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Structural and functional lung impairment in adult survivors of bronchopulmonary dysplasia

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Author contribution: The study was conceived and designed by Lorcan McGarvey, Michael Shields, Chris Patterson and Henry Halliday. Steven Caskey performed data collection and with Lorcan McGarvey prepared the first draft of the manuscript. Michael Shields, Chris Patterson and Henry Halliday assisted with data interpretation and preparation of subsequent versions of the manuscript. Lorcan McGarvey was Principal Investigator and is Guarantor for the manuscript. Scott Gillespie and James Clarke scored CT scans and assisted in manuscript preparation. Jacqui Megarry, Marshall Riley and Paul Nicholls provided assistance with conduct and interpretation of cardiopulmonary exercise testing. Stephen Rowan assisted with the multiple breath washout testing and interpretation.

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

Abstract

Rationale: With increasing survival of preterm infants with bronchopulmonary dysplasia (BPD) it is critical to understand the clinical consequences on adult lung health.

Objectives: To assess structural and functional lung parameters in young adult BPD survivors and preterm and term controls

Methods: Young adult survivors of BPD (mean age 24) underwent spirometry, lung volumes, transfer factor, lung clearance index and fractional exhaled nitric oxide measurements together with high-resolution chest tomographic CT imaging and cardiopulmonary exercise testing.

Measurements and main results: 25 adult BPD survivors, (mean \pm SD gestational age (GA) 26.8 ± 2.3 weeks; birth weight 866 ± 255 g), 24 adult prematurely born non-BPD controls (GA 30.6 ± 1.9 weeks; birth weight 1234 ± 207 g) and 25 adult term birth controls (GA 38.5 ± 0.9 weeks; and birth weight 3569 ± 2979 g) were studied. BPD subjects were more likely to be wakened by cough (OR 9.7, 95% CI: 1.8 to 52.6), $p < 0.01$), wheeze and breathlessness (OR 12.2, 95%CI: 1.3 to 112), $p < 0.05$) than term controls after adjusting for gender and current smoking. Preterm subjects had greater airways obstruction than term subjects. BPD subjects

had significantly lower values for FEV₁ and FEF₂₅₋₇₅ (% predicted and z scores) than term controls (both p<0.001). Although non-BPD subjects also had lower spirometric values than term controls, none of the differences reached statistical significance. More BPD subjects (25%) had fixed airflow obstruction than non-BPD (12.5%) and term (0%) subjects (p=0.004). Both BPD and non-BPD subjects had significantly greater impairment in gas transfer (K_{CO} % predicted) than term subjects (both p<0.05). Eighteen (37%) preterm participants were classified as small for gestational age (birth weight < 10th percentile for gestational age). These subjects had significantly greater impairment in FEV₁ (% predicted and z scores) than those born appropriate for gestational age. BPD survivors had significantly more severe radiographic structural lung impairment than non-BPD subjects. Both preterm groups had impaired exercise capacity compared to term controls. There was a trend for greater limitation and leg discomfort in BPD survivors.

Conclusions: Adult preterm birth survivors, especially those who developed BPD, continue to experience respiratory symptoms and exhibit clinically important levels of pulmonary impairment.

Abstract word count: 350

Children born prematurely and especially those who develop bronchopulmonary dysplasia (BPD) have more respiratory symptoms (1, 2) and greater lung function impairment persisting through adolescence than term born peers (2, 3, 4). Consequently concerns regarding the longer-term consequences of BPD include the early development of chronic obstructive pulmonary disease (COPD) (5, 6). The adult respiratory health outcomes of BPD survivors are not well defined and our recent systematic review highlighted the limited number of small studies, some without suitable study controls (7).

Although we have recently undertaken a study of adult survivors of BPD in their third and fourth decade of life and reported increased respiratory symptoms and substantial and clinically important reductions in lung function variables reflecting airflow obstruction compared to preterm and term controls, important knowledge gaps remain. Specifically, it is unclear whether lung impairment extends beyond the airway and if lung injury in early preterm life is associated with structural damage to surrounding lung tissue.

One small study of highly selected and symptomatic adult BPD subjects reported striking structural damage including emphysema (8). Furthermore lung impairment may only become apparent during exercise and to date results from cardiopulmonary exercise testing have been conflicting. Vrijlandt and colleagues (9) confirmed reduced peak oxygen consumption in young adult BPD subjects compared to healthy controls. Lovering and colleagues (10) confirmed significantly reduced peak work rates and greater leg discomfort during exercise in preterm non-BPD and BPD subjects compared to term controls. In contrast, Narang *et al* (11), found no evidence of exercise limitation in ex preterm subjects compared to term controls.

Based on the accumulating evidence we hypothesised greater structural and functional lung impairment in adult BPD survivors compared to preterm and term controls. Here we report on lung function (spirometry, lung volumes, diffusing capacity), lung clearance index, fractional exhaled nitric oxide (FeNO) measurements, exercise capacity and high resolution CT (HRCT) findings in an index group of adult survivors of BPD compared to preterm and term controls. We used a subset of our Premature Adult Lung Study (PALS) cohort which was previously published (12) and reported in abstract form (13, 14, 15, 16, 17).

Methods

Study design and participants

The PALS cohort comprised adults previously cared for in the Regional Neonatal Intensive Care Unit (NICU) of the Royal Maternity Hospital, Belfast between January 1978 and April 1993. This unit was the regional centre providing a comprehensive neonatal service and received patients from all over Northern Ireland.

