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# Bronchopulmonary dysplasia and expiratory airflow at 8 years in children born extremely preterm in the post-surfactant era

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Authors Contribution Statement:

LWD and JLYC conceived and designed the study. LWD and JLYC were involved in identifying or assessing the children and in data collection. LWD, SR and JLYC were all involved in the data analysis or interpretation. LWD drafted the manuscript. All authors were involved in revising the manuscript and approved the final submitted version, and all agree to be accountable for all aspects of the work.

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Declaration of interests

None of the authors have any conflicts of interests or financial disclosures to declare.

**Abstract**

**Background:** It is unclear if bronchopulmonary dysplasia (BPD) is independently associated with reduced expiratory airflow at school-age.

**Objective**: To determine the independent associations of moderate-severe BPD, mild BPD, gestational age, and birthweight z-score with expiratory airflow in children born extremely preterm (EP; <28 weeks' gestation).

**Methods:** All EP survivors born in Victoria, Australia, in three eras (1991-92, n=225; 1997, n=151; and 2005, n=170) were recruited at birth and 418/546 (77%) had valid spirometry data at 8 years. BPD was classified as moderate-severe (oxygen requirement at 36 weeks' postmenstrual age), or mild (oxygen >28 days but not at 36 weeks' postmenstrual age). Expiratory airflow variables, including the forced expired volume in 1 second ($FEV_1$), were measured and values converted to z-scores.

**Results:** Compared with no BPD (n=94), moderate-severe BPD (n=193) was associated with a substantial reduction in expiratory airflow (e.g., $zFEV_1$ mean difference -0.69, 95% confidence interval [CI] -0.97, -0.41; P<0.001), but mild BPD (n=131) was not ($zFEV_1$ mean difference 0.01, 95% CI -0.28, 0.31; P=0.93). On multivariable analysis, moderate-severe BPD remained strongly associated with reduced airflow ($zFEV_1$ mean difference -0.63, 95% CI -0.92, -0.33; P<0.001), but mild BPD ($zFEV_1$ mean difference 0.04, 95% CI -0.26, 0.34; P=0.27), gestational age ($zFEV_1$ 0.06 mean increase per week, 95% CI -0.05, 0.17; P=0.29) and birthweight z-score ($zFEV_1$ 0.07 mean increase per SD, 95% CI -0.06, 0.20; P=0.28) were not.

**Conclusions:** In children born EP, moderate-severe BPD, but not mild BPD was independently associated with reduced expiratory airflow at 8 years.

**Keywords**: infant, extremely preterm, bronchopulmonary dysplasia, spirometry, expiratory airflow

**What is already known on this topic**

Bronchopulmonary dysplasia is associated with reduced expiratory airflow in children born preterm but recently it has been suggested that gestational age and fetal growth restriction are more important associations, and bronchopulmonary dysplasia itself is not.

**What this study adds**

Moderate-severe bronchopulmonary dysplasia is independently associated with reduced expiratory airflow in 8-year-old children who were born extremely preterm (<28 weeks' gestation), whereas mild bronchopulmonary dysplasia and gestational age are not. The relationship with fetal growth is not so straightforward; expressed as a continuous variable it is not independently associated with reduced expiratory airflow, but expressed as a dichotomous variable (birthweight <10$^{th}$ centile) it is.

**How might this study affect research or policy**

This study confirms that focus should remain on preventing bronchopulmonary dysplasia if expiratory airflows are to improve in survivors born extremely preterm. It also clarifies why different conclusions about the independent associations of bronchopulmonary dysplasia with reduced expiratory airflow might arise, dependent on methodological issues, including sample selection, criteria for bronchopulmonary dysplasia, and the definition of reduced expiratory airflow.

