Manuscript Title

Impaired lung function and Health Status in Adult Survivors of Bronchopulmonary Dysplasia

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Running title

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ABSTRACT (200 words)

Background:
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 (FT) controls.

Method:
Respiratory symptoms (European Community Respiratory Health Survey) and HRQoL [EuroQol 5D (EQ-5D)] were measured in 72 adult BPD survivors [mean(SD) study age 24.1(4.0)y; mean(SD) gestational age (GA)=27.1(2.1)wk; mean(SD) birth weight (BW)=955(256)g] cared for in the Regional Neonatal Intensive Care Unit, Belfast (between 1978 and 1993) were compared with 57 non-BPD controls [mean(SD) study age 25.3(4.0)y; mean(SD) GA 31.0(2.5)wk; mean(SD) BW 1238(222)g] and 78 FT controls [mean(SD) study age 25.7(3.8)y; mean(SD) GA=39.7(1.4)wk; mean(SD) BW=3514(456)g] cared for at the same hospital. Spirometry was performed on 56 BPD, 40 non-BPD and 55 FT participants.

Results:
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 FEV1 and FEF25–75 than both the preterm non-BPD and FT controls (all p<0.01). Mean EQ-5D was 6 points lower in BPD adults compared to FT controls (p < 0.05).

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

Abbreviations: BPD=bronchopulmonary dysplasia; EP=extremely preterm; FT=full term; VLBW=very low birth weight; FEV1=forced expiratory flow at 1 second; FVC=forced vital capacity; FEV1/FVC=ratio of FEV1/FVC; FEF25–75=forced mid-expiratory flow.

Most important findings
Adult BPD survivors are significantly more likely to have respiratory symptoms, impaired health status and airflow obstruction than preterm and term controls.
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 grams accounting 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 (EP) and found abnormal baseline spirometry in almost half of 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-preterms than in the general population which was most evident among women [12]. The same group reported a greater prevalence of obstructive spirometry and impaired exercise capacity in preterms 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 (FT) 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, Northern Ireland.
between January 1978 and April 1993. The index group comprising subjects who developed BPD (n=72) were 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 gender and birth date matched (within two 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 (figure 1) is comprehensively detailed in the online supplement. 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 NICHD/NHLBI/ORD workshop criteria which defined BPD as the requirement for supplemental oxygen >28 postnatal days and radiographic changes and severity (mild, moderate or severe) according to oxygen requirements at 36 wk postmenstrual age (PMA) respectively [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 (ORECNI) (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 2 parts; the EuroQol 5 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 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 the lung function tests were performed using a portable spirometer, a MicroLab ML3500 Mk8 spirometer (Micro Medical Ltd, UK) according to European Respiratory Society (ERS) lung
function testing guidelines [19]. All assessments were carried out by one researcher (AG). Each participant performed a minimum of three reproducible assessments. The following indices were recorded; forced expiratory volume in 1s (FEV₁), forced vital capacity (FVC), the ratio of FEV₁/FVC and forced mid-expiratory flow (FEF₂₅–₇₅%). 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, Illinois). Categorical variables were compared using chi-square analysis and continuous variables, by independent samples t test or analysis of variance (ANOVA) where appropriate. ECRHS symptoms were adjusted for potential confounders, female gender, maternal smoking status and history of smoking in 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 gender were considered where appropriate. BPD and non-BPD groups were randomly matched for gestational age and comparisons in lung function endpoints between the matched pairs were performed using the paired t-test.

RESULTS
One hundred fifty three consecutive preterm neonates who developed BPD between January 1978 and April 1993 and were cared for in the NICU, Royal Maternity Hospital, Belfast were identified from hospital records. One hundred twenty-eight (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. One hundred sixty-eight preterm infants without BPD and 307 FT births were traced and invited to participate. Of the 66 (39%) former preterms without BPD who consented, 57 completed the questionnaires of which, 40 completed spirometry. Eighty-four (27%) traced FT born subjects consented to participate and of these 78 (25%) returned the ECRHS and 54 (18%) completed spirometry. All study participants were Caucasian. A flow chart of participant recruitment is provided in the online supplement. Demographic details of participants for each stage of the study are detailed in Table 1. The BPD group marginally younger (24.1 vs. 25.8 years; p=.012) than the FT controls but with no significant difference in gender.
Non-responder analysis
There were no significant differences in baseline characteristics between BPD participants and those who did not respond to the invitation [mean birth weight: 955(256) vs. 1030(243) g; mean gestational age: 27.1(2.1) vs. 27.5(2.2) wk]. See Table E1 in online supplement.

