory dysfunction in this population. The use of a contemporary control group in this type of study is mandatory and was achieved with extremely close matching for age, sex, and ethnic background. Further minimization of any bias between the groups was achieved by randomly selecting one of several potentially eligible control subjects identified by the head teacher. By not excluding children with asthma from our control group, we were able to ascertain the independent effect of prematurity over and above that of asthma. We were initially concerned that the prevalence of asthma in our control group might be elevated because of parents being more willing to participate if there were prior respiratory concerns for their child. However, the 13% prevalence of current asthma observed in the classmate control subjects was similar to that quoted for this age group in the United Kingdom (39) and, in contrast to the EP group, we found no significant difference in lung function between control subjects with and without asthma.

Our study was also strengthened by the strict quality control imposed for all spirometric measurements (20), and by the fact that results were analyzed by pediatric respiratory physiologists completely masked both to birth status and current clinical status of the subjects. The all-age reference equations for spirometry (23) proved to be appropriate for our population, as indicated by mean (SD) z-scores for FEV_1, FVC, and FEV_1/FVC ratio that approximated 0 (1) in the classmate control subjects. This increased the confidence with which we could use the lower limit of normal (LLN) of −1.96 z-scores from these equations to identify children with abnormal lung function.

The major weakness of this respiratory follow-up is that, because children were recruited from a multitude of hospitals with subsequent transfer out to an extended network of neonatal units, we were unable to relate respiratory morbidity and lung function to severity of neonatal disease expressed as a continuum (e.g., total days of supplemental oxygen or ventilatory support) (40, 41). The potential weaknesses of classifying infants simply on the basis of ventilatory requirements at given time points has been extensively discussed (11, 42), and there has been a call for more physiological definitions of oxygen requirements to be used when classifying infants as having BPD (43–46). Nevertheless, results from this study demonstrate that despite its crudeness, the use of a pragmatic definition for BPD based on supplemental oxygen at 36 weeks PMA remains strongly predictive of subsequent outcome.

In theory, preterm survivors of modern neonatal care, who have been treated with antenatal steroids and postnatal surfactant and subjected to far gentler ventilatory regimens than in the past, should have far less evidence of airway injury than their predecessors. Indeed, histological evidence suggests that "new BPD" is characterized by disruption of alveolar development with fewer, larger alveoli but far less airway fibrosis than in the past (12, 44, 47). However, results from this and related studies (8, 10, 12, 26, 28) demonstrate that deficits in FEV_1

during childhood and early adulthood have remained remarkably constant over the past 30 years among survivors of BPD, albeit manifesting in an increasingly immature population. The persistence of airway obstruction in these children is likely multifactorial in nature, potentially reflecting the impact of preterm birth per se (48, 49), the vulnerability of the extremely immature lung even to low ventilatory pressures or oxygen concentrations, increased airway compliance and/or disruption of the collagen infrastructure with fewer alveolar attachments and decreased pulmonary elastic recoil (44, 50–52), and/or reprogramming of key innate immunoregulatory pathways in the lung in response to neonatal hyperoxia (53). Despite the marked differences in subsequent outcome, prenatal and neonatal characteristics were remarkably similar between those who did and did not develop BPD, possibly reflecting variance in genetic susceptibility to BPD (54, 55).

The implications of the potential undertreatment of lung disease in children born preterm have been discussed (29, 56). Although treatment may not relieve all symptoms or normalize lung function completely, a sizeable proportion of children born EP in this study may have benefited from closer surveillance and medication. Despite altered breathing patterns and reduced oxygen capacity at peak exercise, we did not find any difference in physical activity levels at 11 years between children born EP and classmate control subjects, primarily because neither group was undertaking sufficient exercise (57). With increasing age and hence growth of the respiratory system during childhood, respiratory symptoms of cough and wheeze after preterm birth tend to diminish, but deficits of lung function remain. Although Narang and colleagues reported an encouraging improvement in lung function in those born preterm by early adulthood (58), this is in contrast to several other reports (7, 8, 10, 28). Discrepancies may reflect differences in population, attrition, choice of reference equations, and statistical methods. Given that airway function tracks though life (6, 59, 60), those with reduced lung function in childhood are likely to retain this position through to adulthood and are thus likely to be among the first to reach a critical threshold for the onset of chronic obstructive pulmonary disease with subsequent ageing. This situation is likely to be exacerbated by the high prevalence of active smoking (10, 58, 61) and reduced exercise capacity (26, 57) that has been reported in ex-preterm adolescents and adults.

In conclusion, children born extremely preterm remain at high risk for respiratory morbidity, airway obstruction, and increased bronchial responsiveness at 11 years of age. Deficits in lung function and increased bronchial responsiveness persist in many children born EP despite current treatment. There are strong economic incentives for secondary prevention of disability associated with preterm birth, including risk factors for early-onset chronic obstructive pulmonary disease during adulthood. Preventive measures should include minimizing lung injury before and after delivery (44), long-term surveillance and appropriate treatment throughout childhood, and health education for parents and children to promote physical activity and deter smoking. With improved survival of extremely preterm subjects, it will become increasingly important for adult chest physicians to inquire about the neonatal history of their patients.

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