Impaired lung function and health status in adult survivors of bronchopulmonary dysplasia

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ABSTRACT More infants with bronchopulmonary dysplasia (BPD) now survive to adulthood, but little is known regarding persisting respiratory impairment. We report respiratory symptoms, lung function and health-related quality of life (HRQoL) in adult BPD survivors compared with preterm (non-BPD) and full-term controls.

Respiratory symptoms (European Community Respiratory Health Survey) and HRQoL (EuroQol (EQ)-5D) were measured in 72 adult BPD survivors (mean±SD study age 24.1±4.0 years; mean±SD gestational age 27.1±2.1 weeks; and mean±SD birth weight 955±256 g) cared for in the regional neonatal intensive care unit, Royal Maternity Hospital, Belfast, UK (between 1978 and 1993). These were compared with 57 non-BPD controls (mean±SD study age 25.3±4.0 years; mean±SD gestational age 31.0±2.5 weeks; and mean±SD birth weight 1238±222 g) and 78 full-term controls (mean±SD study age 25.7±3.8 years; mean±SD gestational age 39.7±1.4 weeks; and mean±SD birth weight 3514±456 g) cared for at the same hospital. Spirometry was performed on 56 BPD, 40 non-BPD and 55 full-term participants.

BPD subjects were twice as likely to report wheeze and three times more likely to use asthma medication than controls. BPD adults had significantly lower forced expiratory volume in 1 s and forced expiratory flow at 25–75% of forced vital capacity than both the preterm non-BPD and full-term controls (all $p<0.01$). Mean EQ-5D was 6 points lower in BPD adults compared to full-term controls ($p<0.05$).

BPD survivors have significant respiratory and quality of life impairment persisting into adulthood.

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Introduction

Bronchopulmonary dysplasia (BPD) is a major complication of preterm birth and the most common cause of chronic lung disease in infancy [1]. The aetiology of BPD has been attributed to numerous factors, including barotrauma from mechanical ventilation, oxygen toxicity, infection and inflammation causing injury to the immature lung and preventing normal alveolar and distal vascular development [2]. Despite advances in neonatal care, BPD occurs in up to 40% of very low birth weight (VLBW) infants [3] with birth weights <1250 g, which accounts for 97% of cases [4].

BPD survivors have more respiratory symptoms and reduced lung function from infancy [5] through to school age [6, 7]. In the recently reported EPICure study, lung function was measured at 11 years in children born extremely preterm and abnormal baseline spirometry was found in almost half of the children tested, of whom 81% had prior BPD [8]. In contrast, a recent study of survivors of extreme prematurity reaching mid-childhood reported encouraging pulmonary outcomes, but most of those studied had either no or only mild BPD [9]. In the study by DOYLE *et al.* [10], subjects born with VLBW and who developed BPD had poorer lung function in late adolescence than those without BPD, with evidence of more rapid decline in lung function. The respiratory health outcomes of those reaching adulthood are less certain and the few studies conducted to date have been limited by small sample size and highly selected populations [11]. A follow-up study of young adults born prematurely and studied at 19 years of age found a significantly greater prevalence of ''physician-diagnosed asthma'', reported wheeze and breathlessness in ex-preterm subjects than in the general population, which was most evident among females [12]. The same group reported a greater prevalence of obstructive spirometry and impaired exercise capacity in preterm subjects compared to term-born but not non-BPD preterm subjects [13]. In a recently reported postal survey, despite greater use of healthcare services and prescription drugs, adults born preterm and who developed BPD had similar respiratory symptoms and health status to preterm and term controls [14]. Although there is concern that adults born prematurely and who develop BPD may be at risk of chronic lung disease, there does not appear to be wide appreciation of this among clinicians as only a minority consider early life factors when managing their adult respiratory patients [15].

Here we report on respiratory symptoms, lung function and health status in the largest study to date of adult survivors of BPD compared with non-BPD preterm and full-term controls.