Respiratory Symptoms
The ECRHS screening questionnaire was completed by 72 former preterms with BPD, 57 non-BPD preterm and 78 FT participants and results are presented in Table 2. Compared to FT 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% vs. 12.8% p=0.008) and significantly more likely to have a physician’s diagnosis of asthma (40.3% vs. 14.1%, p<0.001). BPD survivors were almost three times more likely to report wheeze than non-BPD terms (OR 2.86 (1.14 to 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 preterms although these differences were not statistically significant. Among BPD survivors, those reporting a ‘physician diagnosis of asthma’ had lower birth weights (mean birth weight; 927g vs. 974g) and gestational age (mean gestational age; 26.6wk vs. 27.5wk), 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% vs. 20.7%, p=0.119).
Lung Function

Lung function data was obtained on 56 participants born preterm with BPD, 40 non-BPD preterm and 55 FT participants (Table 1). There were significant differences between the BPD and FT groups for all percent predicted spirometric endpoints (Table 3). The BPD group had significantly lower FEV\textsubscript{1} and mid-expiratory flow rates (FEF\textsubscript{25-75}) compared with both the non-BPD and FT controls. When z scores were generated for lung function indices, significant differences (p<0.001) remained evident among the groups (Table 3). Compared to term the non-BPD group had significantly lower FEV\textsubscript{1}/FVC and FEF\textsubscript{25-75} z scores (p<0.05) and also FEV\textsubscript{1}/FVC and FEF\textsubscript{25-75} percent predicted scores (p<0.001). Adjustments were made for birth weight, gestational age and maternal smoking which had little effect on the findings with only differences in FEV\textsubscript{1}/FVC values between BPB and non-BPD 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\textsubscript{1} (p<0.01) and FEF\textsubscript{25-75} (p<0.05) in the BPD preterm adults compared to non-BPD preterm adults (see online table E2).

While all lung function parameters measured were also lower in non-BPD preterms compared to FT, the mean differences were smaller than those observed when BPD were compared suggesting 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 (online supplement Table E3).

Although BPD participants who received surfactant were marginally lighter at birth (mean BW= 899g vs. 958g), required a longer duration of ventilation (median 816 vs. 750 hours), had a longer hospital stay (median 99 days vs. 94 days) and a greater proportion of severe Grade 3 BPD (28% vs. 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\textsubscript{1}< 80% predicted, FEV\textsubscript{1}/FVC < 70%, FEF\textsubscript{25-75}<60% and ≤ -1.96z scores) were compared among groups and scatter plots of results are displayed in online Figure E1.3. Significantly more BPD adults had airflow reductions in the abnormally low range on all pulmonary endpoints with almost 40% of the BPD group having FEV\textsubscript{1} <80% compared to only 6% of the FT group. Similarly, almost 50% of the BPD group had <60%
compared to less than 10% of the FT group. Comparing the BPD and non-BPD groups, significantly more BPD participants scored in the abnormally low range for FEV₁ and FEF₂₅₋₇₅. 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 FEV₁ \( z \) 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 FEV₁ (63% versus 36%) and FEF₂₅₋₇₅ (75% vs. 43%) although this failed to attain statistical significance (online supplement Table E4).

As BPD participants scored significantly worse on FEV₁, FVC and FEF₂₅₋₇₅ pulmonary function endpoints, multiple linear regression models within the BPD population were performed, with each endpoint regressed on the following perinatal variables: birth weight, gestational age, duration of IPPV and gender. 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 FT controls as measured by both the EQ-5D utility score \( (p=0.007) \) and EQ-5D VAS \( (p=0.028) \). Among preterm, 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 FT 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% vs. 12%) and self-care (13% vs. 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 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 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 (more than 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 who found that adults born preterm and who developed BPD had similar health status to preterm and term controls despite greater healthcare utilization [13].

