Received: 13 June 2022 | Accepted: 11 September 2022

DOI: 10.1002/ppul.26151

ORIGINAL ARTICLE

WILEY

Influence of bronchopulmonary dysplasia on lung function in adolescents who were born extremely prematurely

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Funding information

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Abstract

Objectives: To assess if a previous diagnosis of bronchopulmonary dysplasia (BPD) was associated with poorer lung function at 16 to 19 years of age, regardless of whether postnatal corticosteroids had been administered.

Working Hypothesis: Infants with BPD will have poorer lung function at 16 to 19 years of age.

Study Design: Prospective follow-up study.

Patient-Subject Selection: One hundred and sixty-one participants aged between 16 and 19 years who were born at less than 29 weeks of gestation; 87 had had BPD.

Methodology: Lung function was assessed by spirometry (FEV_1, FVC, FEV_1/FVC, FEF_{75}, FEF_{50}, FEF_{25}, FEF_{25-75}, PEF), impulse oscillometry (R5Hz and R20Hz), plethysmography (FRC_{pleth}, TLC_{pleth}, RV_{pleth}), diffusion capacity of the lungs for carbon monoxide (D_LCO, D_LCO/VA) and lung clearance index (LCI). Questionnaires were used to quantify respiratory symptoms and a shuttle sprint test to assess exercise capacity.

Results: At 16 to 19 years, those who had had a diagnosis of BPD had poorer airway function (FEV_1, FEF_{75}, FEF_{50}, FEF_{25-75}) compared to those without. FVC and D_LCO were also poorer in those who had BPD. Those differences remained significant after adjusting for sex, gestational age, and maternal smoking. When excluding those who had received postnatal corticosteroids, differences remained significant in FEV_1, FVC, and FEF_{75}. There were no significant differences in exercise capacity or respiratory symptoms between those with and without BPD.

Conclusions: In adolescents and young adults born prematurely, those who had BPD had poorer lung function compared to those without, regardless of whether they had received postnatal corticosteroids.

KEYWORDS

Chronic lung disease, postnatal corticosteroids, young adults

Janet Peacock and Anne Greenough are joint senior authors.

1 | INTRODUCTION

The incidence of prematurity has increased and the survival of prematurely born individuals improved.[1] There has, however, been no reduction in respiratory morbidity with up to 60% of infants born at less than 26 weeks of gestational age being diagnosed with bronchopulmonary dysplasia (BPD).[1] As a consequence, more infants who had BPD are surviving to adulthood. Studies have shown that BPD is a predictor of respiratory morbidity in infancy[2] and childhood.[3] The European Respiratory Society (ERS) has recently produced guidelines regarding the follow-up of those who had BPD suggesting they require dedicated care following discharge from the neonatal unit.[4]

A large population study has suggested that poor lung function at 18 years predicts subsequent chronic obstructive pulmonary disease in later adult life.[5] It is, therefore, important to understand whether BPD within a prematurely born cohort can predict poor lung function after puberty, the latter being the last positive effect on lung development.[6] We, therefore, aimed to assess the lung function of 16 to 19-year-old born before 29 weeks of gestation who had or had not developed BPD, in a cohort who were routinely exposed to antenatal corticosteroids and postnatal surfactant (more than 90% received both treatments). A study of 123 19-year-old adults born at less than 25 weeks of gestation showed that those who had BPD had poorer airway function (FEV_1) compared to those without BPD.[7] Seventy-three percent of that study population, however, had been exposed to postnatal corticosteroids, an intervention we have shown to be associated with a dose dependent negative effect on airway function.[8,9] Thus, it is important to determine if a diagnosis of BPD per se rather than administration of postnatal corticosteroids results in poorer lung function at follow-up. Additionally, therefore, we will compare the lung function of those who did or did not develop BPD, but did not receive postnatal corticosteroids.

2 | METHODS

Infants born at less than 29 weeks of gestational age born between 1998 and 2001, and recruited into the United Kingdom Oscillation Study[10] were invited to attend King's College Hospital NHS Foundation Trust when they were between 16 and 19 years of age. There, they underwent lung function and exercise testing and completed a health questionnaire. The original UKOS trial was granted ethical approval by the South Thames Multicentre Research Ethics Committee. The follow-up study when the participants were 16 to 19 years of age was approved by The North East-Tyne and Wear South Research Ethics Committee respectively. Participants were invited to attend by letter, email and phone call, and gave written consent to take part in this study.

