Expiratory airflow at 7–8 years of age in children born extremely low birthweight from 14 years before to 14 years after the introduction of exogenous surfactant

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Summary

Background It is unclear if expiratory airflow in survivors born extremely low birth weight (ELBW; 500–999 g) has improved after the introduction of exogenous surfactant into clinical practice in 1991. The primary aim of this study was to describe the changes in airflow at 7–8 years of age of survivors born ELBW in five discrete cohorts from 14 years before to 14 years after the introduction of exogenous surfactant into clinical practice.

Methods The cohorts comprised consecutive survivors born ELBW in 1977–82 and 1985–87 at the Royal Women's Hospital, Melbourne, and in 1991–92, 1997 and 2005 in the state of Victoria, Australia. Survival rates to 2-years of age for infants born ELBW in the state of Victoria rose from approximately 1-in-4 to 3-in-4 over the time of this study. Expiratory airflow measurements at 7–8 years included the forced expired volume in 1 s (FEV_1), converted to z-scores for age, height, sex, and race.

Findings There were 596 ELBW participants with expiratory flow data, 280 (47%) of whom had bronchopulmonary dysplasia (BPD). Overall, there was little change in $zFEV_1$ over the 28-year period (mean change per year; 0.003, 95% CI −0.010, 0.015, P = 0.67). There was, however, evidence of an interaction between BPD and year; $zFEV_1$ in those who had BPD fell over time (mean change per year −0.019, 95% CI −0.037, −0.009, P = 0.035), whereas $zFEV_1$ improved in those who did not have BPD (mean change per year 0.021, 95% CI 0.006, 0.037, P = 0.007).

Interpretation Contrary to recent evidence, expiratory airflow of children born ELBW has not improved with the introduction of surfactant, and may be deteriorating in those who had BPD.

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Keywords: Extremely low birthweight; Expiratory airflow; Bronchopulmonary dysplasia; Surfactant

Introduction

Survival rates beyond infancy for infants born extremely low birthweight (ELBW; 500–999 g birthweight) were low, typically <10%, before the introduction of assisted ventilation into neonatal intensive care in the late 1960s-early 1970s. By the late 1970s the survival rate to 2 years of age had risen to one-in-four for those born ELBW in the state of Victoria.[1] Antenatal corticosteroids for women at risk of preterm birth with the intent of reducing respiratory distress in the infant after birth and

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Research in context

Evidence before this study

Survivors born preterm have reduced expiratory airflow in later life and are destined for higher rates of chronic obstructive pulmonary disease in adulthood than those not born preterm. Variables reflecting expiratory airflow in survivors who were born preterm are reported to be improving with increasing year of birth compared with term-born controls. Survivors born preterm who had bronchopulmonary dysplasia (BPD) are reported to be improving even more than those who did not have BPD.

Added value of this study

We studied school-aged children born extremely low birthweight (ELBW; 500–999 g birthweight) from 14 years before surfactant was introduced into clinical practice in 1991, to 14 years after. Contrary to recent reports, we did not confirm that variables reflecting expiratory airflow were improving with increasing year of birth over the 28-year period of our study in survivors born ELBW. Furthermore, we found some evidence for a deterioration in expiratory airflow over time in those who had BPD.

Implications of all the available evidence

It should not be assumed that changes in perinatal care have improved long-term expiratory airflow for survivors born preterm in recent years. Efforts to reduce lung injury in the newborn period must increase to improve expiratory airflow in later life in survivors born ELBW.

hence to improve infant survival were first used in the 1970s in Victoria. Exogenous surfactant was introduced into clinical care in 1991 in Victoria, with the aim of further reducing respiratory distress and improving survival; by 1997 three-in-four infants born ELBW in Victoria survived to 2 years.[1] Although antenatal corticosteroids and exogenous surfactant reduce lung morbidity, many infants born ELBW or extremely preterm (EP; <28 weeks' gestation) still develop bronchopulmonary dysplasia (BPD),[2,3] which is associated with reduced expiratory airflow and adverse neurodevelopmental outcomes in survivors.[4]

