AJRCCM Articles in Press. Published on April 8, 2010 as doi:10.1164/rccm.200912-1806OC
Media embargo until 2 weeks after above posting date; see thoracic.org/go/embargo

Lung function and respiratory symptoms at 11 years in extremely preterm children: The EPICure Study

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Funding: This research was funded by the Medical Research Council, UK

Running title: Prematurity & lung function at 11y

Descriptor number: 14.7

Drs Fawke and Lum contributed equally to this article

Word count: 4,144

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}w gestation had abnormal baseline spirometry, 27% a positive bronchodilator response and 25% 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 BPD, emphasizing the need for continued monitoring of these children.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

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

Objectives: To assess the degree of respiratory morbidity and functional impairment at 11y in EP children (≤25^{+6}w gestation) in relation to neonatal determinants and current clinical status.

Methods: Pre and post-bronchodilator spirometry were undertaken at school in children born EP and classroom controls. 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 182/219 EP (129 with prior bronchopulmonary dysplasia [BPD]) and 161/169 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 increased in those born EP, changes being most marked in those with prior BPD. EP birth, BPD, current symptoms and treatment with Beta-agonists are each associated independently with lung function z-scores (adjusted for age, sex and height) at 11y. Fifty six percent of EP children had abnormal baseline spirometry and 27% a positive bronchodilator response but less than half of those with impaired lung function were receiving any medication.

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

Words: 245

Keywords (3-5): Prematurity, lung function, bronchopulmonary dysplasia, long-term follow-up

INTRODUCTION

Rates of preterm birth are rising (1;2) and survival following extremely preterm birth 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 prior to 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 extremely preterm (EP) children ($\leq 25^{+6}$w gestation) and shown high rates of respiratory symptoms and medication use, with reduced peak expiratory flows compared with classmates (13). Re-evaluation of the health status of this cohort at 11y provided the opportunity for more detailed respiratory assessment, which is the focus of this paper. The aim of this study was to assess the degree of respiratory morbidity and functional impairment at 11y in EP children 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 EP children with prior BPD, defined pragmatically as receiving supplemental oxygen at 36w 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).

MATERIALS AND METHODS

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

EP children 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 months), sex and ethnic origin, one of whom was randomly selected as a comparison child. No comparison was sought for EP children 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 pre-assessment telephone call to check respiratory medication use and any inter-current 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 12m in children with a doctor-diagnosis of asthma *or* use of asthma medication *and* wheeze in the past 12m even if no prior diagnosis of asthma.

Anthropometry and Physical Examination

Height and weight were measured according to established protocols (20). Height, weight and Body Mass Index (BMI) were expressed as z-scores, i.e. adjusted for sex and age (21). All children underwent a standardized clinical examination.

Spirometry

A portable spirometer (Jaeger Masterscope, Lab Manager,V4.65) was used to measure Forced Expired Volume in 1s (FEV_1), Forced Expiratory Flows (FEF_{25-75}) and Forced Vital Capacity (FVC) as described previously (20). The three pediatricians undertook an intensive three-day spirometry training course at a pediatric respiratory laboratory (UCL, Institute of Child Health [ICH]). This included assessing technical acceptability at time of data collection and opportunities to practice spirometry on local children. These pilot data were reviewed by respiratory physiologists and feedback provided to ensure that repeatable measurements could be obtained prior to 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 20mins after administering a bronchodilator (two puffs of Salbutamol 100µg 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 ICH, masked to clinical and neonatal data.

Feedback regarding overall quality control was sent to pediatricians within a 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 entered on the database, codes regarding birth status and whether the child had had BPD were released (15). Data were verified for accuracy and analyzed using SPSS (v.15.0) and Stata (v10.1) (SL, EH). Differences between groups were analyzed using independent t-tests with 95% confidence intervals (CI) for continuous data and Chi-squared or Fisher's exact tests where 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 using Re-Base software (J7IS Ltd).

RESULTS

Study Population

Within the EPICure cohort, 219 of 307 survivors were evaluated at 11y (range: 10.1 to 12.1y) (Figure 2). Those lost to follow-up were more likely to be of non-white ethnic origin, have unemployed parents, a lower IQ at 6y and higher rates of cognitive impairment (17;18). The majority of assessments were undertaken in mainstream schools, but 29 EP children were evaluated in special schools, 10 at home and 2 in hospital outpatients. Satisfactory baseline spirometry was completed in 182/219 EP children (Figure 2); results being obtained in 174/185 (94%) EP children in mainstream schools and 8/29 (28%) in special schools.

No potential classmates required exclusion from the study on the basis of the exclusion criteria for controls. Among classmates, 161/169 (95%) completed baseline spirometry, two assessments being performed at home. Technically acceptable post-bronchodilator data were obtained in 161 EP children and 149 classmates, drop-out being primarily due to lack of parental consent for Salbutamol (9% EP, 5% classmates; Figure 2).

Perinatal characteristics of EP children 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 in 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 11y and those lost to follow-up (n=88; Table E1, OLS). Among those assessed at 11y, children in whom spirometry could not be obtained had a stormier ante-natal and neonatal course, as indicated by lower maturity (-0.4w, $p<0.01$), increased frequency of ante-partum 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, OLS).

Anthropometry and Respiratory Morbidity

Among those with successful spirometry, questionnaire data were available for 168(92%) EP children 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

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

Findings on clinical examination are summarized on Table 2. 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 sub-groups. Mild coryzal symptoms within the past week were reported by 22/182 (12%) EP and 20/161 (12%) classmates, but no child was tested when unwell.

When compared with classmates, EP children 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 12m. Among the EP group, significantly more with prior BPD reported wheeze in the past 12m (Table 2).

Spirometry: Baseline and post BDR

After adjustment for age, sex and body size by using z-scores, EP children 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% percent predicted respectively; Table 3 and Figure 3A). The most marked reductions were seen in EP children with prior BPD, in whom lung function was significantly lower than either classroom controls or those born EP but without BPD. Abnormally low baseline lung function (i.e.