A detailed neonatal history was available from records taken during the original study.[10] Any postnatal steroid exposure was recorded and subsequent correspondence with participating units had clarified the type of postnatal corticosteroid used. Two patients had received hydrocortisone, all the others dexamethasone. All were classified as having been exposed to postnatal steroids. Details regarding length of course have previously been described.[8] For the purpose of these analyses, BPD was defined as an oxygen requirement at 36 weeks corrected gestational age.

Lung function assessments were done in accordance with ERS/ATS guidelines[11–19] as described previously.[20] Spirometry (FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75}), plethysmography (TLC_{pleth}, FRC_{pleth}, RV_{pleth}), airways resistance by impulse oscillometry (R at 5 and 20 Hz), diffusing capacity for carbon monoxide of the lungs (D_LCO, D_LCO/VA) and the lung clearance index using sulfur hexafluoride (LCI) were measured. The results were further examined by a respiratory physiologist and deemed acceptable if they adhered to ERS/ATS standards. Lung function results were converted to *z* scores.[12,21,22] As described previously[23] abnormal lung function was defined as lung function below the 5th centile.[21] Participants were asked not to take inhalers on the day of the study until the assessments had been completed. If a participant was unwell on the day of assessment, they were asked to rebook their appointment.

Exercise capacity was assessed by a modified shuttle sprint test where participants were asked to travel between cones 10 m apart in time to prerecorded tones where the time between tones became incrementally shorter each minute.[23] Participants were also asked how many hours of exercise they performed each week. Asthma and wheeze were assessed by self-report using a questionnaire.

Puberty was previously assessed by questionnaire in this cohort when they were between 11 and 14 years of age.[24] At that assessment, 90% had entered puberty indicated by a Tanner score of two or more.

2.1 | Analysis

Demographic factors, lung function, exercise and respiratory symptoms were compared in those with and without BPD and all analyses allowed for the nonindependence of multiple births using random effects multiple regression (continuous outcomes)[25] or logistic regression (categorical outcomes).[26] Analyses of lung function are given with adjustment for confounders ("unadjusted") and after adjusting for antenatal steroid use (yes/no), birthweight, gestation, sex of infant, postnatal corticosteroids (dexamethasone), maternal smoking in pregnancy and the participant's age at assessment. The percentage of participants with abnormal lung function was calculated for all lung function measures reported as *z* scores (all except LCI), using the distributional approach [27] and using $z < -1.64$ as the cut-off for "abnormal" for lung function measures where a smaller value indicates poorer function and $z > 1.64$ for measures where a larger value is worse. Lung function results followed a reasonably symmetric distribution and so were not transformed following our previous analysis strategy.[20,24] Exercise test distance and self-reported exercise were categorized as their distributions were irregular and could not be transformed to normal. These and the

other categorical outcomes were adjusted for postnatal corticosteroids only as numbers were too small for full adjustment as used for the continuous data. A sensitivity analysis of lung function by BPD was conducted in those who had not received postnatal dexamethasone to enable estimates to be compared between the full sample and this subset. Results of modeling are presented as estimates with 95% confidence intervals (CIs). Analyses were done using Stata v17.

3 | RESULTS

One hundred and fifty young people completed the study. BPD was associated with lower mean gestational age and birthweight and increased use of postnatal steroids (Table 1).

The young people who had had BPD had significantly poorer mean airway function (FEF_{75}, FEF_{50}, FEF_{25}, FEF_{25-75}, FEV_1, FVC, FEV_1/FVC, PEF, DLCO, DLCO/VA) with mean differences ranging from 0.38 to 0.97 *z* scores. Differences remained statistically significant for FEV_1, FVC, and FRC_{He} after adjustment (Table 2). There was a high percentage of young people with abnormal lung function for several assessments, even after adjustment, with most being more than 5% points and 6% over 10% points (Table 2). There was no significant relationship between exercise distance and BPD before or after adjustment and similarly there was no evidence of a significant relationship with self-reported exercise. The proportion reporting wheeze in the past 12 months was significantly greater in those who had had BPD (22% vs. 9.9%) (Table 3).