Survival rates for infants born extremely preterm (EP; <28 weeks' gestation) have increased dramatically with the advent of neonatal assisted ventilation and subsequent advances in perinatal care over the past 50 years. One of the major advances was the introduction of exogenous surfactant into clinical practice in the early 1990s to treat respiratory distress in infants born preterm who lacked their own surfactant after birth. Today, almost 9-in-10 livebirths at 22-27 weeks' gestation who are offered intensive care are expected to survive into adulthood.[1] Worryingly, adults born EP are destined for higher rates of chronic obstructive pulmonary disease than are adults born at term.[2]

Bronchopulmonary dysplasia (BPD) affects approximately 50% of survivors born EP,[3] and is strongly associated with reduced expiratory airflow in later life in survivors born preterm.[2, 4-6] A recent report suggests that it is not BPD per se that is associated with reduced expiratory airflow, but it is increasing prematurity and fetal growth restriction that are more important in infants born <35 weeks' gestation.[7] If that is so, efforts to reduce BPD alone without reducing prematurity or fetal growth restriction are unlikely to improve long-term expiratory airflow. Moreover, the conclusions from that study seem to differ from reports of survivors born very preterm (<32 weeks' gestation) or very low birthweight (<1500 g) where BPD was clearly associated with reduced expiratory airflow in childhood, adolescence, and adulthood.[2, 4, 8, 9] Such associations persisted after adjustment for gestational age and fetal growth restriction;[2] however, the studies included in the latter report predominantly arose from survivors born in the pre-surfactant era, when far fewer infants born EP survived.

The aim of this study was to determine the independent associations of BPD, including moderate-severe and mild BPD, gestational age, and birthweight z-score with expiratory airflow in children born EP in Victoria, Australia, at 8 years of age in the years since exogenous surfactant has been available to treat surfactant deficiency in newborn infants. We hypothesised that moderate-severe BPD would be independently associated with

reduced expiratory airflow, but that mild BPD, gestational age and birthweight z-score would not.

## METHODS

The only four neonatal intensive care units in the state of Victoria, Australia, have collaborated with government data collection agencies and the state-wide transport service to obtain population-based data on long-term outcomes for discrete cohorts of infants born initially with birthweight <1000 g from the late 1970s, and since the early 1990s those born EP have been included. Antenatal corticosteroids have been used clinically in Victoria since the late 1970s, and exogenous surfactant was introduced into clinical care in 1991.

All survivors born EP in the state in three discrete eras 1991-92 (24 months), 1997 (12 months), and 2005 (12 months) were recruited at birth and followed longitudinally. Perinatal data, including gestational age, birthweight, and BPD were collected prospectively. Moderate-severe BPD was defined as dependence on oxygen at 36 weeks' postmenstrual age, as per the consensus definition of BPD.[10] Mild BPD was defined as treatment with oxygen for at least 28 days but not after 36 weeks' postmenstrual age.[10] Birthweight z-scores were computed relative to revised British Growth Reference data.[11]

### Respiratory Function Studies

At 8 years of age, corrected for preterm birth, expiratory airflow was measured by spirometry according to American Thoracic Society guidelines[12] in accredited respiratory function laboratories by respiratory scientists who were blinded to clinical details of the participants. Maximum expiratory flow-volume curves were recorded with the child seated. Flow was measured with a pneumotachograph, and volume obtained by integration of flow from the flow-versus-time data. Variables reflecting expiratory airflow included the forced

expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC, and forced expiratory flow from 25% to 75% of vital capacity ($FEF_{25-75\%}$). Results at body temperature and pressure saturated with water vapour were converted into z-scores, percentiles, and % predicted for age, height, sex, and ethnicity.[13] Poor expiratory airflow was defined as an $FEV_1$ <5$^{th}$ percentile (z-score equivalent <-1.645 SD; % predicted equivalent <80%).

Data on respiratory function at 8 years of age have been reported previously for all three cohorts,[3, 14, 15] in some cases not only for children born EP, but also combined with those weighing <1000 g at birth.

**Statistical Analysis**

Data were analysed using Stata 17.0. The relationships of the expiratory flow variables as continuous z-scores with BPD (categorised as moderate-severe, mild, or nil), gestational age, and birthweight z-score were analysed by linear regression, first univariably, and then with all three variables in the model to assess the independent associations of each variable adjusted for the other two. We also evaluated univariable and multivariable associations of the proportions with poor expiratory airflow ($FEV_1$ <5$^{th}$ percentile) with BPD, gestational age and birthweight z-score by logistic regression.