Methods

Study design and participants

The study population comprised 129 preterm adult survivors previously cared for in the regional neonatal intensive care unit (NICU) of the Royal Maternity Hospital (Belfast, UK) between January 1978 and April 1993. The index group, comprising subjects who developed BPD (n=72), was compared to preterm controls (n=57), also cared for in the NICU but who did not develop BPD or receive mechanical ventilation or prolonged respiratory support. A second control group (n=78) comprised sex- and birth date-matched (within 2 weeks of the index group) full-term individuals, born in the same hospital and without evidence of respiratory difficulties during hospital stay. The tracing and recruitment of study participants (fig. 1) is comprehensively detailed in the online supplementary material. Briefly, individuals were indentified from hospital records and traced through the Business Services Organisation (BSO) of the Department of Health, Social Services and Public Safety and subsequently *via* their general practitioner (GP). BPD was defined according to the widely used National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases workshop criteria, which defined BPD as the requirement for supplemental oxygen at >28 post-natal days and radiographic changes and severity (mild, moderate or severe) according to oxygen requirements at 36 weeks post-menstrual age [16]. Individuals with physical or mental disability such that they could not perform lung function testing or complete questionnaires were excluded.

Birth weights were obtained from labour and maternal records and gestation age was based on maternal report of last menstrual period and early pregnancy ultrasound scans.

All participants gave written informed consent and the study was approved by the Office for Research Ethics Committees Northern Ireland (08/NIR02/22).

Postal questionnaires (stage 1)

Participants in stage 1 completed a postal questionnaire comprising the European Community Respiratory Health Survey (ECRHS) screening tool [17], which is a well-validated questionnaire asking about asthma and asthma-like symptoms, and the EuroQol [18]. The EuroQol is a generic health-related quality of life (HRQoL) questionnaire comprising two parts: the EuroQol five-dimension component (EQ-5D) index, which rates mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and the EuroQol visual analogue scale (EQ-VAS), which contains a visual rating scale (0: worst possible health, 100: best

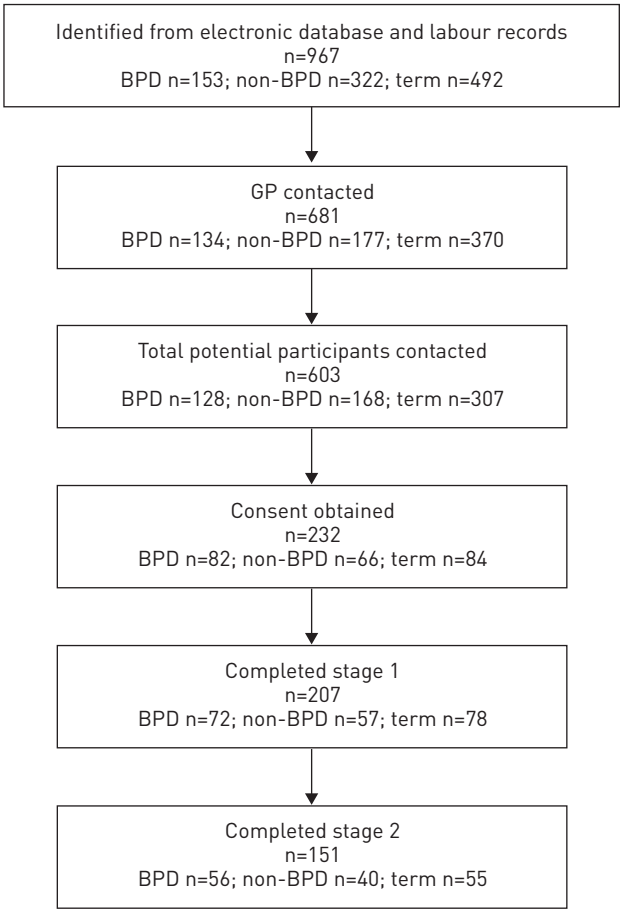

FIGURE 1 Flow chart summarising participant tracing and recruitment. BPD: bronchopulmonary dysplasia; non-BPD: preterm subjects who did not develop BPD; term: full-term birth date- and sex-matched controls; GP: general practitioner.

possible health). The EuroQol is designed for self-completion by respondents and is ideally suited for use in postal surveys. It is cognitively undemanding, taking only a few minutes to complete.