FEV_1, FEV_1/FVC or FEF_{25-75} <-1.96 z-scores) was observed in 14/161 (9%) classmates, 17/53(32%) of children with EP but no prior BPD and 85/129 (66%) children with prior BPD. Among the EP children with abnormal lung function who returned questionnaire data, only 5/16 (31%) of those without BPD and 24/75 (32%) with BPD were receiving any respiratory medication.

Following 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 prior BPD (Table 3, Figure 3B). Nevertheless, post-bronchodilator lung function remained significantly lower in EP children than their classmates, suggesting that airway obstruction was only partially reversible (Table 3). A positive bronchodilator response (BDR), as indicated by a within-subject increase in FEV_1 by >12% compared with baseline (24) occurred more frequently in EP children (27%) than in classmates (8%), and in EP children with prior BPD (32%) than in those without (16%) (Figure 3C, Figure E1, OLS). Among those born EP with prior BPD, both baseline and post-bronchodilator 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 controls or those born EP but without BPD. Among those with complete data, only 17/37 (46%) of EP children with both abnormal lung function and increased BDR had received any respiratory medication over the past 12 months (Table E4; Figure E2, OLS).

Determinants of lung function in children born EP: **univariable analysis**

Ethnicity and sex: FEV_1 was lower among children of non-white 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 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 EP children.

***Maternal and perinatal factors*:** Associations between lung function at 11y 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,OLS), none of the perinatal or maternal factors were associated with spirometric lung function at 11y.

Respiratory morbidity and current exposures: Associations between lung function at 11y and characteristics at time of test (Table 2) were also investigated. On univariate analysis, current asthma and recent asthma medication were negatively associated with all baseline spirometry outcomes (Table E3, OLS) but not with post-bronchodilator lung function (data not shown). The effect of being an asthmatic on $zFEV_1$ was, however, only significant 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, EP without BPD, and EP with BPD respectively (see Table E3, OLS for details of univariable analysis). The impact of EP delivery on lung function at 11y 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 EP without BPD and -1.5 (-1.8; -1.2; p<0.001) lower in EP with BPD when compared with non-asthmatic classroom controls. A similar pattern was found with $zFEF_{25-75}$ 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 the

child's growth centiles, current smoke exposure, family history of atopy, socio-economic status or maternal education (Table E3, OLS).

Of the 124 EP children 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 (Figs E2 and E3, and Table E4, OLS). By contrast, only 4/52 EP children without prior BPD who returned the questionnaire, had abnormal spirometry *and* a positive BDR, and all but one of these was being treated. Of the 15 EP children with a diagnosis of asthma plus medication in the past 12 m *and* a positive BDR, 12 (80%) were symptomatic. By contrast, although 15/18 (83%) EP children without a previous diagnosis of asthma but with a positive BDR had abnormal baseline spirometry, only 2(11%) were symptomatic.

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 0.7z-score for FEV_1, 0.6z-score for FEF_{25-75} and 0.5z-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 controls, which equates to reductions of 28% and 47% respectively if expressed as percent predicted (23). "Asthma ever" was associated with a further mean reduction of 0.4 zFEV_1/FVC (Table 4). No other birth, neonatal or 11year factors were associated with baseline or post-bronchodilator 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, OLS.

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, while respiratory outcome in 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 survivors of EPICure (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 recent published 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). Recent 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 LF indices at 11 years, so no causal association can be implied.

The magnitude of reduction in lung function among non-white participants in the current study is in keeping with well recognised 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 ETS 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 cigarette smoking exposure may have different etiologies in those surviving EP birth compared to term controls. However, within our study, after adjustment for BPD, both maternal smoking in pregnancy

and current ETS exposure were marginally associated with wheeze in the past 12 months [OR: 1.90 (1.00; 3.61) p=0.050 and OR = 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 11y were representative of the entire cohort. Those in whom spirometry could not be successfully obtained at the 11y assessment tended to be more severely disabled and to have had a stormier neonatal course suggesting that, if anything, our results may slightly under-estimate 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 controls identified by the head teacher. By not excluding asthmatics 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 due to 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 controls was similar to that quoted for this age group in the UK (39) and, in contrast to the EP group, we found no significant difference in lung function between controls with and without asthma.

Our study was also strengthened by the strict quality control imposed for all spirometric measurements (20), and the fact that results were analysed by pediatric respiratory physiologists completely masked both to birth status and current clinical status of the subjects. The recently published '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 which approximated 0(1) in the classmate controls. This increased the

confidence with which we could use the lower limit of normal (LLN) of -1.96z-scores from these equations to identify children with abnormal lung function.

The major weakness of this respiratory follow-up is that, since 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 ventilatory requirements at given time points has been extensively discussed in recent years(11;27;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 36w PMA remains strongly predictive of subsequent outcome.

In theory, preterm survivors of modern neonatal care, who have been treated with ante-natal steroids and postnatal surfactant and subjected to far gentler ventilatory regimes than in the past, should have far less evidence of airway injury than their predecessors. Indeed, histological evidence suggests that 'new BPD' is characterised 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 in survivors of BPD, albeit manifesting in an increasingly immature population. The persistence of airway obstruction in these children is likely multi-factorial 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 immuno-regulatory 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 that has been identified recently(54;55).

The implications of the potential under-treatment of lung disease in children born preterm have been discussed recently (29;56). While treatment may not relieve all symptoms or normalise lung function completely, a sizeable proportion of EP children in this study may have benefitted 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 11y between EP children and classmate controls, primarily because neither group were undertaking sufficient exercise (57). With increasing age and hence growth of the respiratory system during childhood, respiratory symptoms of cough and wheeze following preterm birth tend to diminish, but deficits of lung function remain. Whilst Narang et al. 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 COPD 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 EP children despite current treatment. There are strong economic incentives for secondary prevention of disability associated with preterm birth, including risk factors for early onset COPD during adulthood. Preventative 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 enquire about the neonatal history of their patients.