Impairment in lung function persisting beyond childhood in those surviving BPD has been well described. Doyle and colleagues reported that subjects born VLBW with BPD had worse lung function in late adolescence (mean age 18.8 years) than those without BPD [10]. 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<sub>25-75</sub> < 60% predicted and ≤-1.96 z scores). Northway and colleagues [22] studied subjects born preterm with BPD at mean age 18.3 years and reported significant reductions in mean FEV<sub>1</sub> and mean FEF<sub>25-75</sub> compared to term controls. However the subjects in that study were considerably heavier at birth (mean birth weight: 1894g) and more mature (mean gestational age: 33.2 wk) than our study population. In contrast, Narang and colleagues found no significant difference in lung function between preterm and controls although the actual number with BPD in the preterm group was small (7 of 60) [23]. Whilst 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 preterms 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 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 6 BPD and 4 non-BPD individuals. Our analysis of non responders (either not traced or declined participation) identified no significant differences in birth weight, gestational age or BPD severity compared to BPD adults recruited suggesting 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 postnatal steroids were used predominately 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 postsurfactant era and studied in mid-childhood (mean age 10±1.5 years), the majority of those who developed BPD had only mild disease (21 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 decade 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 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 3 fold increase in asthma medications among BPD adults (with mean gestational age of 27.1 weeks) compared to 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 (COPD) are strongly supported by our findings. As preterm birth has increased globally in the last thirty 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.

Acknowledgements

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contributed to the design and analysis of data and with drafting and final approval of the version to be submitted. Dr McGarvey was Principal Investigator and is Guarantor for the manuscript. None of the authors have any competing interests or apparent conflict of interests in relation to the manuscript.

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REFERENCES


### Table 1: Perinatal characteristics of bronchopulmonary dysplasia (BPD) and control groups completing questionnaires (Stage 1) and who underwent spirometric testing (Stage 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>BPD</th>
<th>Non-BPD</th>
<th>TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage 1: n=72</td>
<td>Stage 2: n=56</td>
<td>Stage 1: n=57</td>
</tr>
<tr>
<td>Age at Study, years</td>
<td>24.1 (4.0)</td>
<td>-</td>
<td>25.3 (4.0)</td>
</tr>
<tr>
<td>Gestational Age, wk</td>
<td>27.1 (2.1)</td>
<td>27.1 (2.1)</td>
<td>31.0 (2.5)</td>
</tr>
<tr>
<td>Birth Weight, g</td>
<td>955 (256)</td>
<td>939 (246)</td>
<td>1238 (222)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>39 (54%)</td>
<td>31 (55%)</td>
<td>22 (39%)</td>
</tr>
<tr>
<td>Antenatal Steroids</td>
<td>18 (25%)</td>
<td>16 (29%)</td>
<td>22 (39%)</td>
</tr>
<tr>
<td>Maternal Smoking</td>
<td>16 (29%)</td>
<td>11 (25%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Duration Hospital Stay, days</td>
<td>104 (43)</td>
<td>106 (45)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Median Apgar Score 1 min</td>
<td>5.0 (3-6)</td>
<td>5.0 (3-6)</td>
<td>6.0 (4-7.5)</td>
</tr>
<tr>
<td>Median Apgar Score 5 min</td>
<td>8.0 (7-8.8)</td>
<td>8 (27-9)</td>
<td>9.0 (8-9)</td>
</tr>
<tr>
<td>Postnatal Steroids</td>
<td>23 (32%)</td>
<td>19 (34%)</td>
<td>-</td>
</tr>
<tr>
<td>Median Duration O₂ &gt;60%, h</td>
<td>10.5 (2.8-53.8)</td>
<td>10.0 (2-63.5)</td>
<td>-</td>
</tr>
<tr>
<td>Median Duration IPPV, h</td>
<td>841.0 (449.8-1347)</td>
<td>783 (425.8-1478.8)</td>
<td>-</td>
</tr>
<tr>
<td>Surfactant</td>
<td>22 (31%)</td>
<td>18 (32%)</td>
<td>-</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>16 (22%)</td>
<td>11 (18%)</td>
<td>17 (30%)</td>
</tr>
</tbody>
</table>

Continuous variables are reported as Mean (SD) or Median (IQR) categorical variables are reported in numbers (%); SD: Standard Deviation; IPPV: Inhaled pressure ventilation; *: p<.001; CI: Confidence Intervals; Current Smoker included those who were daily smokers at the time of testing, n=1 missing data, n=2 missing data, n=4 missing data, n=7 missing data.
Table 2: Respiratory Symptoms reported on the ECRHS amongst BPD adults and control participants.