Lung function measurements (stage 2)

In stage 2 lung function tests were performed using a portable MicroLab ML3500 Mk8 spirometer (Micro Medical Ltd, Basingstoke, UK) according to European Respiratory Society lung function testing guidelines [19]. All assessments were performed by one researcher (A. Gough). Each participant performed a minimum of three reproducible assessments. The following indices were recorded: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), the FEV_1/FVC ratio and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$). Lung function data were expressed both as percentage of predicted scores [20] and z-scores.

Statistical analysis

Data were edited and analysed using SPSS (version 18; SPSS Inc, Chicago, IL, USA). Categorical variables were compared using Chi-squared analysis and continuous variables, by independent samples t-test or ANOVA where appropriate. ECRHS symptoms were adjusted for potential confounders, female sex, maternal smoking status and history of smoking in the respondent. Multiple linear regressions on lung function indices were performed to establish predictors of lung function and to adjust for the confounding variables birth weight, gestational age, maternal smoking and sex where appropriate. BPD and non-BPD groups were randomly matched for gestational age and comparisons in lung function end-points between the matched pairs were performed using the paired t-test.

Results

153 consecutive preterm neonates who developed BPD between January 1978 and April 1993 and were cared for in the NICU, Royal Maternity Hospital were identified from hospital records. 128 (84%) were traced *via* BSO and contacted, of which 82 consented and were enrolled in the study. Of these, 72 completed the questionnaires and 56 completed spirometry testing. 168 preterm infants without BPD and 307 full-term births were traced and invited to participate. Of the 66 (39%) former preterm subjects without BPD

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who consented, 57 completed the questionnaires, of which 40 completed spirometry. 84 (27%) traced full-term-born subjects consented to participate and of these 78 (25%) returned the questionnaire and 55 (18%) completed spirometry. All study participants were Caucasian. A flow chart of participant recruitment is provided in the online supplementary material. Demographic details of participants for each stage of the study are detailed in table 1. The BPD group was marginally younger (24.1 years *versus* 25.8 years; $p=0.012$) than the full-term controls, but there was no significant difference in sex.

Nonresponder analysis

There were no significant differences in baseline characteristics between BPD participants and those who did not respond to the invitation to participate (mean±SD birth weight 955±256 g *versus* 1030±243 g; mean±SD gestational age 27.1±2.1 weeks *versus* 27.5±2.2 weeks) (table E1).

Respiratory symptoms

The ECRHS screening questionnaire was completed by 72 former preterm subjects with BPD, 57 non-BPD preterm and 78 full-term participants; the results are presented in table 2. Compared to full-term controls, BPD survivors were significantly more likely to report wheeze and shortness of breath ($p<0.05$). The BPD group were more likely than those born at term to be defined as ''symptomatic'' using the ECRHS scoring tool (30.6% *versus* 12.8%, $p=0.008$) and significantly more likely to have a physician's diagnosis of asthma (40.3% *versus* 14.1%, $p<0.001$). BPD survivors were almost three times more likely to report wheeze than non-BPD full-term subjects (OR (95% CI) 2.86 (1.14–7.16), $p<0.05$). BPD survivors also reported more breathlessness and coughing and were more likely to have a physician's diagnosis of asthma than non-BPD preterm subjects, although these differences were not statistically significant.