Acknowledgements: The EPICure Investigators Group: K Costeloe (London), ES Draper (Leicester) EM Hennessy (London), N Marlow (Nottingham and UCL; Chief Investigator), J Stocks (London). **Developmental Panel:** Pediatricians: Joseph Fawke, Susan Thomas and Victoria Rowell; Psychologists: Sam Johnson, Rebecca Smith, Rebecca Trikic; Study Administrator: Heather Palmer. Respiratory Physiologists**:** Sooky Lum, Jane Kirkby, Liam Welsh.

The EPICure Study Group comprises the pediatricians in 276 maternity units across the UK and Ireland who contributed 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 studies at 11 years. We would like to thank Liam Welsh, who assisted with data analysis; Sam Johnson for collating all the 11 year data; Sanja Stanojevic for assistance with expressing PEF as z-scores and in particularly the children and families who participated in this study.

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FIGURE LEGENDS

Figure 1: Study Protocol

Figure 2: Study population at 11 year follow-up

Figure 3: Pre and post bronchodilator responsiveness according to diagnostic group

Similar changes were observed for forced expired flows;

Table 1: Perinatal data in children born EP in whom spirometry was obtained

	ALL EP	**BPD**	**no BPD**	**BPD - no BPD**
	mean (SD)	**mean (SD)**	**mean (SD)**	**Δ (95% CI)**
n	182	129	53	
Gestation Age, GA (wk)	25.0 (0.7)	24.9 (0.8)	25.1 (0.6)	**-0.22 (-0.5; 0.0) ***
Birth weight (kg)	0.75 (0.12)	0.74 (0.12)	0.78 (0.12)	-0.04 (-0.1; -0.0)
Birth weight z-score[§]	-0.15 (0.76)	-0.18 (0.71)	-0.05 (0.87)	-0.13 (-0.37; 0.11)
Maternal Age (yrs)	29.0 (5.4)	29.1 (5.5)	28.5 (5.2)	0.6 (-1.2; 2.3)
	n (%)	**n (%)**	**n (%)**	**Δ (95% CI)**
GA <25 weeks	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 hours)	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 (days)**	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%)** [‡]

≤ 4 cases with missing data for each variable. * p<0.05, [†] p<0.01, [‡] p<0.001

Abbreviations: Δ (95% CI): Differences in means or proportions between groups with 95% confidence intervals. [§] Child Growth Foundation Standards(21). [‖] Maternal smoking in pregnancy; PET = pre-eclamptic toxaemia; APH: ante-partum hemorrhage; PROM: premature rupture of membranes more than 24 hours prior to delivery.

** Data presented as Median (range); p-value calculated from non-parametric 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: noBPD	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 (yrs)	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%)
‖ Resp morbidity in past 12m						
Current asthma[2]	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 12m						
• 1 - 3	19 (11%)	14 (9%)		17 (15%)	2 (4%)	
• 4 - 12	12 (7%)	5 (3%)	**p=0.039 ****	8 (7%)	4 (8%)	p=0.061**
• > 12	4 (2%)	0 (0%)		4(3%)	0 (0%)	
Sleep disturbed by wheeze						
• < 1 night / week	11 (7%)	7 (5%)	p=0.073**	9 (8%)	2 (4%)	p=0.43**
• ≥ 1 night / week	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 > 16y	121 (67%)	119 (77%)	**-10% (-19; 0%)***	83 (65%)	38 (72%)	-7% (-20; 9%)

Results presented as mean (SD) or n (%); * p<0.05; † p<0.01; ‡ p<0.001;

§ physical exam in 181 EP and 160 classmates

‖ Amongst those with successful spirometry, the respiratory questionnaire was returned by 168 EP children (116 with BPD, 52 no BPD) and 148 classmates

** p-value calculated from non-parametric test for trend

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

Table 3: Comparison of Pre and Post Bronchodilator results

	EP: no BPD	EP: BPD	All EP	Classmates (C)	EP - C Δ (95% CI)	EP only BPD - no BPD Δ (95% CI)	EPnoBPD-C p-value**
Baseline (n)	**53**	**129**	**182**	**161**			
Resp rate / min	20 (3)	20 (3)	20 (3)	18 (3)	**2 (1; 3)** ‡	0.0 (-1; 1)	**<0.001**
FEV_1 z-score§ (z)	-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 to -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**			
z FEV_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**
% Δ 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
Δ in FEV_1 > 12%	7 [16%]	37 [32%]	44 [27%]	12 [8%]	**19 (11; 27)%** ‡	**16 (3; 30)%***	0.55

Results expressed as mean (SD) or n [%]. Δ (95% CI) = Difference in means (95% confidence interval of this difference)

* p<0.05, † p<0.01 ‡ p<0.001

** Sidak's p-value: adjusted for the three comparisons. When the BPD vs. no BPD in the EP children were adjusted for the 3 comparisons, the p-values remained in the same categories with the exception of **$zFEV_1/FVC$** which had a p-value = 0.053. Given the large numbers and greater magnitude of difference in all lung function parameters between BPD vs. Classmates, these differences were all highly significant but, due to space constraints, are not displayed .

§ Results expressed as z-scores(23) which adjust for sex, height and age. % pred: Percent predicted based on Stanojevic 2009 (23)

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 11y)[‖]	NA	NA	**-0.38 (-0.66; -0.11)** †	**0.12 (0.01; 0.24)** *
BPD + βAgonist (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 m*) which were not significantly associated with the LF outcomes after adjusting for the above 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)
Steroids 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)

Data presented as coefficient (95% CI); * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$;

[§] Results expressed as z-scores (23) which adjust for sex, height and age.

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

Abbreviations: NA = Not applicable: factor not included in the model as it was not significantly associated with the LF variable; int: interaction term.

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 EP children without BPD compared to control children assuming other significant factors are similar. Where BPD and the interaction term of BPD and βAgonists are independently significant, the coefficient for BPD children is the effect of being BPD without βAgonists compared to EP children without BPD, and the coefficient of BPD and βAgonist is the effect of BPD children taking βAgonist compared to the other BPD children. Where the interaction of BPD and βAgonist is not in the model, the BPD coefficient is the additional effect of being BPD compared to EP children without BPD. Hence the BPD children taking βAgonists have a mean FEV_1 z-score (0.81 +0.67 +0.90) = 2.38 Standard Deviations lower than control children assuming the same ethnicity of their mothers.