Forty two percent of those with a neonatal diagnosis of BPD (33/78) and 11% of those without (8/72) were exposed to postnatal corticosteroids. When excluding those who had postnatal corticosteroids, 109 remained and the same pattern of confounders was seen among demographic variables as for the whole sample (Supporting Information: E-Table 1). The sensitivity analysis in those without exposure to postnatal corticosteroids showed that the differences in mean lung function were similar to those observed in the whole sample (Table 4). The sizes of differences were very similar in the unexposed subset to the whole sample. The main difference was the wider CIs due to smaller numbers when those exposed to corticosteroids were removed. The relationships between BPD and exercise were similar in those unexposed to postnatal corticosteroids and not statistically significant. Wheeze and asthma remained more common among those who had had BPD, but this was not statistically significant (Supporting Information: E-Table 2).

TABLE 1 Demographics by BPD status

	BPD	No BPD	*p* Value[a]
N (max)	78	72	
Male	42 (54%)	28 (39%)	0.090
Gestation (wks)	26.3 (1.4)	27.5 (1.2)	<0.001
Birthweight (*g*)	829 (208)	981 (203)	<0.001
Birthweight *z* score	−0.65 (1.09)	−0.49 (0.92)	0.351
Antenatal steroids	69 (88%)	66 (93%)	0.375
Postnatal surfactant	70 (97%)	75 (96%)	0.719
HFOV (vs. CV) at birth	36 (50%)	35 (51%)	0.930
Postnatal steroids	33 (42%)	8 (11%)	<0.001
Age at assessment (years)	18.1 (0.8)	17.8 (0.8)	0.173
Height at assessment (cm)	167.1 (9.3)	167.1 (8.5)	0.866
Weight at assessment (kg)	63.3 (16.9)	63.8 (15.0)	0.830
Maternal smoking in pregnancy	18 (25%)	10 (15%)	0.129
Smokes	9 (12%)	9 (13%)	0.862
Past history of asthma	23 (30%)	18 (25%)	0.548

Note: Data are demonstrated as the mean (SD) or *n* (%).

Abbreviations: BPD, bronchopulmonary dysplasia; CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation; SD, standard deviation.

[a]*p* Value allows for nonindependence due to multiple births.

4 | DISCUSSION

We have demonstrated that a diagnosis of BPD was associated with poorer lung function in adolescence, including in those who had not received postnatal corticosteroids. Furthermore, those with BPD were more likely to have abnormal lung function deemed clinically significant, for example, 38% of participants had an abnormal value for FEV_1 compared to 22% of those who did not have BPD. Approximately in one half of the lung function results there were differences between those with BPD and no BPD greater than 10% points (Table 5).

Our data showed deficits in airway function (FEV_1 and FEF_{75}) and vital capacity (FVC) were associated with a diagnosis of BPD which remained significant after correcting for possible confounders. A study of 164 25-year-old born before 28 weeks of gestation assessing airway function by spirometry demonstrated significantly worse lung function in those who had had BPD (mean difference in FEV_1 −0.66, 95% CI −0.99 to −0.33, $p<0.001$).[28] There was also more evidence of airways obstruction (FEV_1:FVC) (−0.55 95% CI −0.92 to −0.19, $p=0.003$), but with preserved FVC. In that study, only 74% were exposed to antenatal steroids and 40% received postnatal surfactant. In our study, over 90% of those with or without BPD were exposed to antenatal steroids and received postnatal surfactant. The routine use of antenatal steroids and postnatal surfactant may have altered the subsequent course of lung development[29] and explain the relative lack of obstructive lung disease seen in our study. In another study of adults aged 19 years born prematurely in the post surfactant