In a supplementary analysis we explored associations of expiratory airflow with any BPD (mild + moderate-severe) and fetal growth restriction (birthweight <10$^{th}$ centile; birthweight z-score <-1.282), along with gestational age, using linear and logistic regression analyses, in order to replicate the methods of Hart et al.[7]

All regression models were fitted using Generalised Estimating Equations with robust error estimates to account for clustering within multiple births. Mean differences or odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, where appropriate. Data were interpreted based on magnitude of any differences and their 95% CIs, and not just on p-

values alone. We did not impute for missing data as it was unlikely that missing data occurred at random.

The individual cohort studies that provided data were approved by the Human Research Ethics Committee at the Royal Women's Hospital, Melbourne. Informed consent was provided by parents for the 2005 cohort but was not required for the earlier cohorts where follow-up to school age was considered to comprise usual clinical care.

## RESULTS

Of 949 consecutive livebirths born between 22 and 27 completed weeks over the three eras combined, 546 (58%) survived to 8 years of age. Of the 546 survivors, 501 (92%) were seen at 8 years. Valid expiratory flow data were obtained from 418 (77%) of all survivors at a mean age of 8.3 years, corrected for prematurity (Table 1). In the 418 with expiratory flow data, 46% (n=193) had moderate-severe BPD, 31% (n=131) had mild BPD only, and 22% (n=94) had no BPD; other perinatal characteristics are shown in Table 1.

Perinatal characteristics between those with and without expiratory airflow data were mostly similar, although there were fewer who were from multiple pregnancies in those without expiratory airflow data (Supplementary Table 1). At 8 years of age 45% (37/82) of those without expiratory airflow data had a major neurodevelopmental disability (IQ <-2 SD relative to normal birthweight controls, moderate/severe cerebral palsy, blindness or deafness) compared with 12% (49/417) of those for whom valid expiratory airflow data were available.

### Associations of BPD with expiratory airflow

Mean expiratory airflow z-scores were substantially lower than the expected value of zero for all variables, regardless of whether the children had BPD or not (Table 2). Overall, 21% (89/418) had an $FEV_1$ <5$^{th}$ percentile.

On univariable analysis, there was strong evidence that moderate-severe BPD was associated with substantial reductions in z-scores for $FEV_1$, FVC, and $FEF_{25-75\%}$, but not $FEV_1$/FVC (Figure 1), and with higher odds of having clinically important airway obstruction (Figure 2). However, there was little to no evidence that mild BPD was associated with airway obstruction, expressed either continuously or dichotomously (Figures 1 and 2).

On univariable analysis there was evidence that increasing gestational age was associated with increases in z-scores for $FEV_1$ and FVC, and lower odds for clinically important airway obstruction, but there was little evidence that increasing birthweight z-score was associated with any expiratory flow variables, or clinically important airway obstruction (Table 2; Figures 1 and 2).

On multivariable analysis, the strong evidence that moderate-severe BPD was associated with substantial reductions in z-scores for $FEV_1$, FVC and $FEF_{25-75\%}$, and with an increase in the odds of clinically important airway obstruction persisted, with little effect on the point estimates compared with the unadjusted analyses (Figures 1 and 2). The lack of evidence for associations of mild BPD with airway flows or airway obstruction persisted on multivariable analysis. The evidence for an increase in $zFEV_1$ with increasing gestational age diminished, but persisted for FVC on multivariable analysis. The lack of evidence for associations of airflows with increasing birthweight z-score persisted.