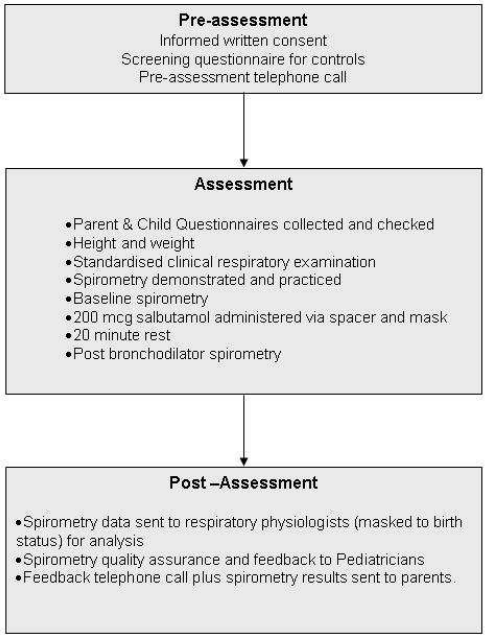

Figure 1: Study Protocol
254x190mm (96 x 96 DPI)

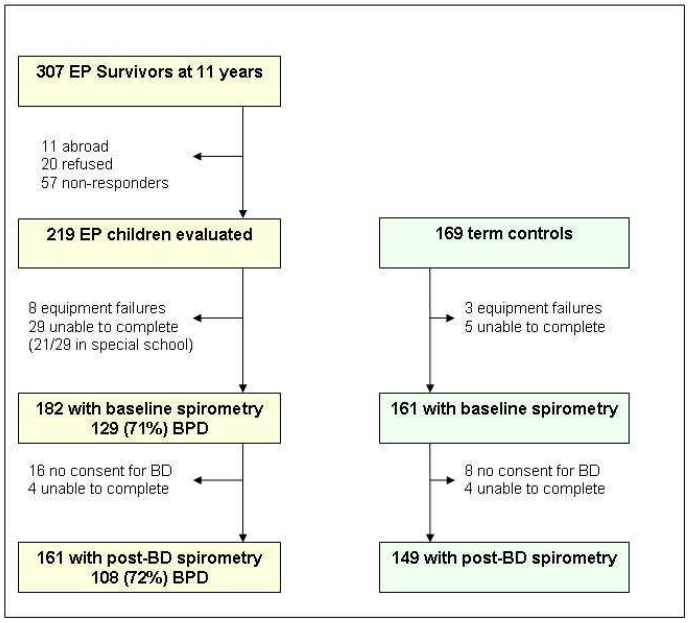

Figure 2: Study population at 11 year follow-up
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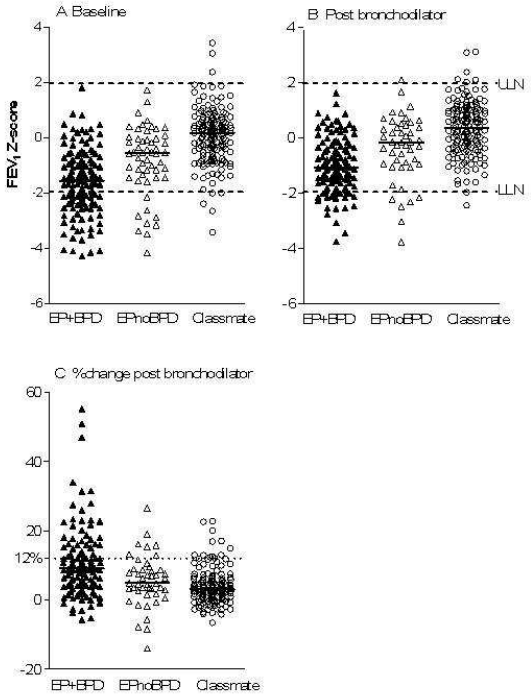


Figure 3: Pre and post bronchodilator responsiveness according to diagnostic group
Similar changes were observed for forced expired flows

254x190mm (96 x 96 DPI)

Lung function and respiratory symptoms at 11 years in extremely preterm children: The EPICure Study

Joseph Fawke, Sooky Lum, Jane Kirkby, Enid Hennessy, Neil Marlow, Victoria Rowell, Sue Thomas, Janet Stocks

On-line supplement

Additional Results

For reasons of space the following information could not be presented in the main manuscript. The mean birthweight for all live admissions <25^{+6} w GA to neonatal intensive care units in the UK in 1995 (n = 811) was 700g, and the mean birthweight for those who survived to discharge (n=314) was 744g. Mean birthweight of the cohort in whom spirometry was assessed was 750g (table E1) and hence representative of all EP babies surviving to discharge.

As commonly undertaken in such studies, extreme factors that could affect lung growth and development such as TB, whooping cough, pneumonia or hospitalisation for respiratory illness were exclusion criteria for controls. However, in practice no potential controls required exclusion from the study.

Table E1: Perinatal data in children born EP in whom spirometry was obtained at 11 years in comparison with those in whom it was not