<table>
<thead>
<tr>
<th>Respiratory symptoms in the previous 12 months</th>
<th>BPD (n=72)</th>
<th>Non-BPD (n=57)</th>
<th>Term (n=78)</th>
<th>BPD vs. Non-BPD Unadjusted Odds ratio (95% CI)</th>
<th>BPD vs. Non-BPD Adjusted Odds ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>BPD vs. Term Unadjusted Odds ratio (95% CI)</th>
<th>BPD vs. Term Adjusted Odds ratio (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 1: Wheeze?</td>
<td>34 (47%)</td>
<td>19 (33%)</td>
<td>24 (31%)</td>
<td>1.79 (0.87 to 3.67)</td>
<td>2.86 (1.14 to 7.16)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>2.01 (1.03 to 3.92)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>2.29 (1.14 to 4.59)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Item 1.1: Wheeze and breathless?</td>
<td>19 (26%)</td>
<td>13 (23%)</td>
<td>13 (17%)</td>
<td>1.21 (0.54 to 2.73)</td>
<td>1.16 (0.44 to 3.06)</td>
<td>1.79 (0.81 to 3.96)</td>
<td>2.23 (0.96 to 5.16)</td>
</tr>
<tr>
<td>Item 1.2: Wheeze when did not have a cold?</td>
<td>23 (32%)</td>
<td>14 (25%)</td>
<td>13 (17%)</td>
<td>1.44 (0.66 to 3.15)</td>
<td>1.89 (0.70 to 5.14)</td>
<td>2.35 (1.08 to 5.09)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>2.61 (1.17 to 5.82)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Item 2: Woken with tightness in chest?</td>
<td>20 (28%)</td>
<td>12 (21%)</td>
<td>12 (15%)</td>
<td>1.44 (0.64 to 3.27)</td>
<td>2.09 (0.73 to 5.96)</td>
<td>2.12 (0.95 to 4.72)</td>
<td>2.64 (1.13 to 6.19)</td>
</tr>
<tr>
<td>Item 3: Shortness of breath</td>
<td>11 (15%)</td>
<td>9 (16%)</td>
<td>3 (4%)</td>
<td>0.96 (0.37 to 2.51)</td>
<td>0.86 (0.26 to 2.85)</td>
<td>4.51 (1.20 to 16.89)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>4.93 (1.27 to 19.10)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Item 4: Coughing</td>
<td>24 (34%)</td>
<td>16 (28%)</td>
<td>16 (21%)</td>
<td>1.31 (0.61 to 2.79)</td>
<td>1.37 (0.53 to 3.55)</td>
<td>1.98 (0.95 to 4.14)</td>
<td>2.17 (1.01 to 4.67)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Item 5: Attack of asthma</td>
<td>7 (10%)</td>
<td>6 (11%)</td>
<td>1 (1%)</td>
<td>0.92 (0.29 to 2.89)</td>
<td>0.41 (0.07 to 2.38)</td>
<td>8.29 (0.99 to 69.16)</td>
<td>8.90 (1.04 to 76.25)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Item 6: Use Asthma medication</td>
<td>19 (26%)</td>
<td>13 (23%)</td>
<td>7 (9%)</td>
<td>1.21 (0.54 to 2.73)</td>
<td>1.68 (0.60 to 4.71)</td>
<td>3.64 (1.43 to 9.38)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>3.78 (1.45 to 9.88)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Item 7: Nasal Allergies</td>
<td>22 (31%)</td>
<td>17 (30%)</td>
<td>28 (36%)</td>
<td>1.04 (0.49 to 2.21)</td>
<td>1.23 (0.46 to 3.25)</td>
<td>0.79 (0.40 to 1.55)</td>
<td>0.83 (0.41 to 1.67)</td>
</tr>
<tr>
<td>Symptomatic ECRHS Score</td>
<td>22 (31%)</td>
<td>18 (32%)</td>
<td>10 (13%)</td>
<td>0.95 (0.45 to 2.02)</td>
<td>1.27 (0.50 to 3.20)</td>
<td>2.99 (1.30 to 6.88)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>3.03 (1.29 to 7.12)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Physician Diagnosis of Asthma</td>
<td>29 (40%)</td>
<td>22 (39%)</td>
<td>11 (14%)</td>
<td>1.07 (0.53 to 2.19)</td>
<td>1.17 (0.50 to 2.70)</td>
<td>4.11 (1.86 to 9.08)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>4.30 (1.91 to 9.72)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Results are expressed as n (%) unless otherwise stated; *: p<0.001; **: p<0.01; ***: p<0.05 between BPD and Term groups only; CI: Confidence Intervals; <sup>a</sup>: adjusted for female gender, maternal smoking and having ever smoked; <sup>b</sup>: adjusted for female gender and having ever smoked.
### Table 3: Lung function tests compared between groups