TABLE 2 Lung function by BPD status

	Total[a]	BPD mean (SD)	No BPD mean (SD)	Difference (95% CI) (BPD–no BPD)[b]	Adjusted difference (95% CI)[c] (BPD–no BPD)	*p* value
FEF_{75}	150	−1.47 (1.24)	−0.49 (1.10)	−0.97 (−1.35, −0.59)	−0.42 (−0.84, 0.00)	0.051
FEF_{50}	150	−1.24 (1.05)	−0.68 (1.00)	−0.58 (−0.92, −0.25)	−0.11 (−0.49, 0.26)	0.544
FEF_{25}	150	−0.88 (1.12)	−0.34 (1.14)	−0.52 (−0.88, −0.16)	−0.13 (−0.53, 0.27)	0.523
FEF_{25-75}	150	−1.89 (1.26)	−0.96 (1.12)	−0.93 (−1.32, −0.54)	−0.36 (−0.78, 0.06)	0.092
FEV_1	150	−1.47 (1.25)	−0.49 (1.20)	−0.96 (−1.37, −0.56)	−0.54 (−1.00, −0.07)	0.024
FVC	150	−0.54 (1.34)	0.09 (1.28)	−0.59 (−1.02, −0.16)	−0.52 (−1.03, −0.00)	0.049
FEV_1/FVC	150	−1.37 (1.22)	−0.86 (1.16)	−0.56 (−0.94, −0.17)	−0.05 (−0.48, 0.38)	0.816
PEF	150	−0.64 (1.10)	−0.23 (1.05)	−0.35 (−0.69, −0.01)	−0.08 (−0.46, 0.31)	0.697
DLCO	146	−1.22 (0.97)	−0.76 (1.18)	−0.49 (−0.86, −0.13)	−0.35 (−0.78, 0.09)	0.119
DLCO/VA	146	−2.24 (0.90)	−1.89 (0.87)	−0.38 (−0.67, −0.09)	−0.10 (−0.44, 0.24)	0.558
FRC_{pleth}	149	0.60 (1.36)	0.60 (1.33)	0.00 (−0.43, 0.43)	−0.43 (−0.93, 0.07)	0.091
FRC_{He}	144	0.31 (1.89)	0.93 (2.14)	−0.67 (−1.34, 0.01)	−0.98 (−1.79, −0.18)	0.017
RV	149	1.09 (1.35)	1.00 (1.33)	0.09 (−0.34, 0.51)	−0.37 (−0.85, 0.12)	0.136
TLC	149	0.72 (1.29)	0.96 (1.01)	−0.24 (−0.62, 0.15)	−0.41 (−0.86, 0.04)	0.077
RV/TLC[d]	149	30.9% (8.3)	30.1% (7.5)	0.8% (−1.8, 3.3)	−1.0% (−4.0, 2.0)	0.505
Resistance at 5 H_z	148	−0.08 (1.20)	−0.22 (1.04)	0.15 (−0.21, 0.51)	0.04 (−0.38, 0.46)	0.841
Resistance at 20 H_z	148	0.25 (1.01)	0.37 (1.01)	−0.12 (−0.44, 0.21)	−0.03 (−0.41, 0.34)	0.856
LCI	120	8.97 (1.53)	9.50 (1.61)	0.52 (−0.05, 1.08)	0.38 (−0.26, 1.03)	0.246

Note: Lung function is demonstrated as *z* scores, with the exception of LCI.

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; LCI, lung clearance index; SD, standard deviation.

[a]Totals vary due to missing data.

[b]Difference allows for nonindependence of multiple births.

[c]Lung function adjusted for antenatal steroids, birthweight, gestation, sex of infant, postnatal dexamethasone, maternal smoking in pregnancy, UKOS participant age at assessment and allows for nonindependence of multiple births.

[d]RV/TLC is calculated using raw values and presented as a percentage.

era, there was significantly poorer airway function (FEV_1) and obstruction (FEV_1/FVC) in those with BPD compared to those without.[7] In that cohort 76% of those studied had received postnatal corticosteroids compared to less than 30% in our cohort. We have previously shown that postnatal corticosteroid exposure was associated with poorer FEV_1/FVC and this may explain the differences in the results seen between the two cohorts.[8,9] Approximately 10% in both groups had abnormal RV/TLC ratios, this could be suggestive of early signs of physiology (gas trapping) consistent with COPD.

We found that 16% of participants without BPD and 37% with BPD were found to have clinically abnormal lung function. The higher rates of abnormal lung function in those with BPD compared with those without were observed alongside more than a two-fold significant increase in the proportions reporting wheeze, but there were no significant differences in the proportions diagnosed with asthma. Those data are in keeping with the results of 24 young adults who had a diagnosis of BPD compared to 63 without when studied at 26 years of age.[30] In that study, there were significant differences in FEV_1, FVC and FEV_1:FVC between the two groups, but there was no significant difference in the proportion who had asthma (30% vs. 25%, $p = 0.62$).