	EP seen at 11y N = 219		EP not seen N = 88		
	Spirometry N = 182	No Spiro N = 37		Spiro – no spiro	Spiro- not seen
	mean (SD)	mean(SD)	mean (SD)	Δ (95% CI)	Δ (95% CI)
Gestation Age, GA (w)	25.0 (0.7)	24.6 (0.8)	25.0 (0.6)	**0.4 (0.1; 0.7)** †	-0.1 (-0.2; 0.1)
Birth weight (kg)	0.75 (0.12)	0.71(0.10)	0.75 (0.11)	0.04 (-0.0;0.08)	0.00 (-0.03; 0.03)
Birthweight z-score§	-0.15 (0.76)	-0.17(0.99)	-0.22 (0.70)	0.02 (-0.27; 0.31)	0.09 (-0.10; 0.27)
Maternal Age (yrs)	29.0 (5.4)	28.0 (7.1)	27.7 (6.2)	1.0 (-1.1; 3.0)	1.2 (-0.2;2.7)
	n (%)	n (%)	n (%)	Δ (95% CI)	Δ (95% CI)
BPD	129 (71%)	31 (84%)	65 (74%)	-13% (-26; 1%)	-3% (-14; 8%)
GA <25 weeks	68 (37%)	24 (65%)	33 (38%)	-28% (-44;-11%)	-0% (-13; 12)
Male	79 (43%)	22 (59%)	48 (55%)	-16% (-33; 1%)	-11% (-24; 2.0)
White mother	151 (83%)	28 (76%)	57 (65%)	8% (7; 23%)	**19% (7;30%)**‡
Multiple Births	52 (29%)	9 (24%)	18 (20%)	5% (11; 20%)	9% (-1; 20%)
Antenatal steroids	148 (82%)	30 (81%)	66 (75%)	1% (-13, 15%)	7% (-3; 18%)
Maternal Smoking ‖	63(35%)	9 (28%)	21 (30%)	7% (-24, 10%)	5% (-8; 18%)
Maternal PET	5 (3%)	2 (5%)	1 (1%)	-3% (-10; 5%)	2% (-2; 5%)
Maternal APH	34 (19%)	15 (41%)	25 (29%)	**-22%(-38; -5%)**†	-9% (-20; 2%)
Received surfactant	153 (85%)	33 (89%)	76 (86%)	-5% (-16; 5%)	-2% (-11; 7%)
Chorioamnionitis	41 (23%)	6 (16%)	29 (33%)	7% (-7; 20%)	-9% (-22; 2%)
PROM (>24 hr)	47 (26%)	10 (27%)	28 (32%)	-1% (-16; 15%)	-6 (-17; 6%)
Postnatal steroids	125 (69%)	33 (89%)	64 (73%)	**-20% (-32; -8%)***	-4% (-15; 8%)
SupplO_2 at discharge	50 (28%)	16 (47%)	28 (41%)	**-19% (-37; -1%)***	**-13% (-27; 0%)***

Δ (95% CI) = differences in means or proportions between groups with 95% confidence intervals

≤ 4 cases with missing data for each variable; * p<0.05, † p<0.01, ‡ p<0.001

§ Child Growth Foundation (1). ‖maternal smoking in pregnancy;

Abbreviations: PET = pre-eclamptic toxemia; APH: ante-partum hemorrhage; PROM: premature rupture of membranes > 24h prior to delivery

Table E2: Group characteristics and respiratory morbidity in EP children with and without spirometry results

	EP seen at 11y N = 219		
	Spirometry	**No Spiro**	**Spiro – No Spiro Δ (95% CI)**
N	182	37	
% boys	43%	59%	-17% (-32; 1%)
Age (yrs)	10.9 (0.4)	10.9 (0.4)	-0.0 (-0.2; 0.1)
N (%) in special school	8 (4%)	21 (57%)	**-52% (-67; -36%)‡**
Height z-score	-0.48 (0.99)	-0.93 (1.10)	**0.45 (0.09; 0.81)***
Weight z-score	-0.41 (1.29)	-0.47 (1.21)	0.07 (-0.40; 0.53)
BMI z-score	-0.27 (1.4)	0.04 (1.2)	-0.30 (-0.8; 0.20)
§Physical examination			
• **Chest asymmetry**	6 (3.3%)	1 (3%)	1% (-5%; 7%)
• **Harrison's sulci**	16 (9%)	3 (8%)	1% (-9%; 10%)
• **Pectus excavatum**	29 (17%)	6 (17%)	0 (-14%; 13%)
• **Pectus carinatum**	2 (1%)	1 (3%)	-2% (-7%; 4%)
‖Resp morbidity in past 12m			
Wheeze	35 (21%)	4 (18%)	3% (-14%; 20%)
Number of wheeze attacks over past 12m			
• 1 - 3	19 (11%)	1 (5%)	
• 4 - 12	12 (7%)	2 (9%)	p=0.86 **
• > 12	4 (2%)	1 (5%)	
Sleep disturbed by wheeze			
• < 1 night / week	11 (7%)	1 (5%)	p=0.66 **
• ≥ 1 night / week	7 (4%)	2 (9%)	
Speech limited by wheezing	8 (5%)	1 (5%)	0% (-17; 6%)
Exercise induced wheeze	34 (21%)	1 (5%)	0% (-9%, 10%)
Nocturnal Cough	33 (20%)	7 (32%)	-12% (-32%; 8%)
Seen by respiratory specialist	14 (8%)	1 (5%)	4% (-6%; 14%)
Asthma medication	41 (25%)	4 (17%)	7 (-10%; 23%)
Current asthma††	42 (25%)	4 (17%)	12% (-9%; 24%)

Data presented as Mean (SD) or n (%) as indicated. * $p < 0.05$; † $p<0.01$, ‡ $p<0.001$

§Clinical examination in 181 EP and 160 classmates

Prematurity & lung function at 11y_OLS

‖ Amongst those with successful spirometry, the respiratory questionnaire was returned by 168 EP children (116 with BPD, 52 no BPD) and 148 classmates. Of those with no spirometry, 22 returned their questionnaire.

** p-value calculated from non parametric test for trend

†† Current asthma defined as either: a) doctor-diagnosis of asthma (at any time) and *either* respiratory symptoms *or* asthma medication in the last 12 months, or b) asthma medication and respiratory symptoms in the past twelve months even if no recall of doctor diagnosis.