Among BPD survivors, those reporting a ''physician diagnosis of asthma'' had lower mean birth weight (927 g *versus* 974 g) and mean gestational age (26.6 weeks *versus* 27.5 weeks) than those without, although these did not reach statistical significance. BPD participants who had not received surfactant were almost four times as likely to have a physician diagnosis of asthma compared to those given surfactant, although this did not attain significance (79.3% *versus* 20.7%, $p=0.119$).

Lung function

Lung function data were obtained from 56 participants born preterm with BPD, 40 non-BPD preterm participants and 55 full-term participants (table 1). There were significant differences between the BPD and full-term groups for all per cent predicted spirometric end-points (table 3). The BPD group had significantly lower FEV_1 and $FEF_{25–75\%}$ compared with both the non-BPD and full-term controls. When z-scores were generated for lung function indices, significant differences ($p<0.001$) remained evident among the groups (table 3). Compared to the full-term group the non-BPD group had significantly lower FEV_1/FVC and $FEF_{25–75\%}$ z-scores ($p<0.05$) and also FEV_1/FVC and $FEF_{25–75\%}$ % pred scores ($p<0.001$).

Adjustments were made for birth weight, gestational age and maternal smoking, which had little effect on the findings; only differences in FEV_1/FVC values between BPD and non-BPD were no longer significant (table 3). BPD and non-BPD groups were randomly matched for gestational age, yielding 15 directly matched pairs, and confirmed our findings of significantly lower FEV_1 ($p<0.01$) and $FEF_{25–75\%}$ ($p<0.05$) in the BPD preterm adults compared to non-BPD preterm adults (table E2). While all lung function parameters measured were also lower in non-BPD preterm participants compared to full-term subjects, the mean differences were smaller than those observed when BPD subjects were compared, suggesting that preterm birth alone is not sufficient to explain the extent of lung impairment observed in our adult BPD survivors.

To determine if changes to neonatal care between 1978 and 1993 altered our findings, we compared lung function parameters for three time tertiles (1978–1982, 1983–1987 and 1988–1993). Highly significant reductions in lung function between BPD and term controls, independent of birth date, were observed (table E3).

Although BPD participants who received surfactant were marginally lighter at birth (mean birth weight 899 g *versus* 958 g), required a longer duration of ventilation (median 816 h *versus* 750 h), had a longer hospital stay (median 99 days *versus* 94 days) and a greater proportion of severe grade 3 BPD (28% *versus* 8%), lung function outcomes were similar to those not given surfactant.

Proportion of abnormally low lung function scores between groups

The proportion of abnormally low lung function scores (defined as FEV_1 <80% pred, FEV_1/FVC <70%, $FEF_{25–75\%}$ <60% pred and ⩽ -1.96 z-scores) were compared among groups and scatter plots of results are displayed in fig. E1.3. Significantly more BPD adults had airflow reductions in the abnormally low range on all pulmonary end-points, with almost 40% of the BPD group having FEV_1 <80% pred compared to only

TABLE 1 Perinatal characteristics of bronchopulmonary dysplasia (BPD) and control groups completing questionnaires (stage 1) and who underwent spirometric testing (stage 2)

	BPD		Non-BPD		Term	
	Stage 1	Stage 2	Stage 1	Stage 2	Stage 1	Stage 2
Subjects n	72	56	57	40	78	55
Age at study years	24.1±4.0		25.3±4.0		25.8±3.9**	
Gestational age weeks	27.1±2.1	27.1±2.1	31.0±2.5***	31.2±2.3***	39.7±1.4***	39.8±1.2***
Birth weight g	955±256	939±246	1238±222***	1234±223***	3514±456***	3556±429***
Male	39 (54)	31 (55)	22 (39)	15 (38)	40 (51)	27 (49)
Antenatal steroids	18 (25)	16 (29)	22 (39)	13 (33)		
Maternal smoking	16 (29)	11 (25)	14 (33)	8 (29)		
Duration of hospital stay days	104±43	106±45	50±26***	50±25***		
Median Apgar score 1 min	5.0 (3–6)	5.0 (3–6)[¶]	6.0 (4–7.5)	6.0 (4–8)		
Median Apgar score 5 min	8.0 (7–8.8)	8 (27–9)[+]	9.0 (8–9)	9 (8–9)		
Post-natal steroids	23 (32)	19 (34)				
Median duration oxygen >60% h	10.5 (2.8–53.8)	10.0 (2–63.5)[§]				
Median duration IPPV h	841.0 (449.8–1347)	783 (425.8–1478.8)[¶]				
Surfactant	22 (31)[f]	18 (32)				
Current smoker[#]	16 (22)	11 (18)[f]	17 (30)	8 (18)[¶]	23 (30)	15 (24)[f]