Our study has strengths and some limitations. We did not include a term controls, but compared comprehensive lung function test results in those born prematurely who had or had not had BPD. We felt our study could be underpowered to undertake a subanalysis in only those who received postnatal corticosteroids, but in the cohort overall there were significant differences in lung function between the BPD and the no BPD groups after adjustment for confounders including postnatal corticosteroids. Unfortunately, we did not have data on possible post NICU confounders, such as RSV infection, but we did adjust for a number of other factors including antenatal steroid use, birthweight, gestation, sex of infant, postnatal corticosteroids, maternal smoking in pregnancy and the participant's age at

TABLE 3 Percentage with abnormal lung function (<5th centile) according to BPD

Lung function measure	Total[a]	No BPD % with abnormal lung function	BPD % with abnormal lung function	Adjusted difference: Percentage points (95% CI)[b] (BPD–no BPD)	*p* Value[b]
FEF_{75}	150	22.2%	35.7%	13.5 (4.1, 22.9)	0.051
FEF_{50}	150	22.7%	26.6%	3.9% (−4.9, 12.7)	0.544
FEF_{25}	150	15.7%	18.9%	3.2% (−3.9, 10.4)	0.523
FEF_{25-75}	150	38.2%	51.7%	13.5% (2.6, 24.4)	0.092
FEV_1	150	21.9%	37.8%	15.9% (6.4, 25.3)	0.024
FVC	150	9.4%	18.1%	8.7% (2.5, 14.8)	0.049
FEV_1/FVC	150	32.1%	33.8%	1.7% (−8.4, 11.8)	0.816
PEF	150	11.9%	13.5%	1.6% (−4.2, 7.4)	0.697
DLCO	146	22.2%	32.9%	10.7% (1.4, 20.1)	0.119
DLCO/VA	146	NA			
FRC_{pleth}	149	25.4%	15.7%	−9.7% (−17.6, −1.7)	0.091
FRC_{He}	144	40.7%	23.1%	−17.6% (−27.6, −7.6)	0.017
RV	149	37.0%	26.3%	10.8% (−20.7, −0.8)	0.136
TLC	149	0.9%	2.4%	1.4% (0.2, 2.6)	0.077
RV/TLC[c]	149	11.5%	9.0%	−2.4% (−7.5, 2.6)	0.505
Resistance at 5 H_z	148	4.0%	4.3%	0.4% (−2.1, 2.9)	0.841
Resistance at 20 H_z	148	7.8%	7.2%	−0.5% (−4.5, 3.5)	0.856
LCI	120	NA			

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; LCI, lung clearance index; NA, not available as cannot be calculated.

[a]Totals vary due to missing data.

[b]Adjusted difference in percentages lung function adjusted for antenatal steroids, birthweight, gestation, sex of infant, postnatal dexamethasone, maternal smoking in pregnancy, UKOS participant age at assessment and allows for nonindependence of multiple births.

[c]RV/TLC calculated using raw values. The cut-point for normal is 40%.

TABLE 4 Exercise and respiratory outcomes by BPD

	Total	No BPD *n* (%) in category	BPD *n* (%) in category	Unadjusted *p* Value[a]	Adjusted *p* Value[b]
Exercise distance test	126			0.288	0.460
<1000 m		20 (33%)	30 (46%)		
1000–1249 m		25 (41%)	19 (29%)		
1250–1500 m		16 (26%)	16 (25%)		
Self-reported exercise	143			0.369	0.989
None		15 (21%)	27 (37%)		
Up to 1 h/day		43 (61%)	29 (40%)		
More than 1 h/day		12 (17%)	17 (23%)		
Any wheeze in last 12 months	148	7 (9.9%)	17 (22%)	0.048	0.037
Current asthma	149	4 (5.6%)	10 (13%)	0.133	0.108

Abbreviation: BPD, bronchopulmonary dysplasia.

[a]Logistic regression model that allows for nonindependence of multiple births.

[b]Logistic regression model that allows for nonindependence of multiple births and postnatal steroids.