In the supplementary analysis, there was evidence for associations of both any BPD and fetal growth restriction with reduced z-scores for $FEV_1$, FVC, and $FEF_{25-75\%}$, as continuous variables, and for higher odds of clinically important airway obstruction on univariable analysis (Supplementary Table 2, Supplementary Figures 1 and 2). Univariable

associations with increasing gestational age were unchanged from Table 2 (increases in z-scores for $FEV_1$ and FVC, and lower odds for clinically important airway obstruction). On multivariable analyses of the continuous variables, the evidence for associations of any BPD with reduced $FEV_1$ and $FEF_{25-75\%}$ persisted, but weakened for FVC, whereas the evidence for associations of gestational age and fetal growth restriction was unchanged from the univariable analyses (Supplementary Table 2, Supplementary Figures 1 and 2). The evidence for higher odds of clinically important airway obstruction persisted for fetal growth restriction, but weakened for both any BPD and gestational age.

## DISCUSSION

The major findings in the present study of school-age children born EP in the post-surfactant era are that moderate-severe BPD was associated with lower expiratory airflow and higher rates of poor expiratory airflow in the clinically important range. Importantly, adjustment for gestational age and birthweight z-scores had little effect on the strength of the evidence concerning the associations of moderate-severe BPD with poor expiratory airflow. Although there were some associations of better expiratory airflow with increasing gestational age, the strength of the evidence diminished on some multivariable analyses. The relationships with fetal growth were not straightforward; as a continuous variable there was little evidence that birthweight z-scores were associated with expiratory airflow, but there was evidence that fetal growth restriction (birthweight $<10^{th}$ centile), as a dichotomous variable, was associated with reduced expiratory airflow. There was no evidence that mild BPD was associated with expiratory airflow on either univariable or multivariable analysis. These results were consistent with our hypotheses.

A systematic review in 2013 reported that preterm survivors with and without BPD had substantial reductions in expiratory airflow compared with term-born controls; some

studies defined BPD as oxygen dependency at 28 days after birth, and other studies as oxygen dependency at 36 weeks' postmenstrual age.[16] Regardless of how BPD was defined, expiratory airflow was reduced more in survivors with BPD compared with term-born controls than it was in preterm survivors who had no BPD compared with controls. In the majority of the 59 studies included in the review the participants were born before the 1990s, but some were born in the 1990s when surfactant was clinically available. In the systematic review, there was no adjustment of associations of expiratory airflow with BPD for gestational age or fetal growth restriction.

Our results with respect to the associations of expiratory airflow with the severity of BPD are similar to other studies of survivors born preterm in the surfactant era. Ronkainen et al[17] reported the results of a systematic review of six studies with $FEV_1$ results published between 2000 and 2013; compared with term born controls, survivors born preterm had an increasing reduction in $FEV_1$, from -7.4% predicted for no BPD, to -10.5% predicted for any BPD, to -17.8% for moderate-severe BPD. In a cohort of 35 survivors born EP in Norway in 1991-92, Vollsaeter et al[18] reported that those who had moderate-severe BPD had worse expiratory airflow than those who had mild BPD, who in turn had worse expiratory airflow than those who had no BPD, at mean ages of 10.5 and 17.8 years. In a study of infants born <27 weeks' gestation in Sweden between 2004-2007, Thunqvist et al[19] reported that expiratory airflow at 6½ years was lower in 17 children who had severe BPD compared with 65 children who had moderate BPD. They did not report results for children with mild or no BPD but there cannot have been many because overall 90% of their cohort had either moderate or severe BPD. Although they also reported that children born 22-24 weeks' gestation had worse expiratory airflow than those born 25-26 weeks' gestation, there were no substantial differences in airflow between those with birthweight z-score ≤-2 SD compared with those with birthweight z-score >-2 SD.

