Eur Respir J 2011; 37: 1199–1207
DOI: 10.1183/09031936.00071110

Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age

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ABSTRACT: Advances in neonatal care have resulted in increased survival of children born extremely pre-term (EP). Nevertheless the incidence of bronchopulmonary dysplasia and long-term respiratory morbidity remains high. We investigated the nature of pathophysiological changes at 11 yrs of age to ascertain whether respiratory morbidity in EP children primarily reflects alterations in the lung periphery or more centralised airway function in this population.

Spirometry, plethysmography, diffusing capacity, exhaled nitric oxide, multiple-breath washout, skin tests and methacholine challenge were used during laboratory-based assessments in a subgroup of the 1995 EPICure cohort and in controls.

Results were obtained in 49 EP and 52 control children. Lung function abnormalities were found in 78% of EP children, with evidence of airway obstruction, ventilation inhomogeneity, gas trapping and airway hyperresponsiveness. Levels of atopy and exhaled nitric oxide were similar between the groups. Prior wheeze was associated with significant reductions in forced flows and volumes. By contrast, abnormalities of the lung periphery appear to be mediated primarily through EP birth *per se*.

The prevalence of lung function abnormalities, which is largely obstructive in nature and likely to have long-term implications, remains high among 11-yr-old children born EP. Spirometry proved an effective means of detecting these persistent abnormalities.

KEYWORDS: Bronchopulmonary dysplasia, child, extreme prematurity, respiratory follow-up

Advances in neonatal care over the past few decades have resulted in increasing survival of babies born less than 25 completed weeks of gestation (extremely pre-term (EP)) [1]. Nevertheless, the prevalence of bronchopulmonary dysplasia (BPD), remains high in such infants [2], and our understanding of the implications of EP birth and any subsequent lung injury on lifelong lung function (LF) remains limited.

A diagnosis of BPD was initially limited to early recipients of neonatal mechanical ventilation; the associated pulmonary pathology being primarily attributed to iatrogenic damage from barotrauma and oxygen toxicity during the late saccular–early alveolar phase of lung development, with functional abnormalities persisting to adulthood [2]. Computerised tomography has revealed a high incidence of structural alterations in these early survivors of BPD [3]. By contrast, since widespread introduction of antenatal corticosteroids and neonatal surfactant therapy in the early 1990s, BPD is now largely restricted to more immature infants delivered during the early saccular phase and ''new'' BPD has been reported to be characterised by disruption of alveolar development, with reduced alveolar number and enlarged airspaces, but less pulmonary fibrosis and lung injury than previously described [4]. Nevertheless, the degree of persistent airway obstruction, as reflected by spirometry, has remained remarkably constant [2, 5, 6]. Given that diminished forced expiratory volume in 1 s (FEV_1) is a marker of all-cause premature mortality [7] and that those with low LF at initial assessment tend to remain low at subsequent assessments and *vice versa* [8], there is concern that survivors of preterm birth may be at risk of early onset chronic obstructive pulmonary disease in adulthood [3].

Although a wide range of tests have been used to assess cardio-respiratory function in survivors of

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Received:
May 06 2010
Accepted after revision:
Sept 01 2010
First published online:
Oct 14 2010

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

This article has supplementary material available from www.erj.ersjournals.com
A press release for this article is available from www.erj.ersjournals.com/site/misc/presspack.xhtml

pre-term birth [2, 5, 6, 9, 10], relatively few studies have included the full spectrum of available techniques and spirometric parameters remain the most common outcomes, as used during recent school assessments of survivors of the EPICure cohort at 11 yrs of age [11]. In that study, 56% of children born before $25w^{+6}$ gestation were found to have abnormal baseline spirometry, 27% had a positive bronchodilator response and 25% a diagnosis of asthma (twice that observed in classmates). Apart from BPD, which had a detrimental impact on all spirometric outcomes, and duration of post-natal steroids, none of the perinatal or maternal factors were associated with spirometric lung function at 11 yrs of age [11]. However, if the underlying pathophysiology of new BPD primarily reflects peripheral lung disease, a substantial proportion of functional abnormalities could potentially go undetected in EP children, if assessments are limited to spirometry [12, 13].

The aim of our study was to ascertain whether ongoing respiratory morbidity in EP children born in the 1990s primarily reflects alterations in the lung periphery, as assessed using multiple breath inert gas washout, plethysmography (partitioned lung volumes) and diffusion capacity or more centralised airway function (spirometry and airway resistance), and whether there was any evidence of increased eosinophilic airway inflammation (*i.e.* elevated levels of exhaled nitric oxide fraction (F_{ENO}) in such children). We hypothesised that: 1) LF would be diminished at 11 yrs of age in children born EP when compared with full-term controls; 2) use of spirometry alone would underestimate the true degree of morbidity; and 3) changes in LF would not be accompanied by increased airway inflammation. None of the results presented in this study have been reported previously, except as abstracts.