Prematurity & lung function at 11y_OLS

Table E3: Univariable models of all associated perinatal and current factors for FEV_1, FEV_1/FVC and FEF_{25-75} z-scores in children born EP

Perinatal factors	‖**zFEV_1**	‖**zFEV_1/FVC**	‖**zFEF_{25-75}**
Gestational age per wk	0.10 (-0.16, 0.35)	0.04 (-0.23, 0.31)	0.04 (-0.23, 0.31)
§zBirthweight	0.11 (-0.12, 0.35)	-0.02 (-0.27, 0.23)	0.01 (-0.24, 0.26)
White mother	**0.71 (0.24, 1.17)** †	-0.10 (-0.61, 0.41)	0.24 (-0.27, 0.75)
Postnatal steroids per wk	**-0.07 (-0.13, -0.02)** †	0.03 (-0.03, 0.09)	-0.02 (-0.08, 0.04)
BPD	**-0.86 (-1.23, -0.49)** ‡	**-0.45 (-0.86, -0.03)***	**-0.72 (-1.13, -0.32)** ‡
Maternal smoking in pregnancy	-0.09 (-0.47, 0.28)	0.12 (-0.28, 0.52)	-0.04 (-0.45, 0.36)
Current factors			
§zWeight at 11y	0.07 (-0.07, 0.21)	0.05 (-0.09, 0.20)	0.12 (-0.03, 0.27)
§zHeight at 11y	0.03 (-0.15, 0.21)	0.13 (-0.06, 0.32)	0.17 (-0.02, 0.36)
Asthma ever	**-0.44 (-0.82, -0.06)***	**-0.51 (-0.91, -0.10)***	**-0.53 (-0.94, -0.13)** †
Current asthma	**-0.72 (-1.14, -0.30)** ‡	**-0.50 (-0.96, -0.05)***	**-0.66 (-1.12, -0.20)** †
Steroid treatment past 12m	**-0.66 (-1.15, -0.17)** †	**-0.64 (-1.17, -0.12)***	**-0.69 (-1.21, -0.17)** †
B-Agonists treatment past 12m	**-0.76 (-1.20, -0.32)** ‡	**-0.49 (-0.97, -0.01)***	**-0.64 (-1.12, -0.17)** †
Passive tobacco smoke exposure	-0.08 (-0.47, 0.31)	-0.15 (-0.56, 0.26)	-0.09 (-0.51, 0.33)
Sleep disturbed by wheeze	**-0.46 (-0.86, -0.06)***	-0.18 (-0.62, 0.26)	-0.31 (-0.74, 0.13)
Wheeze on exercise	**-0.66 (-1.12, -0.20)** †	-0.26 (-0.76, 0.24)	-0.44 (-0.94, 0.06)

Data presented as Mean (95% CI); **significant differences shown in bold; * p < 0.05; † p<0.01, ‡ p<0.001**
§Results expressed as z-scores (1) which adjust for sex and age
‖Results expressed as z-scores (2) which adjust for sex, height and age.

Table E4: Association between diagnostic groups, bronchodilator responsiveness, medication and lung function

	EP & BPD		EP noBPD		Classmate	
	Asthma (n=32)	No Asthma (n=82)	Asthma (n=10)	No Asthma (n=42)	Asthma (n=20)	No Asthma (n=131)
BDR positive, no Medication, normal LF	0	1 (2%)	0	0	0	5 (4%)
BDR positive + Asthma Medication + abnormal LF	13 (41%)	1 (2%)	3 (30%)	0	1 (5%)	0
BDR positive, no Medication, abnormal LF	0	19 (23%)	0	1 (2%)	1 (5%)	2 (2%)

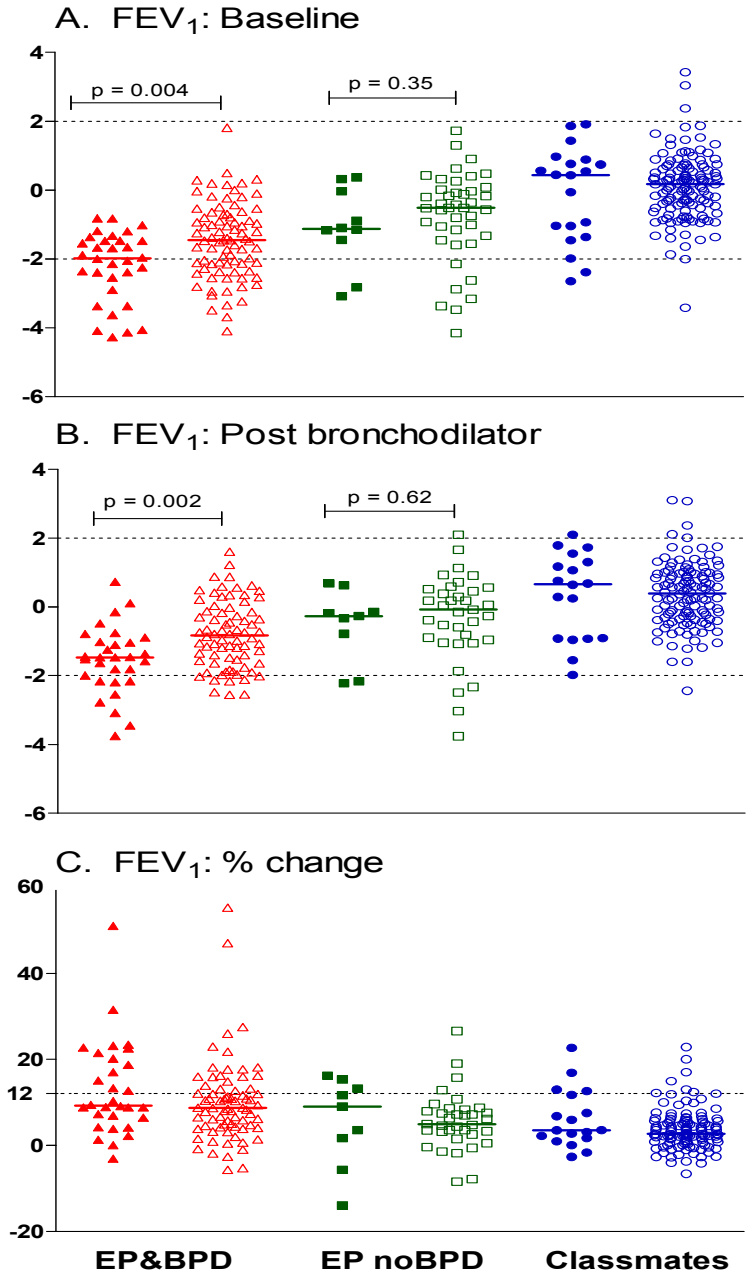
Data presented as n (%) from available questionnaire data only.