A recent study from the pre-surfactant era reported reductions in expiratory airflow at 26 years of age in survivors born <1500 g birthweight who had BPD (oxygen at 36 weeks' postmenstrual age; moderate-severe) compared with no BPD, which persisted after correction for gestational age and growth restriction, among other variables.[5] They did not report relationships relative to severity of BPD, however. Another recent study of survivors born <26 weeks' gestation in the post-surfactant era also showed reductions in airflow at 19 years of age in those who had BPD (oxygen dependency after 36 weeks' postmenstrual age; moderate-severe) compared with those who did not, but they did not adjust for gestational age or growth restriction, and neither was the relationship with severity of BPD explored.[6]

Our findings might seem to differ from those of Hart et al[7] who reported that although any BPD, lower gestational age, and fetal growth restriction were all associated with poorer expiratory airflow at 7-12 years of age in survivors born <35 weeks' gestation on univariable analysis, on multivariable analysis the association with BPD disappeared, but persisted for both lower gestational age and fetal growth restriction. In our study it was the strong associations with moderate-severe BPD that persisted, and associations with lower gestational age diminished on multivariable analysis; there was little evidence for associations with birthweight z-score. However, in our supplementary analysis designed to mirror the methods of Hart et al, our conclusions were more similar to theirs; all of any BPD, gestational age, and fetal growth restriction were associated with poor expiratory airflow on univariable analysis, but only fetal growth restriction was independently related to poor expiratory airflow on multivariable analysis, with associations with both any BPD and gestational age weakening. In our other supplementary analysis, associations of any BPD with expiratory airflow continuous variables were weaker than with moderate-severe BPD, but they did persist on multivariable analysis for both $FEV_1$ and $FEF_{25-75\%}$ as continuous variables. There are several reasons why our study might have reached different conclusions

to Hart et al. Firstly, the upper gestational age for our study was only 27 completed weeks, and hence we had a higher proportion of survivors with moderate-severe BPD (46%) than did Hart et al (12%; 68/544); since it is the moderate-severe BPD group that are largely responsible for the associations with expiratory airflow, Hart et al would have had less power to find any associations with any BPD than we did. Secondly, Hart et al analysed associations only with low expiratory airflow as a dichotomous outcome, which reduces power to find associations compared with expressing expiratory airflows as continuous variables. Thirdly, they chose a cut-off for poor expiratory airflow at <85% predicted for $FEV_1$, rather than a more typical cut-off of <5$^{th}$ centile, which is <80% predicted. Fourthly, they only examined associations with $FEV_1$, whereas we also included FVC, $FEV_1$/FVC, and $FEF_{25-75\%}$. We chose to report outcomes for both mild and moderate-severe BPD separately because moderate-severe BPD is a more important clinical outcome than mild BPD, consistent with the strong independent associations of moderate-severe BPD with expiratory airflow obstruction in our study.

The strengths of our study include recruiting complete geographical cohorts of children born EP, which encompasses any potential differences in care between individual units and hence our results are more generalisable to similar geographical cohorts elsewhere. We also had high follow-up rates into mid-childhood, measured expiratory airflow in approved respiratory function laboratories according to accepted international guidelines, and obtained satisfactory expiratory flow data in most participants.

Limitations include that we were unable to obtain expiratory flow data on all participants; the high rate of major disability in those without valid expiratory flow data is one reason why such data were unavailable for some children who were assessed at 8 years; they were unable to complete satisfactory spirometry. Another limitation is that we did not record the precise inspired oxygen concentration or requirements for assisted ventilation at 36

weeks' postmenstrual age for all infants in all eras, and hence we could not classify moderate-severe BPD into categories of moderate and severe separately. Of note the workshop report that proposed the categorisation of different levels of severity of BPD was published in 2001,[10] after two of the three cohorts in the current study had been born and relevant data on respiratory and oxygen requirements in the newborn period had already been collected. A large study of expiratory flows across all grades of severity of BPD would be worthwhile. We corrected age for prematurity because children were assessed in multiple areas other than expiratory airflow, including IQ. Failure to correct IQ for prematurity results in a known bias in test scores at school-age in children born EP.[20] Had we not corrected age for prematurity, our conclusions would have likely have been unaltered as correction for prematurity has little effect on expiratory airflow z-scores.[21]

In conclusion, our results demonstrate that moderate-severe BPD is strongly independently associated with reduced expiratory airflow and having higher odds of clinically important reductions in expiratory airflow in school-age children who were born EP, whereas mild BPD is not associated with expiratory airflow in these children. Such knowledge may inform counselling of families with children born EP, particularly those who develop moderate-severe BPD, as well as informing clinical follow-up, and potential interventions.