BPD was defined as the continued requirement for supplemental oxygen >28 postnatal days with chronic radiological changes and severity (mild, moderate or severe) was graded according to oxygen requirements at 36 weeks post menstrual age (18). BPD subjects were compared with gender matched preterm non-BPD controls also cared for in the NICU but not requiring mechanical ventilation or prolonged respiratory support. Both preterm groups were of very low birth weights (VLBW: < 1500g). A second control group comprising full term individuals, with no history of respiratory disease was recruited.

Tracing and recruitment to PALS and this sub study (Figure E1) is detailed in the online supplement. Consecutive subjects responding to an invitation to participate in this sub study and meeting study criteria were recruited. Subjects were excluded if physical or cognitive impairment was likely to prevent them undertaking study procedures. (See online supplement for full protocol). All participants gave written informed consent and the study was approved by the Office for Research Ethics Committees Northern Ireland (ORECNI, 11/NI/0042).

Testing Protocol: Visit one

Respiratory symptoms were recorded using the European Community Respiratory Health Survey (ECRHS) screening tool (19). Quality of life was measured using the EuroQol (20) and lung function tests were carried out in the order described below.

Multiple breath washout tests were performed using a modified Innocor™ gas analyser (Innovision™ A/S, Odense, Denmark) and an open-circuit technique (21) with the lung

clearance index calculated. FeNO was measured using the (NIOX™ MINO (Aerocrine AB, Sweden) according to ATS/ERS recommendations (22).

Forced Vital Capacity (FVC), and Forced Expiratory Volume in one second (FEV₁) and mid expiratory flow (FEF₂₅₋₇₅) were measured in accordance with ATS/ERS guidance (23) using a Sensoromics Vmax Encore (Conshohocken, USA). Spirometric results were expressed as percent predicted and z-scores based on prediction equations provided by the Institute of Child Health (24).

Total Lung Capacity (TLC) and Residual Volume (RV) were measured using Helium dilution. Diffusing capacities were measured using single breath diffusing capacity tests. Subjects omitted regular asthma medication the morning of testing.

BPD subjects and non-BPD controls underwent inspiratory and expiratory HRCT imaging of the chest on a 64-slice CT scanner (Siemens AG, Germany). All scans were scored independently and blindly by two expert radiologists (SG, JC) using a validated standardised scoring method (Table E1 online supplement) (25).

Testing Protocol: Visit Two

Exercise testing was performed using a standardised, symptom-limited, maximal exercise protocol, (Modified Bruce Protocol) (26) using ATS guidelines (27). Peak VO₂ was defined as the average VO₂ over the final 30 seconds of exercise. The anaerobic threshold was determined using the V slope method by two experienced observers (SC, JM). Exercise data were plotted as time weighted 10 second averages.

Statistical analysis

Continuous variables were summarised as mean (standard deviation, SD) if normally distributed and median (interquartile range, IQR) if skewed. For normally distributed variables group comparisons were made using one-way ANOVA (with Tukey's post-hoc all pairs simultaneous 95% confidence intervals for mean differences and p-values) or t-tests.

For non-normally distributed variables group comparisons were made using Kruskal-Wallis test (with Dunn's all pairs post-hoc testing) or Mann-Whitney U tests. Categorical variables were summarised as proportions and comparisons performed using the chi-square test (or Fisher's exact test, where appropriate) and summarised as odds ratios.

We used linear regression modelling to compare lung function for those with BPD and Preterm Non BPD whilst adjusting for birth weight, gestational age and year of birth.

Logistic regression was used to compare symptoms between groups whilst adjusting for gender and current smoking status.

We undertook analysis to determine the effect of low birth weight for GA by comparing those born small for gestational age (SGA) with those born at an appropriate weight for gestation (AGA). SGA was defined as a birth weight < 10th percentile for gestational age using the 1990 British Growth Standard (28). These comparisons of SGA and AGA subgroups required weighting to take account of the different selection probabilities for the BPD and non-BPD subgroups inherent in our study design.

SPSS version 20 (IBM Corp., Armonk, New York), Minitab 17 (Minitab Inc., State College, Pennsylvania) and Stata release 12 (Stata Corp, College Stations, Texas) were used in the statistical analysis. A p-value ≤ 0.05 was taken as statistically significant

Results

Twenty five BPD subjects (mean (SD) age 24.0 (3.4)y, range 19 to 33y) were enrolled and compared with 24 non-BPD controls (mean (SD) age 26.4 (3.7)y, range 21 to 34y) and 25 term controls (mean (SD) age 28.3(3.3)y, range 22 to 33y). Of these, 23 BPD subjects (15% of the original 153 identified from labour records) and 23 non BPD (7% of original 322 non-BPD subjects from labour records) completed all parts of this study.

Term controls comprised 12 (2% of original 492 identified from labour records) and 13 healthy volunteers born term with known birth weight and GA recruited from hospital staff. Participant demographics are detailed in Table 1.

BPD subjects had a lower gestational age [mean 26.8 weeks (SD 2.3, range 23 to 30 weeks)] compared to non-BPD subjects [mean 30.6 (SD 1.9, range 26 to 34) weeks] and lower birth weight [mean 866 (SD 255, range 510 to 1490) grams] compared to non-BPD subjects [mean 1234 (SD 205, range 760 to 1500) grams, (both $p < 0.001$)].

Current smoking status, BMI and physician diagnosed asthma were not significantly different among groups. One BPD subject was receiving inhaled corticosteroids and a short acting beta 2 agonist and 2 others were prescribed short acting beta 2 agonists alone. No non-BPD subjects were prescribed inhaled corticosteroids although one was prescribed a short acting

beta 2 agonist. One term control had been prescribed an inhaled corticosteroid/long acting beta 2 agonist while 3 others took short acting beta 2 agonists alone.

There were no significant differences in gestation between BPD subjects recruited and those not responding to invitation but the responders were on average 150 lighter in birth weight (Table E2, online supplement).