METHODS

EPICure is a population-based study of all births at $\leqslant 25^{+6}$ weeks of gestation in the UK and Republic of Ireland between March and December 1995 [11, 14]. The laboratory-based investigation described below was part of an extensive assessment performed at 11 yrs of age, which included spirometric measurements in the entire school cohort [11]. An age, sex and ethnic-group matched classmate for each EP child was sought. Classmates were excluded if they had been born at <37 weeks gestational age, had been previously hospitalised for a respiratory complaint or had suffered from TB, pneumonia or whooping cough. Asthma and atopy were not exclusion criteria. Asthma classification was based on parental report of doctor-diagnosed asthma. Our operational definition of ''current asthma'' was use of asthma medication or wheeze in the past 12 months by children with doctor-diagnosed asthma or use of asthma medication and wheeze in the past 12 months even if no prior diagnosis of asthma had been reported.

Index and control children living within reasonable travelling distance of London (UK) were recruited for extensive respiratory assessments at the UCL, Institute of Child Health (ICH; London, UK) (fig. 1). The study was approved by the ICH Research Ethics Committee. Parental written consent and assent from each child were obtained.

Lung function tests (LFTs) were performed according to American Thoracic Society/European Respiratory Society standards with investigators blinded to birth status. Assessments

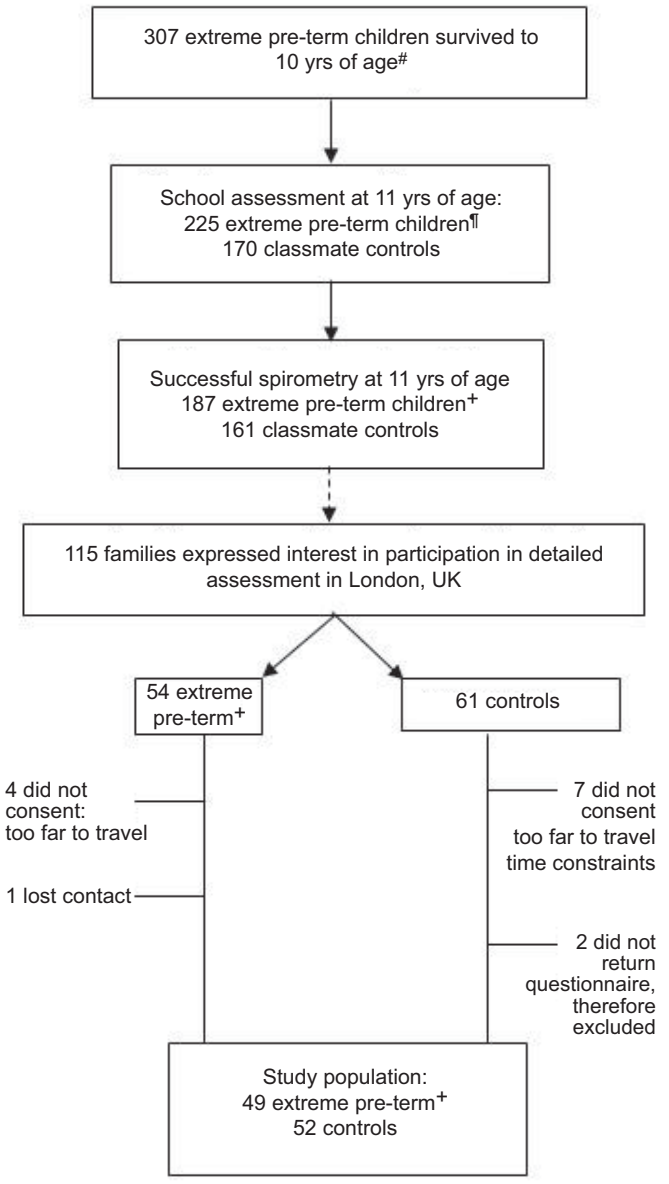

FIGURE 1. Study population: subject recruitment and accrual. #: includes one child not identified in 1995, but eligible to be in the 1995 EPICure cohort; ¶: includes six children born in January 1996 who were recruited to the EPICure study but not included in the cohort analyses, as they were born after December 31, 1995; +: including two out of the six children in born in January 1996.

included spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide, F_{ENO}, multiple-breath inert-gas washout to assess ventilation inhomogeneity, skin allergy test and methacholine challenge (refer to supplementary data). Doctor-diagnosed asthma, medication use and current respiratory symptoms including wheeze were determined by parental response to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Each child was requested to rate his/her own pubertal status [15]. This extensive study protocol was performed in two laboratory sessions within a 3-week interval.

Power of study

A sample size of 50 children in each group would provide at least 80% power to detect differences in lung function >0.57SD between index and control groups, at the 5% significance level.

Data management and statistical analysis

Codes regarding birth status were not released until lung function data collection and analysis had been completed. Neonatal data [16] were used to identify the EP children who had had BPD, defined as those still receiving supplemental oxygen at 36 weeks post-menstrual age [2].