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. IPPV: intermittent positive pressure ventilation. [#]: those who were daily smokers at the time of testing; [¶]: n=2 missing data; [+]: n=4 missing data; [§]: n=7 missing data; [f]: n=1 missing data. **: p<0.01; ***: p<0.001.

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TABLE 2 Respiratory symptoms in the previous 12 months reported on the European Community Respiratory Health Survey (ECRHS) among bronchopulmonary dysplasia (BPD) adults and control participants

	BPD	Non-BPD	Full-term	BPD *versus* non-BPD unadjusted OR (95% CI)	BPD *versus* non-BPD adjusted OR (95% CI)[#]	BPD *versus* full-term unadjusted OR (95% CI)	BPD *versus* full-term adjusted OR (95% CI)[¶]
Subjects n	72	57	78				
Item 1: wheeze?	34 (47)	19 (33)	24 (31)	1.79 (0.87–3.67)	2.86 (1.14–7.16)*	2.01 (1.03–3.92)*	2.29 (1.14–4.59)*
Item 1.1: wheeze and breathless?	19 (26)	13 (23)	13 (17)	1.21 (0.54–2.73)	1.16 (0.44–3.06)	1.79 (0.81–3.96)	2.23 (0.96–5.16)
Item 1.2: wheeze when did not have a cold?	23 (32)	14 (25)	13 (17)	1.44 (0.66–3.15)	1.89 (0.70–5.14)	2.35 (1.08–5.09)*	2.61 (1.17–5.82)*
Item 2: woken with tightness in chest?	20 (28)	12 (21)	12 (15)	1.44 (0.64–3.27)	2.09 (0.73–5.96)	2.12 (0.95–4.72)	2.64 (1.13–6.19)
Item 3: shortness of breath	11 (15)	9 (16)	3 (4)	0.96 (0.37–2.51)	0.86 (0.26–2.85)	4.51 (1.20–16.89)*	4.93 (1.27–19.10)*
Item 4: coughing	24 (34)	16 (28)	16 (21)	1.31 (0.61–2.79)	1.37 (0.53–3.55)	1.98 (0.95–4.14)	2.17 (1.01–4.67)*
Item 5: attack of asthma	7 (10)	6 (11)	1 (1)	0.92 (0.29–2.89)	0.41 (0.07–2.38)	8.29 (0.99–69.16)	8.90 (1.04–76.25)*
Item 6: use asthma medication	19 (26)	13 (23)	7 (9)	1.21 (0.54–2.73)	1.68 (0.60–4.71)	3.64 (1.43–9.38)**	3.78 (1.45–9.88)**
Item 7: nasal allergies	22 (31)	17 (30)	28 (36)	1.04 (0.49–2.21)	1.23 (0.46–3.25)	0.79 (0.40–1.55)	0.83 (0.41–1.67)
Symptomatic ECRHS score	22 (31)	18 (32)	10 (13)	0.95 (0.45–2.02)	1.27 (0.50–3.20)	2.99 (1.30–6.88)**	3.03 (1.29–7.12)*
Physician diagnosis of asthma	29 (40)	22 (39)	11 (14)	1.07 (0.53–2.19)	1.17 (0.50–2.70)	4.11 (1.86–9.08)*	4.30 (1.91–9.72)***

Data are presented as n (%), unless otherwise stated. [#]: adjusted for female sex, maternal smoking and having ever smoked; [¶]: adjusted for female sex and having ever smoked. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ between BPD and full-term groups only.