Respiratory symptoms

BPD subjects were at almost 10 times more likely to report being woken by coughing (OR 9.7, 95% CI: 1.8 to 52.6), $p < 0.01$), and were over 4 times more likely to report being breathless when wheezing (OR 4.3, 95%CI: 1.1 to 16.8), $p < 0.05$) in the last 12 months compared to term controls after adjusting for gender and current smoking (Table E3 online supplement). BPD subjects had significantly lower EQ-5D utility score than term controls ($p < 0.01$) and reported lower scores on EQ-5D VAS compared with non-BPD, although this was not statistically significant (Table E4, online supplement).

Lung function

Significant differences were apparent between the 3 groups in all lung function tests with the exception of RV % predicted, TLC % predicted and RV/TLC ratio (Table 2 and Figure 1). BPD subjects had significantly lower values for all spirometric measures than term controls. Although non-BPD subjects also had lower spirometric values than term controls, none of the differences reached statistical significance.

BPD subjects had significantly lower mean values for FEV₁, FVC and FEF₂₅₋₇₅ compared to non-BPD controls whether expressed as percent predicted or z-scores (Table 2). Of the 7 BPD

subjects who had an FEV₁/ FVC ratio < 70 % predicted only 2 had significant reversibility defined as change in FEV₁ of > 400mls and FEV₁ % predicted > 15 % after bronchodilator (23).

While not statistically significant, RV/TLC ratios were higher in the BPD subjects than preterm and term controls. Diffusing capacities TL_{CO} and K_{CO} % predicted values were similar in BPD and non-BPD subjects and both were significantly lower than term controls (both $p < 0.001$).

Significantly more BPD subjects had airflow reductions in the abnormally low range defined as FEV₁ < 80% predicted, FEV₁/FVC <70%, FEF₂₅₋₇₅ < 60% predicted, TL_{CO} % predicted < 80%, K_{CO} % predicted <80%). Almost one quarter of the BPD group had FEV₁ <80% compared to none of the term controls. Similarly, 60% of BPD subjects had FEF₂₅₋₇₅ <60% compared to less than 5% of term controls.

Abnormally increased RV/TLC ratios (i.e. >120 % predicted) were recorded in 38% of BPD subjects compared with less than 5% of term controls. 43% of BPD subjects had abnormally low TL_{CO} % predicted and 23 % abnormally low K_{CO} % predicted compared to term controls (4% and 0% respectively) (both $p < 0.01$) . Compared to non-BPD controls, significantly more BPD subjects had abnormally low FEF₂₅₋₇₅ % predicted values ($p < 0.01$) (Table E5 online supplement).

As our study population comprised adults born preterm over a 15 year time span we considered the possibility that our comparisons of groups could be confounded by birth cohort effects as well as by birth weight and gestational age differences. Regression analysis of the lung function measurements (Table E6 online supplement).

Lung Clearance Index

Lung clearance index scores were significantly higher in BPD subjects [median (IQR) 7.0 (6.7-7.9)] compared to non-BPD [6.1 (5.9-6.9)] and term controls [6.6 (5.9-7.0)] ($p=0.016$ and $p=0.003$). Using our recently published normal values [mean (SD) 6.5 (0.5)] for lung clearance index by multiple breath washout on the same device in a cohort ($n=30$) of healthy controls (Section E1.2) (29) more BPD subjects ($n=6$) had abnormal lung clearance index values (> 1.96 SD score *i.e.* > 7.5) compared with non-BPD ($n=2$) and term ($n=1$) controls ($p=0.055$). Thirty percent of BPD subjects with normal FEV₁ ($>80\%$ predicted) had abnormal lung clearance index measurements (22).

FeNO measurements

Although FeNO measurements were lower in both BPD subjects (median 19, IQR: 12 to 28 ppb) and non-BPD controls (median 19, IQR: 12 to 28 ppb) compared to term controls (median 27, IQR: 14 to 43 ppb) neither result attained statistical significance.

Lung function of subjects with low versus appropriate birth weight for gestational age

Eighteen (37%) preterm participants were classified as SGA (birth weight $< 10^{\text{th}}$ percentile for gestational age). Data are presented in table 3. The SGA participants had been born at significantly greater gestational age than AGA (mean difference (95%CI), -2.4 weeks (1.5 to 4.1), $p < 0.001$). SGA subjects had significantly greater impairment in FEV₁ (% predicted than those born AGA (mean difference (95%CI), -9.8 (-19.3 to -0.2), $p<0.05$) but this difference did not retain its significance after weighting the analysis to allow for the higher sampling

fraction of BPD subjects than non-BPD subjects. Those with BPD were no more likely to be SGA as preterm non-BPD (32% versus 42%, chi-squared $p=0.69$).

HRCT chest Imaging

BPD subjects had higher HRCT scan severity scores than non-BPD ($p=0.0001$) and all BPD subjects had some degree of HRCT abnormality (Figure E2 and E3, Table 4). Sub-pleural opacities were the most common abnormality detected, and more common in BPD than non-BPD subjects (96% v 43%, $p<0.001$). Hypoattenuation on expiration (gas trapping) and bullous disease were significantly more common in BPD than non-BPD (65% v 30%, and 22% v 0%, both $p<0.05$). There were no significant differences in emphysema, bronchiectasis or bronchial wall thickening between groups.

When all preterm subjects were considered together, increasing HRCT score severity correlated significantly with measures of airflow obstruction (lower FEV₁ z-scores, FEV₁/FVC z-scores, FEF₂₅₋₇₅ z-scores) and hyperinflation (increased RV/TLC ratio). When only BPD subjects were considered, only the correlation between HRCT score and RV/TLC ratio remained significant.