With the exception of the Lung Clearance Index (LCI), which, in health, is relatively constant throughout life [12], lung function results were expressed as Z-scores to adjust for height, sex and age [17–20]. Results were classified as: normal when total lung capacity (TLC), forced vital capacity (FVC), FEV_1 and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) all fell within the normal range; obstructive, when FEV_1/FVC was less than the lower limit of normal (LLN) and/or residual volume (RV)/TLC was greater than upper limit of normal; or restrictive when TLC and/or FVC were less than LLN or FEV_1 and/or $FEF_{25–75\%}$ was reduced in the presence of a normal FEV_1/FVC [21]. The extent to which extreme prematurity (EP) and respiratory morbidity were associated with lung function at 11 yrs of age was examined using multiple linear regression (MLR) (SPSS version 15.0; SPSS, Chicago, IL, USA). Data management was undertaken using Re-Base software (J7 Group, Rickmansworth, UK).

RESULTS

Population characteristics

Successful lung function assessments and completed questionnaires were obtained from 49 EP and 52 classroom controls (fig. 1), recruited from 20 out of 39 counties in England, UK. No potential controls had to be excluded due to prior hospitalisation or serious respiratory morbidity (see exclusion criteria). Table 1 summarises group characteristics according to birth status.

How representative was the study population?

With the exception of exposure to maternal smoking during pregnancy, which was higher among children who were only tested in school, the subgroup of EP children attending the extended respiratory assessments at ICH was representative of the entire cohort tested in school with respect to neonatal and maternal characteristics, neonatal history, respiratory morbidity and spirometry (table 2). Similarly there was no significant difference between the control group assessed in the laboratory and those assessed at school (data not shown). The ethnic mix of the subgroup of EP children attending laboratory testing was representative of those tested at school. However, although classroom controls were well matched for ethnic group with the EP children during school assessments of the entire cohort [15], slightly fewer non-White controls attended the laboratory assessments (table 1).

At time of the test, EP children were shorter and lighter than controls (table 3). After adjustment for prematurity, age at test was similar between EP children and controls (10.9 *versus* 11.0 yrs respectively), while anthropometric differences remained highly

TABLE 1 Group characteristics of extreme pre-term (EP) children with and without prior bronchopulmonary dysplasia (BPD) compared to classmate controls

	EP with BPD	EP without BPD	All EP	Control	95% CI of difference (EP–control)
Neonatal characteristics					
Subjects n	34	15	49	52	
Boys	35	40	37	37	-18–18
Gestational age weeks	24.8±0.8	25.0±0.6	24.9±0.7	40.1±1.6	-15.7–14.7***
Birth weight kg	0.740±0.101	0.762±0.093	0.747±0.098	3.361±0.450	-2.75–2.48***
Birth weight Z-score#	-0.06±0.71	-0.03±0.80	-0.05±0.74	-0.24±1.14	-0.57–0.20
BPD	100	0	69		
Post-natal steroids	70	67	69		
Maternal/family details					
Antenatal steroids	85	87	86		
PROM	15	31	19		
Chorioamnionitis	21	39	26		
Smoking in pregnancy	25	14	22	22	-16–17
Current smoking exposure	18	7	15	26	-27–4
Maternal asthma	12	0	8	12	-16–9
FH of asthma	38	33	37	33	-14–22
Maternal ethnicity White	74	87	78	94	-30–3*
Maternal education after age 16 yrs	52	57	53	73	-38–0*
Non-manual occupation¶	74	79	76	69	-10–29

Data presented as % or mean±SD, unless otherwise indicated. BPD is defined as oxygen given at or beyond 36 weeks post-menstrual age. PROM: prolonged rupture of membranes (>24 h). *: $p<0.05$; **: $p<0.01$; ***: $p<0.0001$. #: according to Child Growth Foundation algorithms [22]; ¶: classification based on either parent with a non-manual occupation.

TABLE 2 Comparison of children who did and did not attend the respiratory laboratory at the Institute of Child Health (ICH; London, UK) for extended assessments

	EP		95% CI of difference (school–ICH)
	School tested	ICH tested	
Subjects (% males)	140 (44)	49 (37)	-9–22
Gestational age weeks	25.0±0.7	24.9±0.7	-0.13–0.35
Birth weight kg	0.749±0.126	0.747±0.098	-0.033–0.037
Birth weight Z-score#	-0.17±0.78	-0.05±0.73	-0.36–0.13
BPD	71	69	-12–16
Received ANS	80	86	-16–8
History of chorioamnionitis	22	26	-18–10
Wheeze in last 12 months	23	22	-13–14
Current asthma¶	26	27	-16–13
Ethnicity White	84	78	-8–19
Smoking in pregnancy	39	22	-31–2*
FEV_1 Z-score+	-1.4±1.2	-1.6±1.1	-0.3–0.5
$FEF_{25–75\%}$ Z-score+	-2.0±1.3	-2.0±1.2	-0.4–0.4

Data presented as mean±SD or %, unless otherwise stated. BPD: bronchopulmonary dysplasia, defined as oxygen given at or beyond 36 weeks post-menstrual age; ANS: antenatal steroid; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow at 25–75% forced vital capacity. Comparison of FEV_1 and $FEF_{25–75\%}$ Z-scores was undertaken by using data obtained from both groups during school assessments. *: $p<0.05$. #: according to [22]; ¶: defined as currently symptomatic and/or with doctor-diagnosis of asthma and on medication during past 12 months; +: according to [20].

significant. A similar proportion of EP and controls had reached the onset of puberty at the time of the test.