Abbreviations: BDR = bronchodilator response; LF = Lung function

Of the 33/124 (27%) EP&BPD with both positive BDR and abnormal LF, 19 (58%) had not received any treatment over the past 12 months. Only 4/52 (8%) EP without prior BPD had a positive BDR and abnormal LF, and all but one of these were receiving treatment. An abnormal LF with a positive BDR was only found in 4/151 (3%) classmates, 3 of whom were not being treated.

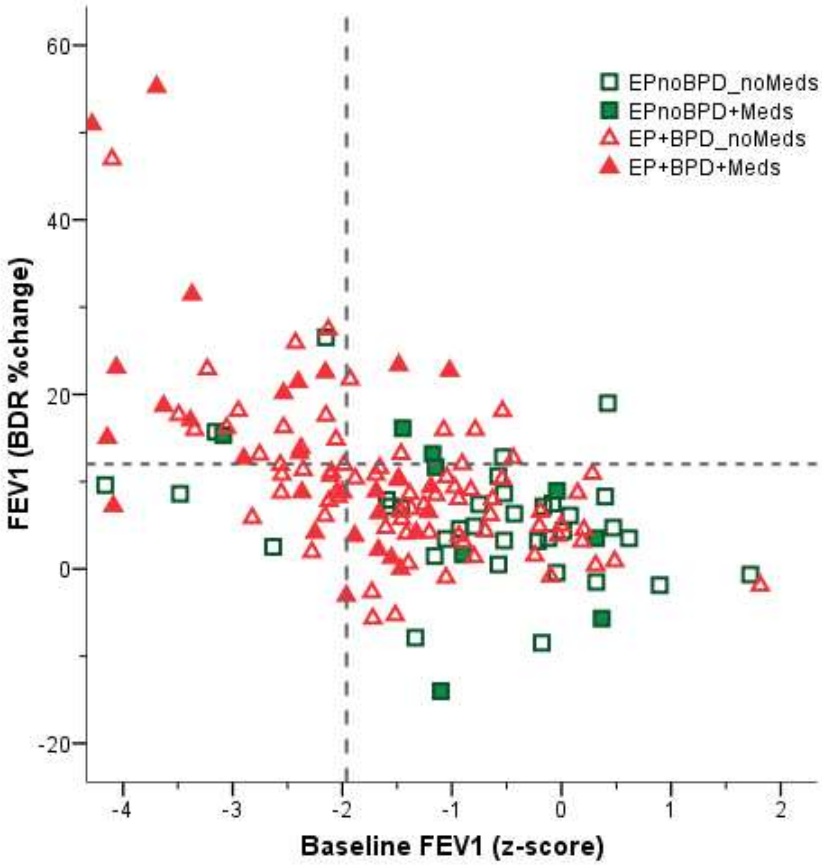
Prematurity & lung function at 11y_OLS

Figure E1: **Pre and post bronchodilator responsiveness according to birth status and current asthma**



Footnote: open symbols represents those with no asthma and closed symbols those with current asthma. When data were examined *within* diagnostic groups, pre and post bronchodilator FEV_1 were significantly lower in those with asthma only if they had been born EP and had had prior BPD. (Figure E1A and E1B). More reversibility of airway obstruction was observed in children born EP (with or without BPD) than classmates (Fig E1C and Table 3, main MS). Within the sub-groups there was no difference in the degree of reversibility according to asthma diagnosis among either the BPD group or classmates. Similar changes were observed for forced expired flows.

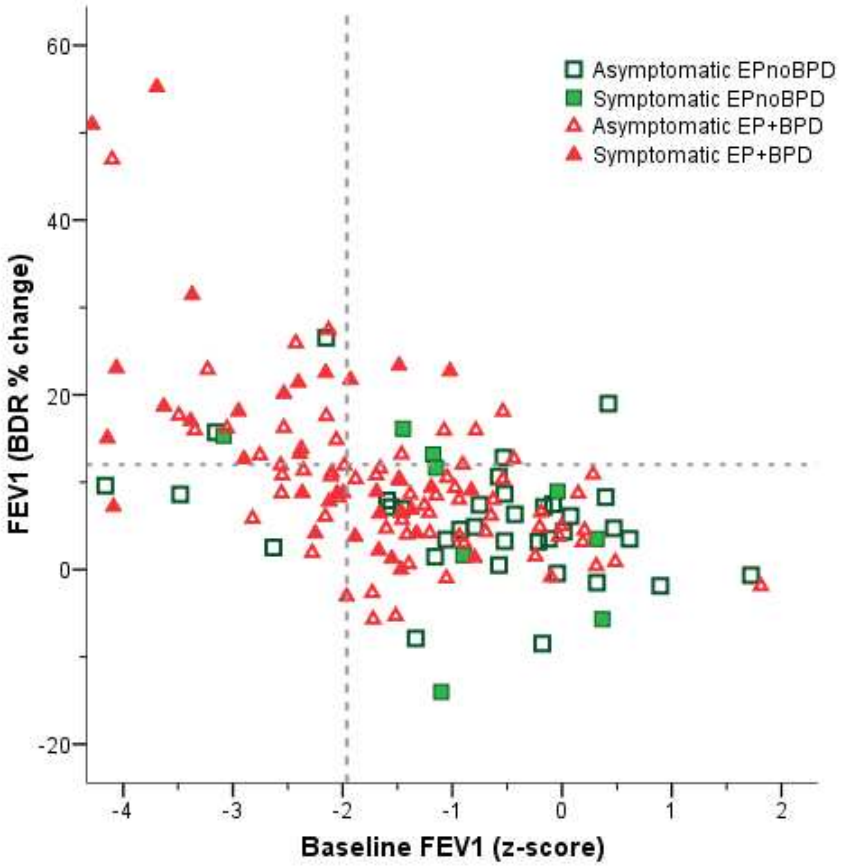
Figure E2: Associations between lung function and current asthma medication (last 12 m) in children born extremely preterm