<table>
<thead>
<tr>
<th></th>
<th>BPD n=56</th>
<th>Non-BPD n=40</th>
<th>Term n=55</th>
<th>BPD vs. Non-BPD Unadjusted Mean Difference (CI 95%); p</th>
<th>BPD vs. Non-BPD Adjusted Mean Difference (CI 95%); p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>BPD vs. Term Unadjusted Mean Difference (CI 95%); p</th>
<th>Non-BPD vs. Term Unadjusted Mean Difference (CI 95%); p</th>
</tr>
</thead>
<tbody>
<tr>
<td>zFEV₁</td>
<td>-1.41 (1.25)</td>
<td>-0.19 (1.16)</td>
<td>0.14 (0.96)</td>
<td>-1.22 (-1.72 to -0.72)***</td>
<td>-1.83 (-2.76 to -0.90)***</td>
<td>-1.55 (-1.97 to -1.13)***</td>
<td>-0.33 (-0.76 to 0.11)</td>
</tr>
<tr>
<td>FEV₁ %</td>
<td>81.89 (15.90)</td>
<td>96.98 (15.22)</td>
<td>101.16 (11.40)</td>
<td>-15.08 (-21.50 to -8.66)***</td>
<td>-22.63 (-34.34 to -10.91)***</td>
<td>-19.27 (-24.48 to -14.06)***</td>
<td>-4.19 (-9.61 to 1.23)</td>
</tr>
<tr>
<td>zFVC</td>
<td>-0.79 (1.14)</td>
<td>0.17 (0.98)</td>
<td>0.12 (0.94)</td>
<td>-0.96 (-1.40 to -0.52)***</td>
<td>-1.53 (-2.22 to -0.84)***</td>
<td>-0.91 (-1.30 to -0.52)***</td>
<td>0.05 (-0.35 to 0.44)</td>
</tr>
<tr>
<td>FVC%</td>
<td>90.11 (14.46)</td>
<td>101.85 (12.60)</td>
<td>101.67 (10.83)</td>
<td>-11.74 (-17.38 to -6.10)***</td>
<td>-19.25 (-27.99 to -10.50)***</td>
<td>-11.57 (-16.38 to -6.75)***</td>
<td>0.18 (-4.61 to 4.97)</td>
</tr>
<tr>
<td>zFEV₁/FVC</td>
<td>-0.68 (0.22)</td>
<td>-0.13 (1.22)</td>
<td>0.34 (0.89)</td>
<td>-0.55 (-1.16 to -0.06)</td>
<td>-0.36 (-1.51 to 0.79)</td>
<td>-1.02 (-1.52 to -0.53)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.47 (-0.90 to -0.40)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV₁/FVC%</td>
<td>94.32 (13.41)</td>
<td>98.45 (10.32)</td>
<td>102.67 (7.18)</td>
<td>-4.13 (-9.15 to 0.89)</td>
<td>-3.00 (-12.56 to 6.56)</td>
<td>-8.35 (-12.41 to -4.29)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-4.22 (-7.79 to -0.66)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>zFEF₂₅-₇₅</td>
<td>-1.80 (1.10)</td>
<td>-1.13 (1.02)</td>
<td>-0.56 (1.45)</td>
<td>-0.67 (-1.11 to 0.23)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-0.90 (-1.72 to 0.26)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-1.24 (-1.73 to -0.769)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-0.57 (-1.10 to -0.43)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEF₂₅-₇₅ %</td>
<td>61.63 (23.59)</td>
<td>74.93 (22.06)</td>
<td>90.96 (21.55)</td>
<td>-13.30 (-22.74 to -3.86)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-20.99 (-36.78 to -5.40)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>-29.34 (-37.84 to -20.84)&lt;sup&gt;***&lt;/sup&gt;</td>
<td>-16.04 (-25.02 to -7.06)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Results are expressed as mean (SD) unless otherwise stated; *: p<0.05; **: p<0.01; ***: p<0.001; <sup>a</sup>: Adjusted for maternal smoking, having ever smoked, birth weight and gestational age.