Prior respiratory morbidity (table 3) was significantly more common in the EP children and both current and inactive asthma were almost twice as frequent than in controls, but there was less difference in atopic status (eczema and/or positive skin test) or prevalence of hayfever (table 3). In the 12 months prior to testing, significantly more EP children with prior BPD were symptomatic (*i.e.* wheezed or had been treated for respiratory illness), although only one child was receiving antibiotics at testing. Incidence of wheeze in the 3-month period preceding LFTs (table 4) was generally similar in EP children without prior BPD to that in controls, except when associated with a cold. In contrast, prior BPD was associated with significantly more recent wheeze, irrespective of how it was categorised (table 4). Wheeze with colds was associated with EP status (OR 8.1, 95% CI 1.7–38.4; p=0.008) and among EP children, prior BPD was associated with shortness of breath during exercise (OR 5.7, 1.4–24.1; p=0.017).

LF results

Effect of extreme prematurity

With the exception of static lung volumes (functional residual capacity, TLC and alveolar volume), significant impairments in all LF variables were found among EP children when compared with controls (table 5, fig. 2), with evidence of airway obstruction (decreased forced expiratory flows and volumes, elevated specific airways resistance), ventilation inhomogeneity, gas trapping (elevated RV/TLC) and airway hyperresponsiveness abnormalities being most marked in EP children with BPD. By contrast, levels of F_{ENO} and incidence of atopy were similar between EP and control children. Details of univariable analysis are presented in table E1 in the supplementary data.

Associations between airway function, extreme prematurity and respiratory morbidity

On multivariable analysis, after adjusting for ethnicity, being born EP was significantly associated with decrements in all LF outcomes, while respiratory morbidity (wheeze ever) was associated with further decrements of central airway function (table 6), but not with markers of more peripheral lung function such as LCI (coefficient 0.2, 95% CI -0.1–0.6; p=0.19), gas trapping (RV/TLC 0.4, 95% CI -0.05–0.8; p=0.08) or diffusing capacity (0.1, 95% CI -0.3–0.5; p=0.69).

Extent to which spirometry identified respiratory abnormalities in EP children

In the EP children, 11 (22%) had no LF abnormalities (although two of these had incomplete tests) and 38 had some LF abnormalities. Spirometry identified 24 (63%) EP children with LF abnormalities, LCI 20 (58%) EP children and sReff 17 (45%) EP children, while a combination of spirometry and sReff identified 30 (79%) out of the 49 EP children with abnormalities.

Of the 47 out of 49 EP children with acceptable spirometry and plethysmography, 21 (45%) exhibited an obstructive pattern, of whom 14 (67%) had a history of wheeze and 10 (48%) a diagnosis of asthma, while only five (11%) had evidence of restrictive lung disease on spirometric criteria (all of whom had a history of wheeze, but only one a diagnosis of asthma). Of these five, technically acceptable results of partitioned lung volumes were only available from two, of whom one had a reduced TLC.

DISCUSSION

This study represents the most extensive respiratory assessments in children of such low gestation to date, and reveals a wide spectrum of functional abnormalities in both the larger airways and lung periphery at 11 yrs of age in children

TABLE 3 Group characteristics of extreme pre-term (EP) children with and without prior bronchopulmonary dysplasia (BPD) compared to classmate controls at 11 yrs of age

	EP with BPD	EP without BPD	All EP	Control	95% CI (EP–control)
Subjects (% boys)	34 (35)	15 (40)	49 (37)	52 (37)	-18–18
Test age yrs	11.2±0.4	11.2±0.5	11.2 (0.4)	11.0±0.5	0.0–0.4*
Height cm	141.5±5.7	143.0±8.5	142.0±6.6	146.1±6.7	-6.7–1.5*
Height Z#	-0.47±0.92	-0.29±1.08	-0.41±0.97	0.35±0.96	-1.14–0.38***
Weight kg	35.5±8.7	38.0±8.8	36.3±8.7	39.8±8.8	-7.04–0.10*
Weight Z#	-0.34±1.19	-0.05±1.42	-0.25±1.26	0.43±1.05	-1.14–0.22**
BMI Z#	-0.13±1.33	0.27±1.12	-0.01±1.27	0.35±1.08	-0.82–0.11
Puberty¶	29	29	29	29	-18–18
Respiratory morbidity					
Bronchiolitis	44	36	42	2	25–54***
Pneumonia+	19	9	17		
Wheeze ever	62	27	51	21	12–48**
Wheeze last 12 months§	29	7	23	10	-2–27
Inactive asthmaf	15	13	14	8	-6–20
Current asthma##	29	20	27	13	-3–28
Hay fever ever	32	33	33	30	-15–20
Eczema ever	41	40	41	33	-11–25
Skin test positive	6	13	9	4	-6–16
Medication in last 12 months					
β-agonist	9 (26)	3 (20)	12 (25)	5 (10)	0–30*
Inhaled steroids	9 (26)	2 (13)	11 (22)	6 (12)	-4–26
Antibiotics	8 (24)	1 (7)	9 (18)	2 (4)	2–28*
Current medication					
β-agonist	8 (24)	1 (7)	9 (18)	4 (8)	-3–24
Inhaled steroids¶¶	3 (9)	2 (13)	5 (10)	4 (8)	-9–15