Cardiopulmonary exercise testing

Exercise data were obtained from 22 BPD subjects, 20 non-BPD and 24 term controls (Table 5). Two BPD subjects were unable to perform the test because of cerebral palsy. One BPD subject, 2 non-BPD and 1 term control failed to attend. A greater proportion of term controls exercised more than 3 hours/week with no other significant differences in weekly activity levels among study groups. Fatigue and dyspnoea were the most common reason for

terminating the test in each group. More subjects with BPD (n=7) reported leg discomfort during exercise than non-BPD (n=4) and term controls (n=3).

BPD subjects had significantly lower peak VO_2 than term controls [Mean (SD) ml/kg/min: 35.6 (7.5) vs. 45.2 (11.3) ($p < 0.01$)] and travelled significantly less distance than term controls [Mean (SD) m: 966 (245) vs. 1402 (333) ($p < 0.001$)]. Non-BPD controls had significantly lower peak VO_2 than term controls [39.3 (8.8) vs. 45.2 (11.3) ($p < 0.05$)] and also travelled significantly less distance than term controls [1143 (303) vs. 1402 (333), $p < 0.05$]. A number of BPD subjects (n=6) failed to attain $>84\%$ of their predicted target heart rate. Even when these subjects were excluded the significant differences in peak VO_2 between BPD subjects and term controls remained [Mean (SD) ml/kg/min: 36.9 (7.2) vs. 46.1 (10.8) ($p < 0.01$)]. BPD subjects achieved lower peak VO_2 and travelled shorter distances than non-BPD but these differences were not statistically significant.

At peak exercise, BPD subjects had significantly lower peak heart rates than term controls (mean (SD) bpm: 173(13) vs. 186 (14), $p < 0.001$). Ventilatory equivalents for CO_2 and O_2 at the AT were greater in the BPD group than in the term controls, but there were no significant differences in ventilatory reserve or maximum respiratory rates between BPD subjects and term controls. BPD subjects had significantly lower minute ventilation (VE l/min) [Mean (SD) (l/min): 78.3 (22.7) vs. 109.5 (36.2); ($p < 0.01$)] and smaller tidal volume (V_t , L) [1.75 (0.45) vs. 2.75 (0.67); ($p < 0.001$)] at peak exercise than term controls.

Measures of airflow obstruction [FEV₁ % predicted ($r=0.29$, $p=0.001$), FEV₁/FVC ratio ($r=0.01$, $p=0.05$) and FEF₂₅₋₇₅ % predicted ($r=0.32$, $p=0.04$)] were significantly correlated with impaired exercise capacity in adult survivors of BPD. However, HRCT scan severity scores were not associated with exercise capacity in preterm adults. There were no neonatal factors that could significantly predict impaired exercise capacity in preterm subjects.

Discussion

In this study, we confirm that individuals born prematurely, in particular those who developed BPD, have clinically important levels of respiratory morbidity persisting into adulthood. Young adult BPD survivors reported more wheeze, breathlessness and wakening with cough than non-BPD or term controls and significantly more had fixed airflow obstruction in the presence of normal or low FeNO levels and decreased diffusion capacity. BPD survivors had radiological evidence of more severe structural lung impairment than non-BPD controls. We also observed that both preterm groups had impaired exercise capacity compared to term controls with a trend for greater exercise limitation and more leg discomfort during exercise in BPD survivors.

Our findings reaffirm the evidence suggesting adverse long term consequences of preterm birth and BPD on adult respiratory health (4, 11, 29-31). We extend our previous observations and suggest lung function abnormalities are not confined solely to spirometric end points, but include air trapping and impaired gas transfer (12). In the majority (75%) of BPD survivors, airflow obstruction was fixed or only partially reversible and was associated with normal or low FeNO values suggesting a non-asthmatic or at least a non-eosinophilic cause for airflow limitation.

This observation adds support to the concern that perinatal lung injury may predispose to early COPD (6).

In a recent study by Landry and colleagues (32), adults born prematurely with BPD were more likely to have mild airflow obstruction and bronchial hyperresponsiveness than those born prematurely who did not experience BPD. We did not undertake methacholine challenge testing but the presence of fixed airflow obstruction in a number of our subjects suggests that distinct phenotypic variants of airflow limitation exist in adult survivors of preterm birth.

Significantly lower FVC (% predicted and z scores) were observed in BPD subjects compared to term born although restrictive defects were not seen as no subjects had FVC and/or TLC measurements below the lower limit of normal. Although mean birth weights were lower in BPD subjects compared to non-BPD adjustment for birth weight did not alter our findings. As none of the non-BPD preterms were ventilated we suspect the inflammatory effects on lung development in early neonatal life due to hyperoxia and barotrauma and possible infection during the periods of mechanical ventilation have contributed to differences between the preterm groups. Lung clearance index measured by multiple breath washout is a measure of ventilation distribution which may become heterogeneous (uneven) early in diseases including asthma (33) and cystic fibrosis (34). We observed a greater proportion of adult BPD survivors with abnormal values compared to term. Although measurements were not as high as reported in bronchiectasis (29) a significant proportion (30%) of BPD subjects with normal spirometry, had abnormal lung clearance index measurements.

We investigated the association between neonatal factors and lung function in our preterm population. We adjusted for year of birth and found no evidence of a birth cohort effect. We

sought to determine whether low birth weight for gestational age could explain some of our findings and report that those born SGA had greater lung function impairment than subjects born AGA. Infants with intra-uterine growth retardation are at increased risk of impaired lung function within the first few years of life (35). Here we provide evidence that impairment extends into adulthood.