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**Table 1. Proportion with expiratory airflow data at 8 years, age when assessed, and perinatal characteristics for participants.**

| | |
|---|---|
| Survivors to 8 years – n | 546 |
| Expiratory airflow data at 8 years – n (% survivors) | 418 (77%) |
| Corrected age when assessed – years – mean (SD) | 8.3 (0.5) |
| **Perinatal characteristics in the 418 with expiratory airflow data** | |
| Antenatal glucocorticoids – n (%) | 335 (80%) |
| Multiple pregnancy – n (%) | 117 (28%) |
| Gestational age – completed weeks – mean (SD) | 25.8 (1.1) |
| Birthweight – g – mean (SD) | 867 (182) |
| Male – n (% with airflow data) | 207 (50%) |
| Birthweight z-score – mean (SD) | -0.34 (0.85) |
| Fetal growth restriction* – n (%) | 30 (7%) |
| Exogenous surfactant – n (%) | 276 (66%) |
| Postnatal glucocorticoids – n (%) | 144 (34%) |
| Moderate-severe bronchopulmonary dysplasia† – n (%) | 193 (46%) |
| Mild bronchopulmonary dysplasia‡ – n (%) | 131 (31%) |
| No bronchopulmonary dysplasia – n (%) | 94 (22%) |

SD=standard deviation. *birthweight z-score <-1.282 (<10$^{th}$ centile); †in oxygen at 36 weeks; ‡oxygen for at least 28 days after birth but not at 36 weeks.

**Table 2. Descriptive data for expiratory airflow in relation to severity of bronchopulmonary dysplasia, and univariable associations with gestational age and birthweight z-score.**

| **Airflow variable** | Bronchopulmonary dysplasia | | | Gestational age | Birthweight z-score |
|---|---|---|---|---|---|
| | Moderate-severe n=193 | Mild n=131 | None n=94 | | |
| **Continuous** | z-scores | z-scores | z-scores | Mean (95% CI) per 1-week increase | Mean (95% CI) per 1 SD increase |
| $FEV_1$ | -1.21 (1.23) | -0.53 (1.10) | -0.51 (1.13) | 0.15 (0.04, 0.25) | 0.09 (-0.05, 0.22) |
| FVC | -0.92 (1.30) | -0.26 (1.19) | -0.32 (1.11) | 0.19 (0.08, 0.30) | 0.14 (-0.004, 0.28) |
| $FEV_1$/FVC | -0.43 (1.49) | -0.37 (1.29) | -0.27 (1.33) | -0.07 (-0.19, 0.05) | -0.08 (-0.22, 0.06) |
| $FEF_{25-75\%}$ | -1.55 (1.13) n=178 | -1.23 (0.97) n=127 | -1.07 (1.05) n=92 | 0.05 (-0.04, 0.14) | 0.08 (-0.04, 0.19 |
| **Dichotomous** | n (%) | n (%) | n (%) | Odds ratio (95% CI) per 1-week increase | Odds ratio (95% CI) per 1 SD increase |
| Low airflow* | 58 (30%) | 19 (15%) | 12 (13%) | 0.79 (0.64, 0.97) | 0.89 (0.67, 1.20) |

Data are mean (standard deviation), unless otherwise specified

$FEV_1$=forced expired volume in 1 s; FVC=forced vital capacity; $FEF_{25-75\%}$=forced expiratory flow from 25-75% of vital capacity.

*$FEV_1$ <5$^{th}$ centile.

**Captions for figures**

Figure 1. Mean differences and 95% confidence intervals for associations of expiratory airflow with bronchopulmonary dysplasia (BPD), gestational age, and birthweight z-score – univariable (solid line) and multivariable (dashed line) analyses.

Figure 2. Odds ratios and 95% confidence intervals for poor expiratory airflow ($FEV_1$ <5$^{th}$ centile) with bronchopulmonary dysplasia (BPD), gestational age, and birthweight z-score – univariable (solid line) and multivariable (dashed line) analyses.

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