TABLE 3 Lung function tests compared between groups

	BPD	Non-BPD	Full-term	BPD *versus* non-BPD	BPD *versus* non-BPD[#]	BPD *versus* full-term	Non-BPD *versus* full-term
Subjects n	56	40	55				
FEV_1 z-score	-1.41±1.25	-0.19±1.16	0.14±0.96	-1.22 (-1.72- -0.72)***	-1.83 (-2.76- -0.90)***	-1.55 (-1.97- -1.13)***	-0.33 (-0.76–0.11)
FEV_1 % pred	81.89±15.90	96.98±15.22	101.16±11.40	-15.08 (-21.50- -8.66)***	-22.63 (-34.34- -10.91)***	-19.27 (-24.48- -14.06)***	-4.19 (-9.61–1.23)
FVC z-score	-0.79±1.14	0.17±0.98	0.12±0.94	-0.96 (-1.40- -0.52)***	-1.53 (-2.22- -0.84)***	-0.91 (-1.30- -0.52)***	0.05 (-0.35–0.44)
FVC % pred	90.11±14.46	101.85±12.60	101.67±0.83	-11.74 (-17.38- -6.10)***	-19.25 (-27.99- -10.50)***	-11.57 (-16.38- -6.75)***	0.18 (-4.61–4.97)
FEV_1/FVC z-score	-0.68±0.22	-0.13±1.22	0.34±0.89	-0.55 (-1.16- -0.06)	-0.36 (-1.51–0.79)	-1.02 (-1.52- -0.53)*	-0.47 (-0.90- -0.40)*
FEV_1/FVC % pred	94.32±13.41	98.45±10.32	102.67±7.18	-4.13 (-9.15–0.89)	-3.00 (-12.56–6.56)	-8.35 (-12.41- -4.29)*	-4.22 (-7.79- -0.66)*
$FEF_{25-75\%}$ z-score	-1.80±1.10	-1.13±1.02	-0.56±1.45	-0.67 (-1.11–0.23)**	-0.90 (-1.72–0.26)**	-1.24 (-1.73- -0.769)***	-0.57 (-1.10- -0.43)*
$FEF_{25-75\%}$ % pred	61.63±23.59	74.93±22.06	90.96±21.55	-13.30 (-22.74- -3.86)**	-20.99 (-36.78- -5.40)**	-29.34 (-37.84- -20.84)***	-16.04 (-25.02- -7.06)***

Data are presented as mean±SD or unadjusted mean difference (95% CI), unless otherwise stated. BPD: bronchopulmonary dysplasia; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC. [#]: adjusted for maternal smoking, having ever smoked, birth weight and gestational age. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

6% of the full-term group. Similarly, almost 50% of the BPD group had $FEF_{25–75\%}$ <60% pred, compared to <10% of the full-term group. Comparing the BPD and non-BPD groups, significantly more BPD participants scored in the abnormally low range for FEV_1 and $FEF_{25–75\%}$. When differences between the BPD and non-BPD groups were adjusted for maternal smoking, birth weight and gestational age, significant differences remained between the groups, with the addition of a significant difference in FEV_1 z-score ($p<0.018$).

When stratified for BPD severity, compared to mild BPD, a greater proportion of those with severe BPD had values in the abnormally low range for FEV_1 (63% *versus* 36%) and $FEF_{25–75\%}$ (75% *versus* 43%), although this failed to attain statistical significance (table E4).

As BPD participants scored significantly worse on FEV_1, FVC and $FEF_{25–75}$ pulmonary function end-points, multiple linear regression models within the BPD population were performed, with each end-point regressed on the following perinatal variables: birth weight, gestational age, duration of intermittent positive pressure ventilation and sex. No perinatal variable was found to be significantly predictive of lung function in adult survivors of BPD.