Structural lung abnormalities on CT scans have been reported in children and adolescents surviving BPD (25, 36). We found that BPD subjects have significantly more radiological abnormality compared to non-BPD controls. Subpleural opacities were the most common abnormality observed in almost all (96%) of our BPD subjects compared with less than half (46%) of non-BPD subjects. They are thought to be related to fibrotic change within the lung arising from neonatal insults such as hyperoxia and mechanical ventilation. We did not see significant bullous lung disease contrasting the findings of Wong *et al*, (8). We observed significant inverse relationships between spirometry measurements and HRCT score severity and highlight important 'structure-function' consequences of preterm birth on adult lung health. We observed significantly impaired exercise capacity in preterm subjects (BPD and non BPD) compared to term controls. Following adjustments for sub-maximal exercise tests (Table E9) and general activity levels, these significant differences remained. BPD subjects had numerically greater reductions in peak VO_2 and distance travelled on the treadmill than the preterm non-BPD controls which could possibly be due to patient effort as they achieved lower peak heart rates lower RERs. At least some of the reduction in exercise capacity in both our preterm groups may have been due to deconditioning as the VO_2 at AT/peak VO_2 was lower in these groups than in term controls. The slightly low oxyhemoglobin saturation and elevated ventilatory equivalents in BPD subjects suggest mild impairment of gas exchange during exercise, but these abnormalities did not limit exercise

as indicated by the normal ventilatory reserve. Our finding of impaired exercise capacity in adults born preterm is in line Vrijlandt *et al* (9) but contrasts Narang and colleagues (11), who observed no differences between preterm and term subjects. Their preterm group had relatively well preserved lung function and included few ($n=7$) BPD subjects. A recent study by Lovering and colleagues (10) identified reduced exercise capacity in adult preterm survivors which was independent of BPD or exercise induced expiratory flow limitation. We did not undertake measurements of expiratory flow or dynamic hyperinflation during exercise. However reduced lung function and low lung diffusion capacity alone do not appear to explain the reduced exercise capacity observed in adult survivors of preterm birth (37). Other unidentified aspects of BPD which might influence exercise performance include deconditioning or perception of fatigue. Landry and colleagues reported that BPD subjects tended to be more sedentary than non-BPD and term subjects (32). In line with Lovering and colleagues (10) a greater proportion of our preterm subjects reported leg discomfort during exercise which may simply reflect deconditioning but does raise the possibility of impaired peripheral muscle function as an additional longer term consequence of preterm birth.

Strengths and Limitations

A key strength was the ability to trace and study in adulthood, a group of carefully characterised preterm infants (BPD subjects and non-BPD controls) all cared for in the same hospital. Further, our study size was larger than many identified in our systematic literature review (7).

A potential limitation of our study was the relatively low recruitment rates of preterm adults from the infants identified in the original labour records. This may have introduced bias such as exclusion of the most severely affected although the similarity of birth demographics

between the PALS cohort and those not responding to the study invitation suggests our findings are broadly representative of the general preterm population.

Although less applicable to infants with 'new' BPD arising from extreme prematurity, our findings are relevant to the large number of BPD survivors currently in their third and fourth decade of life many of whom may have unrecognised or incorrectly diagnosed respiratory disease. There is a need for increased awareness as recent evidence suggests that few physicians enquire about neonatal events when assessing their adult patients with pulmonary complaints (38).

None of the non-BPD subjects were ventilated during the neonatal period which does raise a potential bias when directly comparing BPD and non-BPD subjects. Further, non-BPD preterms had higher mean GA and birth weight than BPD preterms and although we undertook linear regression to simultaneously correct for these variables were we not able to adjust for all potential factors.

Finally, as this is a cross-sectional study we have no information on earlier or later lung function trajectories for this cohort. Following preterm cohorts from early life through adulthood into later life is crucial to a complete understanding the consequences of lung injury in the neonatal period.

Conclusions

Adult survivors of preterm birth have evidence of airflow obstruction which is fixed or only partially reversible. In addition we observed impaired levels of exercise capacity in those

born preterm compared to full term which could not be explained solely by structural changes or lung function impairment. Whether this impairment is progressive requires longitudinal follow up of preterm cohorts.

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Figure legend

Figure 1: Graphical summary of % predicted (mean \pm SD) for airflow and gas transfer variables between study groups. BPD subjects had significantly lower values for all displayed measures than term controls groups (FEV₁, FVC and FEF₂₅₋₇₅, all $p < 0.001$; K_{CO} $p < 0.001$). Non-BPD subjects also had lower spirometric values than term controls but none of the differences reached statistical significance. BPD subjects had significantly lower mean values for FEV₁ and FEF₂₅₋₇₅ (% predicted) (both $p < 0.01$) compared to non-BPD controls.