Data presented as n (%), mean±SD or %, unless otherwise as stated. BMI: body mass index. *: $p<0.05$; **: $p<0.01$; ***: $p<0.0001$. #: according to Child Growth Foundation algorithms [22]; ¶: defined as having reached Tanner Stage 3 in their physical and pubic hair development [15]; +: exclusion criteria for controls; §: detailed description of wheeze 3 months prior to test is given in table 3; f: defined as those who had been diagnosed with asthma by a doctor but not symptomatic over past 12 months; ##: defined as currently symptomatic and/or with doctor diagnosis of asthma and on medication for past 12 months; ¶¶: flixotide, becotide or pulmicort.

born EP. After adjusting for prematurity, prior wheeze was the strongest predictor for decrements in spirometric airway function, while current asthma was associated with significant increases in airways resistance. Had assessments been limited to spirometry, 37% of LF abnormalities would have gone undetected. Nevertheless, spirometry remained the most discriminative test in this population, as well as being the most feasible for use in field studies.

Strengths and limitations

Strengths of this study include the fact that the EP subset who attended laboratory tests were representative of the national cohort [11]. As measurements were limited to children who were sufficiently coordinated to perform the extensive range of laboratory-based tests, findings may underestimate the true extent of lung dysfunction. Investigators were blinded to birth status, and recruitment of a prospective control group that was representative of the local population, including incidence of asthma [23], allowed us to assess the effects of EP birth over and above that of asthma [11]. By categorising functional abnormalities based on limits of normality derived from local healthy controls (supplementary table E2), we avoided potential errors that may occur when relying simply on published reference data (www.growinglungs.org.uk) [6, 24]. A reduction in spirometric parameters among Black and Asian subjects when compared to those of White European descent is well recognised [24], and was confirmed in this study, but differences between groups remained similar whether or not the relatively few non-White children were included in the analyses.

The extensive nature of laboratory assessments, which also included exercise [14] and neuro-sensory testing [25], and the need to travel to central London, limited the sample size and hence the power with which subgroup analyses could be reliably undertaken. Nevertheless, the trends towards increased morbidity and functional deficits in those with prior BPD who participated in the laboratory assessments mirrored the significant changes found in the entire cohort [11]. As reported previously [11], maternal smoking in pregnancy was not associated with changes in any LF outcome, with the EP children possibly having been delivered before the anticipated adverse effects occurred. We could not examine the potential impact of intrauterine growth retardation in this population [10] due to extremely low survival of such infants at these gestations.

TABLE 4 Pattern of wheeze in the past 3 months

	EP with BPD	EP without BPD	Control
Subjects n	34	15	34
Wheeze during the day	24	7	8
Wheeze with colds	29**	13	4
Wheeze without colds	15	7	6
Wheeze with exercise	26*	7	6
SOB with exercise	59**	20	21#

Data are presented as %, unless otherwise stated. EP: extreme pre-term; BDP: bronchopulmonary dysplasia; SOB: shortness of breath. Exact test for comparison between the three subgroups: *: $p<0.05$; **: $p<0.01$. #: objective assessments of physical activity showed that all children undertook considerably less physical activity than current recommendations of at least 60 min of moderate-vigorous physical activity per day which may explain why 21% of controls experience SOB with exercise.

Respiratory morbidity

While 29% of children with prior BPD had doctor-diagnosed asthma and recent asthma medication, there was no increase in either the prevalence of atopy or levels of F_{eNO} in these children, suggesting a different underlying pathophysiology to that usually observed in childhood asthma [26]. The fact that the airways obstruction observed in these children was only partially reversible raises the issue as to whether these children have been correctly diagnosed, or optimally treated [11]. Consistent with previous reports [9, 10], airway responsiveness was increased among the EP children, although had we not undertaken identical challenges in prospective controls the extent of such hyperresponsiveness would have been overestimated (refer to supplementary data). Children with BPD are known to be at increased risk for symptomatic respiratory illnesses in infancy and childhood. This may largely reflect the effects of diminished airway calibre, as indicated by the increased sReff and decreased expiratory flows and volumes found in this population, such that wheeze can be invoked with minimal further airway narrowing. However, neonatal hyperoxia may also exacerbate inflammatory responses, leading to long-term disruption of key innate immuno-regulatory pathways in such subjects [27].