Health related quality of life

The HRQoL of BPD subjects was significantly lower than full-term controls as measured by both the EQ-5D utility score ($p=0.007$) and EQ-VAS ($p=0.028$). Among the preterm subjects, BPD subjects had lower scores on both the EQ-5D and -VAS compared with non-BPD subjects, although this was not statistically significant (table 4). Significantly more BPD than full-term subjects reported problems with mobility ($p<0.001$), self-care ($p<0.001$) and usual activities ($p=0.004$). BPD subjects were almost twice as likely as non-BPD subjects to report problems with mobility (22% *versus* 12%) and self-care (13% *versus* 7%); however, this did not reach statistical significance.

Discussion

In this large study of BPD survivors we confirm that respiratory symptoms and lung function impairment persists into adulthood. BPD adults reported significantly more wheeze and shortness of breath, were more likely to have an asthma diagnosis, be prescribed asthma medication and rate their quality of life more poorly than full-term controls. All lung function variables reflecting airflow limitation were significantly lower in BPD adults compared to those born at term. In addition, we found that adult BPD survivors had substantial reductions in lung function and significantly more variables within an abnormally low and clinically important range than the preterm controls without BPD.

Our findings add to what is currently known regarding the persistence of respiratory morbidity in preterm infants with BPD surviving beyond childhood. Moreover, we have studied BPD patients at a greater mean age (>6 years older) than any study to date. We believe our finding that adult BPD survivors report greater impairment in quality of life than term controls is important and has not previously been reported. Specifically, BPD survivors in our study reported more problems with mobility and self-care. These findings are at odds with BEAUDOIN *et al.* [13] who found that adults born preterm and who developed BPD had similar health status to preterm and term controls, despite greater healthcare utilisation.

Impairment in lung function persisting beyond childhood in those surviving BPD has been well described. DOYLE *et al.* [10] reported that subjects born with VLBW and who developed BPD had worse lung function in late adolescence (mean age 18.8 years) than those without BPD. In a preterm cohort of 46 survivors (35 with BPD) tested at a mean age of 17.7 years (with similar mean birth weights and gestational ages to our present study), more respiratory symptoms and significantly reduced pulmonary function were noted in the preterm group compared to term controls, with greatest reductions noted in those with severe BPD [21]. In our study three-quarters of those who met criteria for severe BPD had abnormally low mid-expiratory flow rates ($FEF_{25–75\%}$ <60% pred and z-scores $\leqslant$ -1.96). NORTHWAY *et al.* [22] studied subjects born preterm with BPD at mean age 18.3 years and reported significant reductions in mean FEV_1 and mean $FEF_{25–75\%}$ compared to term controls. However, the subjects in that study were considerably heavier at birth (mean birth weight 1894 g) and more mature (mean gestational age 33.2 weeks) than our study population. In contrast, NARANG *et al.* [23] found no significant difference in lung function between preterm subjects and controls, although the actual number with BPD in the preterm group was small (seven out of 60). While respiratory symptoms as reported on the ECRHS did not readily distinguish BPD adults from those born preterm without BPD, we identified distinct differences in the nature and severity of lung function impairment between those born preterm who developed BPD and those who did not. After adjustments for birth weight and gestational age BPD preterm subjects had significantly greater reduction in both large airway and mid-expiratory flow rates compared to non-BPD preterm controls.