Table 1: Demographics of study participants

	BPD	Non BPD	Term	BPD vs. non BPD	BPD vs. Term	Non BPD vs. Term
Number, n	25	24	25			
Birth weight, g	866 (255)	1234 (205)	3569 (297)	-369 (-544 to -194) ***	-2704 (-2877 to -2530) ***	-2335 (-2510 to -2160) ***
Gestational age, wk	26.8 (2.3)	30.6 (1.9)	38.5 (0.9)	-3.8 (-5.0 to -2.6) ***	-11.6 (-12.9 to -10.4) ***	-7.9 (-9.1 to -6.6) ***
Duration of IPPV, h	966 (599-1652)	n/a	n/a			
Duration O₂ >60 %, h	10 (2-99)	n/a	n/a			
Maternal Smoker	7/19 (37%)	8/18 (44%)	n/a	0.7 (0.2 to 2.7)		
Antenatal Steroids	5/25 (20%)	8/24 (33%)	0/25 (0%)	0.5 (0.1 to 1.8)		
Postnatal Steroids	10/25 (40%)	0/24 (0%)	0/25 (0%)			
Surfactant	8/25 (32%)	0/24 (0%)	0/25 (0%)			
Apgar Score 1 min	5 (3-6)	7 (3-8)	n/a	-1 (-3 to 0)		
Apgar Score 5 min	8 (7-9)	9 (8-9)	n/a	-1 (-2 to 0)**		
BPD Moderate or Severe	13/25 (52%)	n/a	n/a			
Gender, male	14/25 (56%)	14/24 (58%)	15/25 (60%)	0.9 (0.3 to 2.8)	0.8 (0.3 to 2.6)	0.9 (0.3 to 2.9)
Age at study, y	24.0 (3.4)	26.4 (3.7)	28.3 (3.3)	-2.4 (-4.8 to 0.0)*	-4.3 (-6.6 to -1.9)***	-1.8 (-4.2 to 0.5)
Height, cm	163.7 (10.8)	166.4 (11.6)	173.7 (7.5)	-2.7 (-9.6 to 4.2)	-10.0 (-16.9 to -3.2)**	-7.4 (-14.3 to -0.5)*
Body mass index, kg/m²	25.0 (5.6)	22.7 (3.4)	24.9 (3.6)	2.3 (-0.9 to 5.4)	0.1 (-3.0 to 3.1)	-2.2 (-5.3, 0.9)
Physician-diagnosed Asthma	4/25 (16%)	1/24 (4%)	4/25 (16%)	4.4 (0.4 to 42)	1.0 (0.2 to 4.5)	0.2 (0.0 to 2.2)
Current smoker†	2/25 (8%)	5/24 (21%)	2/25 (8%)	0.3 (0.1 to 1.9)	1.0 (0.1 to 7.7)	3.0 (0.5 to 17)
Exercise at least 2-3 hr/week	6/24 (25%)	5/22 (23%)	14/22 (64%)	1.1 (0.3 to 4.4)	0.2 (0.1 to 0.7)*	0.2 (0.1 to 0.7)*

Data are presented as mean (SD), median (IQR) or n(%)

Between group comparisons are presented as difference in means (95%CI), differences in medians (95%CI) or odds ratios (95%CI)

n/a – not available

* : p<0.05, **: p<0.01, ***: p<0.001

† Daily smoker at the time of testing.

Table 2 Static lung function and gas transfer tests compared between preterm BPD and control groups

	BPD (n=25)	Non BPD (n=23)	Term (n=25)	BPD vs. non BPD	BPD vs.Term	Non BPD vs. Term
FEV₁ % pred.	88.2 (15.2)	102.0 (14.9)	109.4 (11.8)	-13.8 (-23.5 to 4.1)**	-21.2 (-30.7 to -11.7)***	-7.3 (-10.0 to 2.4)
FEV₁ z-score	-1.19 (1.27)	0.01 (1.27)	0.49 (0.91)	-1.20 (-2.00 to -0.40)**	-1.68 (-2.46 to -0.89)***	-0.48 (-1.27 to 0.32)
FVC % pred.	101.8 (15.0)	110.2 (13.8)	115.7 (9.4)	-8.5 (-17.5 to 0.5)	-14.0 (-22.7 to -5.2)***	-5.5 (-14.4 to 3.5)
FVC z-score	-0.11 (1.22)	0.46 (1.24)	0.77 (0.83)	-0.57 (-1.34 to 0.20)	-0.88 (-1.63 to -0.13)*	-0.31 (-1.07 to 0.46)
FEV₁/FVC ratio % pred.	75.0 (9.1)	80.2 (9.9)	81.1 (7.1)	-5.2 (-11.3 to 0.8)	-6.1 (-12.0 to -0.2)*	-0.9 (-6.9 to 5.2)
FEV₁/FVC z-score	-1.21 (0.99)	-0.45 (1.10)	-0.17 (1.08)	-0.76 (-1.49 to -0.03)*	-1.05 (-1.76 to -0.33)**	-0.28 (-1.01 to 0.45)
FEF₂₅₋₇₅ % pred.	59.0 (21.5)	80.7 (26.0)	90.8 (20.3)	-21.7 (-37.4 to -6.1)**	-31.8 (-47.1 to -16.5)***	-10.1 (-25.7 to 5.6)
FEF₂₅₋₇₅ z-score	-1.55 (1.34)	-0.41 (1.26)	-0.07 (0.96)	-1.14 (-1.97 to -0.31)**	-1.48 (-2.29 to -0.67)***	-0.34 (-1.17 to 0.49)
RV % pred.	108.6 (36.7) ^a	103.5 (32.1) ^b	105.6 (34.2) ^c	5.1 (-20.3 to 30.6)	3.0 (-21.7 to 27.7)	-2.1 (-26.8 to 22.5)
TLC % pred.	104.7 (15.2) ^a	105.6 (10.9) ^b	110.9 (12.4) ^c	-1.0 (-10.5 to 8.6)	-6.3 (-15.5 to 3.0)	-5.3 (-14.6 to 4.0)
RV/TLC ratio %	106.4 (33.4) ^a	96.9 (26.3) ^b	91.5 (19.0) ^c	9.5 (-10.1 to 29.2)	15.0 (-4.1 to 34.0)	5.4 (-13.6 to 24.5)
TL_{CO} % pred.	87.4 (16.8) ^b	90.1 (12.6)	104.9 (11.2)	-2.7 (-12.4 to 7.0)	-17.6 (-27.1 to -8.1)***	-14.8 (-24.3 to -5.3)**
K_{CO} % pred.	86.5 (9.7) ^d	87.1 (10.9) ^c	101.5 (11.3) ^b	-0.6 (-8.3 to 7.1)	-15.0 (-22.6 to -7.4)***	-14.4 (-22.0 to -6.8)***
Lung clearance index	7.0 (6.7 to 7.9) ^e	6.1 (5.9 to 6.9) ^a	6.6 (5.9 to 7.0) ^d	0.9 (0.3 to 1.2)**	0.4 (0.1 to 1.1)*	-0.5 (-0.7 to 0.3)
FeNO ppb	19 (12 to 28)	19 (12 to 28)	27 (14 to 43)	0 (-6 to 6)	-8 (-15 to 2)	-8 (-16 to 2)

Data are presented as mean (SD) or median (IQR).