Nature of underlying pathophysiology

Initial descriptions of new BPD pathology suggested that EP delivery could result in an ''arrest'' of alveolar development [2] but later reviews suggest impaired alveolisation [4], since there is evidence of continued post-natal alveolar formation despite early lung insults [28]. The reduced gas mixing efficiency (elevated LCI) observed in EP children may reflect some parenchymal or small airway changes, secondary to disruption of the interstitial collagen network that has been reported following neonatal positive pressure ventilation [29]. While the LCI has been shown to be an early indicator of airway disease

TABLE 5 Lung function results in extreme pre-term (EP) children compared to classmate controls at 11 yrs of age

	EP with BPD	EP without BPD	All EP	Control (All)	95% CI of difference (EP–control)
Subjects n	34	15	49	52	
zFEV$_1$#	-1.76±1.02	-1.08±1.29	-1.55±1.14	-0.02±0.90	**-1.94–1.10*** **
zFEF$_{25–75\%}$#	-2.18±1.07	-1.55±1.38	-1.98±1.19	-0.59±1.02	**-1.85–0.94*** **
zFVC#	-1.02±0.85	-0.43±1.26	-0.84±1.02	0.22±0.97	**-1.46–0.65*** **
zFEV$_1$/FVC#	-1.27±0.99	-0.98±1.23	-1.17±1.07	-0.40±0.91	**-1.18–0.37*** **
zRV¶	1.84±1.30	1.25±0.57	1.63±1.13	1.17±0.71	**0.05–0.88***
zTLC¶	0.16±0.41	0.41±0.57	0.25±0.66	0.31±0.56	-0.29–0.17
zRV/TLC+	1.26±1.07	0.86±0.86	1.12±1.0	0.44±0.80	**0.27–1.08****
zFRC$_{pleth}$¶	0.47±1.13	0.17±0.72	0.36±1.0	0.16±0.89	-0.20–0.60
FRC$_{pleth-MBW}$ mL·kg^{-1}	12.7±8.8	12.0±6.3	12.4±7.9	8.5±5.3	**0.8–7.1***
ZsReff§	1.11±0.91	0.70±0.76	0.98±0.88	0.42±0.73	**0.24–0.88****
LCI	7.4±1.0	7.1±0.7	7.3±0.9	6.5±0.4	**0.46–1.10*** **
z$D_{L,CO}$¶	-1.08±0.90	-1.40±0.91	-1.20±0.91	-0.42±0.91	**-1.19–0.37***
zV_A¶	1.28±1.24	1.36±0.68	1.31±1.05	1.41±1.17	-0.60–0.41
z$D_{L,CO}/V_A$¶	-2.15±0.80	-2.58±0.67	-2.31±0.77	-1.69±0.78	**-0.97–0.27****
PC$_{20}$ mg·mL^{-1}	0.41±2.90	0.39±2.64	0.41±2.75	1.72±5.31	**0.12–0.46**
F_{eNO} ppb	4.6±2.0	5.5±2.5	4.9±2.2	5.9±2.1	0.6–1.15

Data expressed as mean±SD Z-scores, unless otherwise stated. Data for provocative dose causing a 20% fall in forced expiratory volume in 1 s (FEV_1) (PC_{20}) and exhaled nitric oxide fraction (F_{eNO}) are presented as geometric mean±SD and 95% CI of the geometric mean were calculated from the Log_e of PC_{20} and exhaled NO. BPD: bronchopulmonary dysplasia; $FEF_{25–75\%}$: forced expiratory flow between 25–75% forced vital capacity (FVC); RV: residual volume; TLC: total lung capacity; FRC_{pleth}: plethysmographic functional residual capacity (FRC); $FRC_{pleth-MBW}$: difference in FRC measured using plethysmography and multiple breath washout; sReff: specific effective airway resistance; LCI: lung clearance index; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume. 95% CI of difference in bold denote statistically significant difference. #: according to [20]; ¶: according to [18]; +: according to [19]; §: according to [17]. *: $p<0.05$; **: $p<0.01$; ***: $p<0.0001$.