<table>
<thead>
<tr>
<th></th>
<th>BPD</th>
<th>Non-BPD</th>
<th>Term</th>
<th>BPD vs. Non-BPD</th>
<th>BPD vs. Term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=72</td>
<td>n=56</td>
<td>n=78</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>0.84 (0.26)</td>
<td>0.88 (0.23)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.93 (0.13)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.04 (-0.12 to 0.05); 0.413</td>
<td>-0.09 (-0.16 to -0.03); &lt;sup&gt;0.007&lt;/sup&gt;</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>77.54 (18.35)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79.32 (19.00)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83.35 (12.51)</td>
<td>-1.78 (-8.39 to 4.84); 0.596</td>
<td>-5.80 (-10.86 to -0.74); 0.028</td>
</tr>
<tr>
<td>Decreased Mobility</td>
<td>16 (22%)</td>
<td>7 (12%)</td>
<td>3 (4%)</td>
<td>0.143</td>
<td>&lt;sup&gt;0.001&lt;/sup&gt;</td>
</tr>
<tr>
<td>Difficulty with Self-Care</td>
<td>9 (12%)</td>
<td>4 (7%)</td>
<td>0 (0%)</td>
<td>0.304</td>
<td>&lt;sup&gt;0.001&lt;/sup&gt;</td>
</tr>
<tr>
<td>Problems performing Usual Activities</td>
<td>18 (25%)</td>
<td>11 (19%)</td>
<td>6 (8%)</td>
<td>0.441</td>
<td>&lt;sup&gt;0.004&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pain or Discomfort</td>
<td>15 (21%)</td>
<td>14 (25%)</td>
<td>14 (18%)</td>
<td>0.614</td>
<td>0.655</td>
</tr>
<tr>
<td>Anxious or Depressed</td>
<td>16 (22%)</td>
<td>11 (20%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13 (17%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.723</td>
<td>0.411</td>
</tr>
</tbody>
</table>

Continuous variables are reported as Mean (SD). Differences between groups for mean EQ-5D and VAS scores are expressed as Mean Difference (95% CI), p value. Categorical data are reported in numbers (%); p calculated using Chi-Square Analysis or Fishers Exact Test if any cell ≤5; <sup>a</sup>: n=70; <sup>b</sup>: n=56; <sup>c</sup>: n=77.
Figure Legends

Figure 1: Flow chart summarising participant tracing and recruitment
Key: BPD=Bronchopulmonary Dysplasia; Non-BPD = Preterm who did not develop bronchopulmonary
dysplasia; GP= General Practitioner;
Figure 1. Flow chart summarising participant tracing and recruitment

Identified from electronic database and labour records
n=967
BPD n=153; Non-BPD n=322; Term n=492

G.P contacted
n=681
BPD n=134; Non-BPD n=177; Term n=370

Total potential participants contacted
n=603
BPD n=128; Non-BPD n=168; Term n=307

Consent
n=232
(BPD n=82, Non-BPD n=66, Term n=84)

Completed Stage 1
n=207
(BPD n=72, Non-BPD n=57, Term n=78)

Completed Stage 2
n=151
(BPD n=56, Non-BPD n=40, Term n=55)