Between group comparisons made using ANOVA with Tukey-Kramer (all pairs simultaneous 95% CI) or Kruskal-Wallis ANOVA of ranks followed by Dunn's (all pairs) test.

*: p<0.05, **:p<0.01,***:p<0.001

BPD: bronchopulmonary dysplasia; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF₂₅₋₇₅ %: forced expiratory flow at 25-75% of FVC, % pred.: percent predicted measurements; ppb: parts per billion ^a: n=4 missing data, ^b: n=2 missing data, ^c: n=1 missing data, ^d: n=3 missing data, ^e: n=5 missing data .

Table 3 Comparison of lung function variables between small for gestational age (SGA) and appropriate for gestation age (AGA) preterm adult survivors before and after appropriate weighting for selection probabilities of BDP and non-BPD subjects.

	SGA (n=18)	AGA (n=30)	SGA vs. AGA (crude)	SGA vs. AGA (weighted)
Gestational age, wk	30.4 (2.4)	27.7 (2.6)	2.8 (1.3 to 4.3) ***	2.4 (1.5 to 4.1) ***
FEV₁ % pred.	88.7 (16.6)	98.5 (15.5)	-9.8 (-19.3 to -0.2) *	-9.1 (-19.1 to 0.8)
FEV₁ z score	-1.10 (1.43)	-0.32 (1.31)	-0.78 (-1.60 to 0.03)	-0.72 (-1.58 to 0.14)
FVC % pred.	101.8 (15.4)	108.3 (14.4)	-6.5 (-15.3 to 2.4)	-5.9 (-15.1 to 3.3)
FVC z score	-0.81 (1.39)	0.37 (1.13)	-0.55 (-1.29 to 0.19)	-0.47 (-1.31 to 0.37)
FEV₁/FVC % pred.	75.4 (8.3)	78.8 (10.5)	-3.3 (-9.2 to 2.5)	-3.1 (-9.2 to 2.9)
FEV₁/FVC z score	-1.09 (0.98)	-0.71 (1.16)	-0.38(-1.04 to 0.28)	-0.39 (-1.09 to 0.30)
FEF₂₅₋₇₅ % pred.	62.2 (24.0)	73.7 (26.4)	-11.5 (-26.9 to 3.8)	-10.5 (-27.0 to 6.0)
FEF₂₅₋₇₅ z score	-1.38 (1.28)	-0.78 (1.46)	-0.60 (-1.44 to 0.24)	-0.56 (-1.40 to 0.28)
RV % pred.	108.2 (31.5) ^a	104.9 (36.1) ^a	3.3 (-19.2 to 25.8)	1.2 (-21.4 to 23.7)
TLC % pred.	103.7 (13.2) ^a	106.0 (13.2) ^a	-2.3 (-10.9 to 6.3)	-2.5 (-10.7 to 5.7)
RV/TLC % pred.	108.3 (32.1) ^a	98.0 (28.9) ^a	10.3 (-9.3 to 29.8)	7.2 (-12.6 to 27.1)
TL_{CO} % pred.	87.3 (12.5) ^b	89.5 (16.0)	-2.2 (-11.4 to 7.1)	-2.5 (-10.4 to 5.4)
K_{CO} % pred.	87.3 (11.6) ^a	86.6 (9.6) ^b	0.7 (-5.9 to 7.3)	3.1 (-4.2 to 10.5)
lung clearance index	6.9 (6.1 to 7.0) ^c	6.6 (6.1 to 7.8) ^c	0.3 (-0.8 to 0.6)	Not applicable
FeNO, ppb	23 (12 to 28) ^d	19 (12 to 28)	4 (-4 to 9)	Not applicable

Data are presented as mean (SD) or median (IQR).

Between group comparisons made using ANOVA with Tukey-Kramer (all pairs simultaneous 95% CI) or Kruskal-Wallis ANOVA of ranks followed by Dunn's (all pairs) test.

* : p<0.05, **:p<0.01,***:p<0.001

SGA: small for gestational age; AGA: appropriate for gestational age; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25-75%}: forced expiratory flow at 25-75% of FVC, % pred.: percent predicted measurements. ^an= 3 missing data, ^b n= 2 missing data, ^c n= 5 missing data, ^d n= 1 missing data.