TABLE 5 Lung function by BPD status in those not exposed to postnatal steroids

	Total[a]	BPD mean (SD)	No BPD mean (SD)	Difference (95% CI) (BPD–no BPD)[b]	Adjusted difference (95% CI)[c] (BPD–no BPD)	*p* Value
FEF_{75}	109	−1.16 (1.17)	−0.37 (1.01)	−0.82 (−1.24, −0.40)	−0.43 (−0.90, 0.05)	0.077
FEF_{50}	109	−0.97 (1.06)	−0.58 (0.99)	−0.43 (−0.82, −0.04)	−0.08 (−0.53, 0.37)	0.734
FEF_{25}	109	−0.53 (1.09)	−0.23 (1.12)	−0.31 (−0.74, 0.11)	−0.11 (−0.58, 0.36)	0.641
FEF_{25-75}	109	−1.54 (1.18)	−0.83 (1.06)	−0.73 (−1.16, −0.30)	−0.35 (−0.82, 0.13)	0.157
FEV_1	109	−1.24 (1.23)	−0.35 (1.18)	−0.88 (−1.35, −0.41)	−0.60 (−1.16, −0.05)	0.032
FVC	109	−0.56 (1.36)	0.14 (1.29)	−0.66 (−1.18, −0.15)	−0.59 (−1.21, 0.02)	0.058
FEV_1/FVC	109	−1.03 (1.15)	−0.77 (1.06)	−0.32 (−0.74, 0.10)	0.02 (−0.46, 0.51)	0.922
PEF	109	−0.35 (1.05)	−0.12 (1.05)	−0.20 (−0.59, 0.19)	−0.08 (−0.54, 0.38)	0.723
DLCO	107	−1.32 (1.02)	−0.72 (1.22)	−0.64 (−1.09, −0.19)	−0.39 (−0.92, 0.14)	0.150
DLCO/VA	107	−2.11 (0.97)	−1.85 (0.88)	−0.31 (−0.67, −0.05)	−0.05 (−0.46, 0.36)	0.804
FRC_{pleth}	108	0.12 (1.09)	0.57 (1.38)	−0.45 (−0.94, 0.03)	−0.63 (−1.22, −0.03)	0.039
FRC_{He}	105	0.25 (2.09)	0.89 (2.16)	−0.68 (−1.53, 0.17)	−1.03 (−2.02, −0.03)	0.043
RV	108	0.59 (0.95)	0.95 (1.30)	−0.36 (−0.80, 0.08)	−0.55 (−1.07, −0.03)	0.037
TLC	108	0.45 (1.23)	0.95 (1.03)	−0.50 (−0.94, −0.06)	−0.51 (−1.02, 0.01)	0.055
RV/TLC[d]	107	28.8% (6.0)	30.0% (7.2)	−1.2% (−3.8, 1.4)	−2.3% (−5.4, 0.8)	0.140
Resistance at 5 H_z	109	−0.14 (1.20)	−0.16 (1.06)	0.03 (−0.39, 0.46)	−0.13 (−0.61, 0.34)	0.584
Resistance at 20 H_z	109	0.22 (0.94)	0.47 (1.02)	−0.25 (−0.63, 0.12)	−0.31 (−0.74, 0.12)	0.153
LCI	85	9.40 (1.32)	8.84 (1.54)	0.55 (−0.06, 1.17)	0.75 (0.06, 1.44)	0.034

Note: Lung function is demonstrated as *z* scores, with the exception of LCI ($N = 109$ maximum).

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; LCI, lung clearance index; SD, standard deviation.

[a]Totals vary due to missing data.

[b]Difference allows for nonindependence of multiple births.

[c]lung function adjusted for antenatal steroids, birthweight, gestation, sex of infant, postnatal dexamethasone, maternal smoking in pregnancy, UKOS participant age at assessment and allows for nonindependence of multiple births.

[d]RV/TLC is calculated using raw values and presented as a percentage.

assessment. After that adjustment, there were still significant differences in lung function, being poorer in those who had BPD.

We demonstrated that 16% of participants without BPD had abnormal lung function indicating that prematurity alone impacts on lung function. This is in keeping with another study which showed that in adulthood FEV_1 and FVC *z* scores were lower in those born prematurely without BPD compared to term controls.[7]

In conclusion, we have demonstrated that those who had had BPD compared to those who had not were more likely to have abnormal lung function at 16 to 19 years of age. Those results were independent of postnatal corticosteroid exposure.

AUTHOR CONTRIBUTIONS

Anne Greenough and Christopher Harris designed the study. Christopher Harris, Alan Lunt, and Samuel Morris collected the data. Christopher Harris, Anne Greenough, and Janet Peacock undertook the analysis. Christopher Harris wrote the initial draft. All authors (except Alan Lunt who has sadly died) approved the final version of the manuscript.

ACKNOWLEDGMENTS

Alan Lunt was instrumental in supporting the many studies relating to the UKOS cohort, sadly he died in 2021. We thank Deirdre Gibbons for secretarial assistance. This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data made available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Harris C, Morris S, Lunt A, Peacock J, Greenough A. Influence of bronchopulmonary dysplasia on lung function in adolescents who were born extremely prematurely. *Pediatric Pulmonology*. 2022;57:3151-3157. doi:10.1002/ppul.26151