Legend: This scatter plot shows % change in FEV_1 following administration of a bronchodilator (Salbutamol) vs. baseline FEV_1 (expressed as a z score which adjusts for height, sex and age) according to diagnostic group (with or without BPD) and medication use in the last 12 months. The vertical dashed line denotes the lower limit of normal for FEV_1 (-1.96 z-score) i.e. the datapoints to the left of this line were classified as abnormal FEV_1. The horizontal dashed line denotes the threshold for a positive bronchodilator response (+12%); i.e. those with datapoints above the horizontal line were classified as having a positive bronchodilator response, while those below the line had normal BDR. As can be seen, many of the children in the upper left quadrant were not receiving medication, despite abnormal FEV_1 and a positive BDR (see also Table E4).

Prematurity & lung function at 11y_OLS

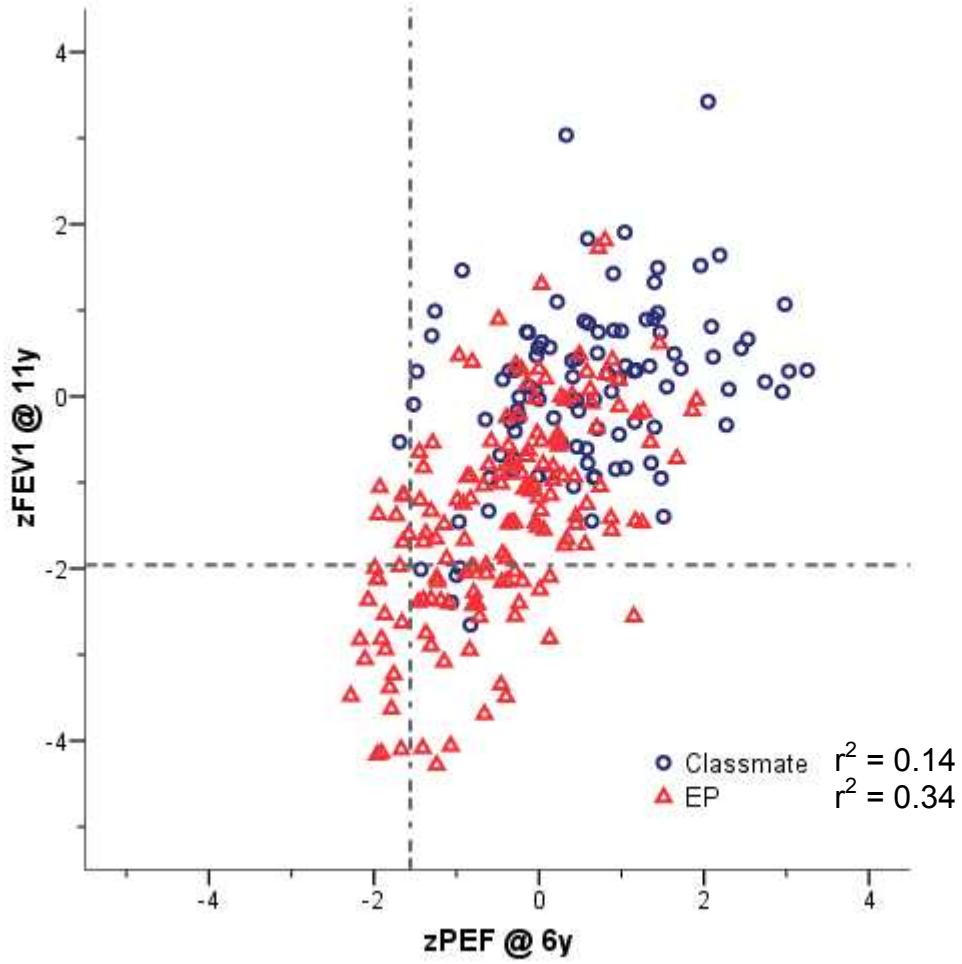
Figure E3 Associations between bronchodilator responsiveness and baseline FEV_1 in EP children (with and without BPD) and respiratory symptoms in the last 12 months



Legend: This scatter plot has an identical layout to Fig E2 but shows % change in FEV_1 following administration of a bronchodilator (Salbutamol) vs. baseline FEV_1 z-score and respiratory symptoms during the last 12 months. Of the 48 EP children reporting current symptoms, 8(17%) had not received any recent asthma medication all of whom had had prior BPD. As can be seen from the plot, many children were asymptomatic despite marked decrements in lung function and increased airway responsiveness.

Prematurity & lung function at 11y_OLS

Fig E4 Association between PEF at 6y and FEV_1 at 11y.



Legend: This scatter plot shows FEV_1 z-score at 11 years vs. peak expiratory flow (PEF) z-score (www.growinglungs.org.uk) at the 6 year follow-up according to diagnostic groups. The horizontal dashed line represents the lower limit of normal for FEV_1 and the vertical dashed/dotted line represents the lower limit of normal for PEF. The latter is set at -1.2 z-scores, which represents the 2.5th centile from the classmates in this study. Despite considerable scatter, there was a significant correlation between PEF at 6y and FEV_1 at 11y particularly in those born EP (r^2 =0.34 for EP [p< 0.001], r^2 =0.14 for classmates [p< 0.001]). As a group, the PEF z-score was significantly lower in the EP children (mean (SD): -0.44 (0.99)) than in classmates (0.60 [.10]; 95% CI difference: -1.28; 0.79; p < 0.0001)

Reference List

1. Cole TJ, Freeman JV, and Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat.Med* 1998;17:407-429.

2. Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, Hall GL, Welsh L, Kirkby J, Nystad W, Badier M, Davis S, Turner S, Piccioni P, Vilozni D, Eigen H, Vlachos-Mayer H, Zheng J, Tomalak W, Jones M, Hankinson JL, and Stocks J. Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. *Am J Respir Crit Care Med* 2009;180:547-552.