Table 4: Comparison of HRCT scores and radiological findings between adult preterm BPD and non-BPD survivors

	BPD (n=23)	Non BPD (n=23)	Odds Ratio (95 %CI)
Median score (interquartile range)	6 (4 to 9)	2 (0 to 4)	Not applicable
Subpleural opacities	22 (96%)	10 (43%)	28.6 (3.3, 250) ***
Hypoattenuation in expiration	15 (65%)	7 (30%)	4.3 (1.2, 14.7) *
Hypoattenuation in inspiration	4 (17%)	0 (0%)	-
Subsegmental atelectasis	4 (17%)	1 (4%)	4.6 (0.5,45.1)
Bullae	5 (22%)	0 (0%)	- *
Increased Bronchial Arterial Ratio	1 (4%)	0 (0%)	-
Bronchiectasis	1 (4%)	2 (9%)	0.5 (0.0, 5.7)
Bronchial wall thickening	1 (4%)	2 (9%)	0.5 (0.0, 5.7)
Emphysema	0 (0%)	1 (4%)	-

n/a: not applicable, * : p<0.05, ***: p<0.001

Table 5: Exercise characteristics compared between study groups

	BPD (n=22)	Non BPD (n=20)	Term (n=24)	BPD vs. Non BPD	BPD vs. Term	Non BPD vs. Term
Peak VO₂, L/min	2.33 (0.56)	2.57 (0.81)	3.40 (1.03)	-0.24 (-0.85 to 0.38)	-1.07 (-1.66 to -0.48) ***	-0.83 (-1.44 to -0.22) **
Peak VO₂, L/min % predicted	81.2 (17.8)	87.7 (17.5)	118.3 (22.4)	-6.5 (-21.0 to 8.0)	-37.1 (-50.9 to -23.3) ***	-30.6 (-44.8 to -16.5) ***
Peak VO₂, ml/kg/min	35.6 (7.5)	39.3 (8.8)	45.2 (11.3)	-3.7 (-10.7 to 3.3)	-9.6 (-16.3 to -3.0) **	-6.0 (-12.8 to 0.9) *
Peak VO₂, ml/kg/min % predicted	81.6 (14.3)	92.0 (17.3)	107.9 (22.8)	-10.5 (-24.3 to 3.39)	-26.4 (-39.6 to -13.2) ***	-15.9 (-28.5 to -2.4) *
Distance completed on treadmill, m	966 (245)	1143 (303)	1402 (333)	-178 (-398 to 43)	-436 (-647 to -226) ***	-259 (-475 to -43) *
Cardiovascular responses						
AT as % peak VO₂	50.5 (12.8)	47.6 (8.1)	63.3 (13.9)	2.9 (-6.0 to 11.8)	-12.8 (-21.3 to -4.2) **	-15.7 (-24.4 to -6.9) ***
Peak heart rate, bpm	173 (13)	180 (13)	186 (14)	-7.3 (-17.3 to 2.7)	-12.9 (-22.5 to -3.4) **	-5.6 (-15.5 to 4.2)
Peak heart rate, % predicted	88.2 (7.0)	92.8 (7.2)	96.6 (7.8)	-4.6 (-10.0 to 0.9)	-8.4 (-13.7 to -3.2) ***	-3.9 (-9.2 to 1.5)
Ventilatory and gas exchange responses						
VE max, L/min	78.3 (22.7)	85.1 (25.7)	109.5 (36.2)	-6.8 (-28.4 to 14.8)	-31.2 (-51.8 to -10.6) **	-24.4 (-45.5 to -3.2) *
VE max, % predicted	64.0 (20.5)	54.6 (6.9)	62.9 (14.6)	9.4 (-1.9 to 20.7)	1.1 (-9.7 to 11.9)	-8.3 (-19.4 to 2.7)
Vt, L	1.75 (0.45)	2.27 (0.77)	2.75 (0.67)	-0.51 (-0.99 to -0.04) *	-1.00 (-1.45 to -0.55) ***	-0.49 (-0.95 to -0.02) *
Vt, % predicted	84.6 (23.9)	88.9 (19.3)	96.2 (14.9)	-4.3 (-18.8 to 10.3)	-11.6 (-25.5 to 2.31)	-7.3 (-21.6 to 6.9)
Ventilatory reserve %	36.3 (20.4)	45.4 (6.9)	37.1 (14.6)	-9.1 (-20.4 to 2.2)	-0.8 (-11.5 to 10.0)	8.3 (-2.7 to 19.4)
Peak respiratory rate	38.6 (9.1)	35.3 (6.3)	36.0 (7.2)	3.2 (-2.4 to 8.9)	2.6 (-2.8 to 8.0)	-0.7 (-6.2 to 4.9)
Respiratory exchange ratio	1.04 (0.07)	1.09 (0.09)	1.09 (0.08)	-0.05 (-0.11 to 0.01)	-0.06 (-0.11 to 0.00)	-0.01 (-0.07 to 0.05)
VE/VO₂ @ AT	23.9 (2.0)	22.8 (2.4)	22.2 (1.7)	1.1 (-0.4 to 2.6)	1.7 (0.2 to 3.2) *	0.6 (-0.9 to 2.1)
VE/VCO₂ @ AT	28.1 (1.9)	27.0 (2.9)	25.9 (2.3)	1.1 (-0.6 to 2.9)	2.2 (0.5 to 3.9) **	1.1 (-0.6 to 2.8)
SpO₂ at peak	96 (95 to 98)	96 (95 to 97)	97 (96 to 98)	0 (-1 to 1))	-1 (-2 to 0)	-1 (-2 to 0) *
Modified Borg score (0- 10)	8 (7 to 10)	9 (8 to 10)	8 (8 to 9)	-1 (-1 to 1)	0 (-1 to 1)	1 (0 to 1)

Data are presented as mean (SD) or median (IQR).

Between group comparisons made using ANOVA with Tukey-Kramer (all pairs simultaneous 95% CI) or Kruskal-Wallis ANOVA of ranks followed by Dunn's (all pairs) test.

*: p<0.05, **: p<0.01, ***: p<0.001.

FEV₁: forced expiratory volume in 1 s , L/min: litres per minute, Vt L: tidal volume litres, Peak VO₂: oxygen uptake at peak exercise, AT: anaerobic threshold, VE/VO₂ @ AT:

Ventilatory equivalent for oxygen, VE/VCO₂ @ AT: Ventilatory equivalent for carbon dioxide.

Figures

Figure 1