A considerable strength of this study was our ability to trace and study in adulthood a group of carefully characterised preterm BPD infants and compare them with both preterm and term controls, all cared for in

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TABLE 4 Health-related quality of life of bronchopulmonary dysplasia (BPD) and control groups

	BPD	Non-BPD	Full-term	BPD *versus* non-BPD		BPD *versus* full-term	
				Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Subjects n	72	57	78				
EQ-5D	0.84±0.26	0.88±0.23[#]	0.93±0.13[¶]	-0.04 (-0.12–0.05)	0.413	-0.09 (-0.16- -0.03)	**0.007**
EQ-VAS	77.54±18.35[+]	79.32±19.00[#]	83.35±12.51	-1.78 (-8.39–4.84)	0.596	-5.80 (-10.86- -0.74)	0.028
Decreased mobility	16 (22)	7 (12)	3 (4)		0.143		**0.001**
Difficulty with self-care	9 (12)	4 (7)	0 (0)		0.304		**0.001**
Problems performing usual activities	18 (25)	11 (20)	6 (8)		0.441		**0.004**
Pain or discomfort	15 (21)	14 (25)	14 (18)		0.614		0.655
Anxious or depressed	16 (22)	11 (20)	13 (17)[¶]		0.723		0.411

Data are presented as mean±SD or n (%), unless otherwise stated. Bold data indicates statistical significance. p-values were calculated using Chi-squared analysis or Fisher's exact test if n⩽5. EQ-5D: EuroQol five-dimension component index; EQ-VAS: EuroQol visual analogue scale. [#]: n=56; [¶]: n=77; [+]: n=70.

the same hospital. However, study design necessitated the exclusion of the most disabled of preterm survivors and general practitioners were asked to determine, after review of the study protocol, whether their patients would be suitable for participation. This resulted in exclusion of only six BPD and four non-BPD individuals. Our analysis of nonresponders (either not traced or declined participation) identified no significant differences in birth weight, gestational age or BPD severity compared to BPD adults recruited, suggesting that an important selection bias was unlikely. Although our study size is relatively small it is still larger than any identified in our recent systematic review [14]. Our study reports on adults born between 1978 and 1993, an era which largely precedes the use of surfactant and corticosteroids in the neonatal period. In our unit during this period post-natal steroids were used predominantly for ventilator-dependent infants with BPD and surfactant was used for treatment of preterm infants with respiratory distress syndrome, rather than prophylaxis which later became accepted practice. In a recent study of infants born preterm in the post-surfactant era and studied in mid-childhood (mean±SD age 10±1.5 years), the majority of those who developed BPD had only mild disease (21 out of 28 studied) with little evidence of lung function impairment compared to preterm and term controls [9]. While our results may not necessarily be generalisable to the later cohorts of preterm infants who develop "new" BPD [24], we believe our findings are applicable to the large number of BPD survivors currently in their third and fourth decades of life who may have unrecognised or incorrectly diagnosed respiratory disease.

Epidemiological studies have suggested an important association between preterm birth and respiratory morbidity and mortality in adulthood. A strong independent inverse association between preterm birth and mortality from respiratory disorders in young adults born in Sweden has recently been reported [25]. The same group reported that young adults born extremely preterm (23–27 weeks gestational age) were 2.4 times more likely to be prescribed asthma medication [26]. Consistent with this we found a three-fold increase in asthma medications among BPD adults (with mean gestational age of 27.1 weeks) compared to those born at term. Lower birth weights in infants born preterm may be a factor; in a population-based case–control study an increased risk of hospitalisation for respiratory disease in adults with low birth weight compared to those with normal birth weight was reported [27]. In a recently reported population-based cohort study, low birth weight and preterm birth were identified as risk factors for the presence of obstructive airway disease in old age [28].

In summary, we confirm that compared to preterm and term controls, BPD survivors have increased respiratory symptoms and impaired lung function which persists well into adulthood. Concerns regarding important respiratory morbidity in adults born prematurely, in particular those who develop neonatal lung disease and who may be at risk of developing chronic obstructive pulmonary disease, are strongly supported by our findings. As preterm birth has increased globally in the last 30 years [29] the longitudinal follow-up of larger cohorts of these infants throughout adulthood is required to improve understanding and raise awareness of long-term health sequelae.

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