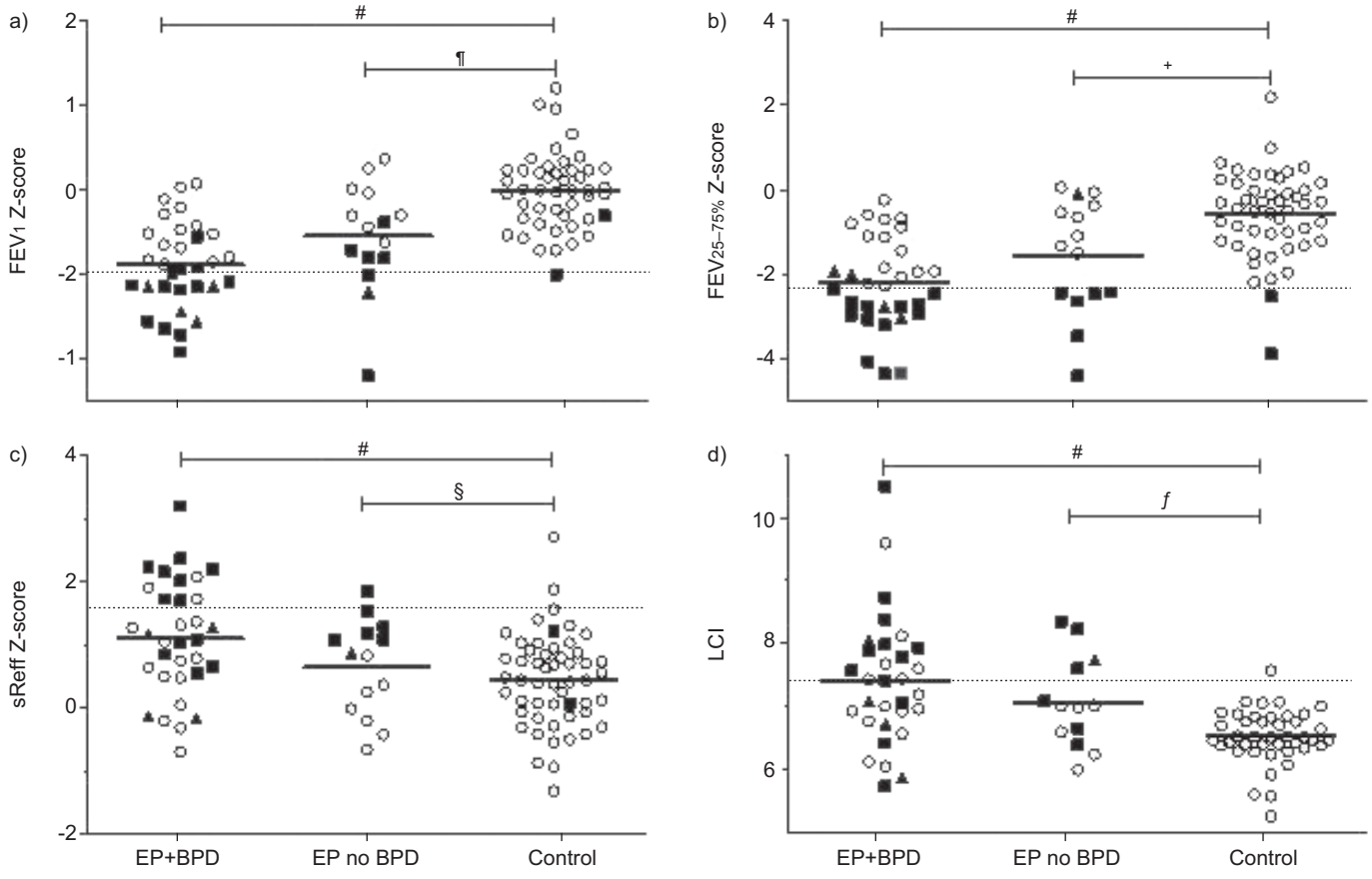

FIGURE 2. Comparison of lung function in children born extremely pre-term with or without bronchopulmonary dysplasia (BPD) and full-term controls according to lung disease categories. ——: mean value for that group. ■: children classified as having obstructive airways disease; ▲: children classified with restrictive lung disease. Evidence of airway obstruction was only evident in one control with a history of asthma, whose z-score forced expiratory flow between 25–75% forced vital capacity ($FEF_{25–75\%}$) was -3.9. The remaining control with forced expiratory volume in 1 s (FEV_1) and $FEF_{25–75\%}$ just below lower limit of normal LLN was not asthmatic but had had a lower respiratory tract infection requiring medication in the last 3 months. Unfortunately, technically acceptable lung clearance index (LCI) results were not obtained in either of these controls. sReff: specific effective airway resistance. ○: no evidence of obstructive or restrictive airway diseases. #: $p<0.0001$; ¶: $p=0.003$; +: $p=0.004$; §: $p=0.18$; *f*: $p=0.02$. a, b) ·····: lower limit of normal; c, d) ·····: upper limit of normal.

in persons with cystic fibrosis [30] it has not been found to be particularly discriminative when assessing BPD or prematurity either during infancy [31, 35] or in the current study. A simplified bronchial tree with fewer generations of peripheral airways may have contributed to the relatively normal LCI observed in EP children at 11 yrs of age and this could potentially have masked some ventilation inhomogeneity. However, it is equally possible that following BPD there may be relatively homogenous airway narrowing and hence minimal impact on the LCI. Whatever the underlying mechanism, it appears that the LCI would not be the method of choice when trying to identify airway abnormalities in children born EP, unless used in conjunction with spirometry. The reduced diffusion capacity amongst those born EP in this study has been previously reported [6] and probably reflects disruption of alveolar development (larger but fewer alveoli), decreased surface area for gas exchange and disrupted angiogenesis [33]. Nevertheless, very few EP children demonstrated evidence of restrictive lung disease, even when using a liberal definition based on both reduced FVC with normal FEV_1/FVC. Of the 37 (76%) EP children with technically acceptable plethysmographic lung volumes, only one (3%) had evidence of restriction. In contrast, evidence of obstructive airway disease was observed in 45% of these children, 91% of whom were correctly identified by spirometry alone. Although it is recognised that plethysmography should be used to confirm restrictive lung disease, this technique may be difficult for young children especially if there is any developmental delay. Therefore, we adopted the more liberal definition including spirometry to ensure we did not underestimate any restriction in this population.

Indeed, although the aetiology of BPD has changed during the past four decades, a similar degree of respiratory dysfunction continues to be observed, albeit in increasingly immature survivors [2]. The increase in sReff among children with prior BPD, but not in those without, may be associated with increased bronchial smooth muscle and airway narrowing associated with the more prolonged and intense ventilatory support received by these children [34]. These findings of functional impairments are consistent with morphometric data from survivors with BPD [35].

The question of whether respiratory dysfunction following pre-term birth is: 1) due to disruption of normal lung development

TABLE 6 Associations between spirometric outcomes and specific airway resistance with extremely preterm birth and other factors

	zFEV1	zFEF25–75%	zFEV1/FVC	ZsReff
Subjects n	94	94	94	100
Variability explained[#] %	41	36	20	13
Constant	-0.11	-0.43	0.28	0.34
EP	-1.31 (-1.73– -0.89)***	-1.14 (-1.59– -0.69)***	-0.58 (-0.99– -0.17)**	0.45 (0.12–0.78)**
Wheeze ever[¶]	-0.71 (-1.16– -0.26)**	-0.84 (-1.32– -0.36)**	-0.66 (-1.09– -0.22)**	0.38 (0.04–0.73)*
Other variables of interest[+]				
BPD	-0.47 (-1.10– -0.15)	-0.38 (-1.05–0.29)	-0.08 (-0.69–0.53)	0.30 (-0.20–0.81)
White mother	0.43 (-0.19–1.05)	NA[§]	NA[§]	NA[§]

Data presented as coefficient (95% CI), unless otherwise stated. FEV1: forced expiratory volume in 1 s; FEF25–75%: forced expiratory flow between 25–75% forced vital capacity (FVC); sReff: specific effective airway resistance; EP: extreme pre-term; BPD: bronchopulmonary dysplasia; NA: not applicable. [#]: adjusted r^2 derived from multiple linear regression using the whole dataset (EP + controls). [¶]: most significantly associated with these lung function outcomes. [+]: not significantly associated with the lung function outcomes after adjusting for the above variables. [§]: factor not included in the model as it was not significantly associated with the lung function variable. With the exception of sReff, once accounted for this variable, additional symptoms and current asthma did not add significantly to the models. Current asthma status was significantly associated with a further increase in sReff by an average of 0.48 Z-score (95% CI 0.07–0.90) (p=0.02) while the contribution from the ''wheeze: ever'' variable was no longer significant (mean Z-score (95% CI) 0.26 (-0.10–0.61)). Although the univariate associations of BPD with lung function and of ethnicity with FEV1 (but not FEF25–75%, FEV1/FVC or sReff) (supplementary table E1) were no longer significant during multiple linear regression, they are reported as additional variables of interest since they show identical trends to those found when analysing the entire cohort [11]. *: p<0.05; **: p<0.01; ***: p<0.0001.

following premature exposure of an immature lung to extrauterine conditions; 2) related to factors contributing to pre-term delivery; or 3) subsequent to lung injury incurred during resuscitation and subsequent ventilatory support during the neonatal period remains controversial due to the close interaction of these factors. While there is clear evidence of disrupted lung development following pre-term birth *per se* [36, 37], both respiratory morbidity and reductions in LF were far more severe in EP children with prior BPD. Indeed, the minority of EP children who survived without BPD were generally functioning remarkably well at 11 yrs of age [11]. The fact that these functional abnormalities have persisted into early adolescence among those born pre-term suggests that the damage observed during infancy [38] may be permanent [2, 3].

Conclusions

There is a high incidence of persistent LF abnormalities among EP children born in the mid-1990s, which is largely obstructive in nature and likely to have long-term implications for future lung health. Spirometry proved to be an effective means of detecting these persistent abnormalities in survivors of EP birth and BPD, although discrimination could be improved in laboratory-based assessments by including measures of specific resistance and/or ventilation inhomogeneity. To minimise the risk of early onset chronic obstructive lung disease in adulthood, efforts should be made to preserve existing lung reserves by encouraging these children to lead a healthy lifestyle with respect to diet, exercise and avoidance of smoking.

SUPPORT STATEMENT

This work was supported by the UK Medical Research Council and Smiths Medical plc (London, UK) and Wellcome Trust Value in People Award. Research at the Institute of Child Health and Great Ormond Street Hospital benefits from R&D funding from the NHS Executive. This paper was presented, in part, at the 2008 American Thoracic Society Conference (Toronto, Canada).

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

EPICure Investigators Group: K. Costeloe (London), E.S. Draper (Leicester), E.M. Hennessy (London), N. Marlow (Nottingham; Chief Investigator) and J. Stocks (London, all UK). Developmental Panel: J. Fawke (Nottingham), S. Thomas (Leeds) and V. Rowell (London; all paediatricians); S. Johnson, R. Smith and R. Trikic (all psychologists); H. Palmer (study administrator). The EPICure Study Group comprises of paediatricians from 276 maternity units across the UK and Ireland who provided the original patients to the study, whose invaluable help we acknowledge in the establishment of these studies. The Investigator group was responsible for the funding and the overall design of the studies at 11 yrs of age. The patients were recruited by J. Fawke, S. Thomas and V. Rowell. We would particularly like to thank the children and families who participated in this study.

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