In a systematic review and meta-analysis of data from births from the mid-1960s to the mid-1990s, Kotecha et al.[5] reported that survivors born preterm (<37 weeks' gestational age) had reduced expiratory airflows in childhood and adolescence compared with controls born at term (37–42 weeks' gestational age) or of normal birthweight (>2499 g birthweight). Survivors born preterm with BPD had even more reduced expiratory airflow compared with controls. Interestingly, they reported that expiratory airflow in survivors with BPD improved over time for births between the mid-1960s to the mid-1990s, whereas values for controls were stable over the same time. Kotecha et al. updated their systematic review and meta-analysis in 2022 to include articles published up to December 2021.[6] The major findings were that the differences between preterm and control groups narrowed between the late 1960s to the mid-2010s, with more improvement in expiratory airflow of preterm survivors who had BPD than in those who did not have BPD. In addition to the wide range of birth years, the systematic reviews comprised studies with different birthweight and gestational age criteria, varied in epidemiological strength from convenience samples all the way through to complete geographical cohorts, and participants had expiratory airflow data obtained over a wide range of ages. Consequently, their summary findings were accompanied by substantial heterogeneity, which was not fully explained, creating uncertainty in their findings and hindering translation of their results into clinical practice. An alternative to meta-analysing summary data from multiple studies is to analyse individual participant data, which facilitates adjustment for confounding among individuals to address the changes over time on expiratory airflow and the impact, if any, of BPD.

The primary aim of the current study of individual participant data for variables reflecting airflow at 7–8 years from survivors born ELBW over five discrete eras was to determine if airflow had altered over time, from 14 years before to 14 years after the introduction of exogenous surfactant into clinical practice in Australia in 1991. Secondary aims were to assess the impact of BPD on airflow and if airflow differed between those with and without BPD over time, and the extent to which airflow differed in the pre-surfactant era versus the post-surfactant era.

Methods

Data reflecting expiratory airflow from the pre-surfactant era were obtained from consecutive survivors born ELBW at the Royal Women's Hospital in two distinct eras; 1) 1st January 1997 to 31st March 1982 (63 months), and 2) 1st January 1985 to 31st December 1987 (36 months). Data from the era after the introduction of exogenous surfactant into clinical practice in Victoria in 1991 were obtained from the Victorian Infant Collaborative Study Group cohorts comprising consecutive survivors born ELBW in the state of Victoria in three distinct eras; the calendar years 1) 1991–92 (24 months), 1997 (12 months) and 2005 (12 months). Births and survivors in the years between cohorts were not enrolled in costly research follow-up programmes, due to lack of resources. Although there are Victorian cohorts born ELBW in 1979–80 and 1985–87 (i.e., the pre-surfactant era), lung function was only measured for those birth cohorts for children born ELBW at the Royal

Women's Hospital. Notably, the neonatal intensive care unit (NICU) at the Royal Women's Hospital has always cared for more survivors born ELBW than any of the other three NICUs in the state of Victoria that contributed to these Victorian cohort studies. Although the Victorian cohorts born after 1991–92 have also included all survivors born extremely preterm (EP, <28 weeks' gestation), data from these children were only included in the main analyses if they were also born ELBW.

Perinatal data were collected at the time participants were in the neonatal nursery. BPD for the cohorts born prior to the 1990s had been defined on a combination of oxygen requirement for at least 28 days and chest x-ray findings consistent with stage 3 or 4 BPD.[7,8] For those born after 1990, BPD was defined as oxygen dependency at 36 weeks' postmenstrual age.[9,10] Data on oxygen dependency at 36 weeks' postmenstrual age were not collected for cohorts born prior to 1990.

All cohorts were assessed around 7–8 years of age, corrected for prematurity. Age was corrected for prematurity because, in addition to lung function, children had cognitive assessments that are biased if age is not corrected for prematurity,[11] whereas correction for prematurity is not essential for assessing expiratory airflow.[12] Forced expiratory flow was measured using spirometry according to the American Thoracic Society and European Respiratory Society guidelines,[13] or equivalent guidelines at the time that the cohorts were studied. The following values were obtained; forced expired volume in 1 s (FEV_1), forced vital capacity (FVC), the ratio FEV_1/FVC, and the forced expiratory flow at 25%–75% of FVC ($FEF_{25\%-75\%}$). Results were converted to z-scores predicted for age, height, sex and ethnicity, relative to the Global Lung Initiative 2012 reference values.[14] Expiratory airflow data at 7–8 years of age have been reported for the 1977–1982 cohort born ELBW,[8] for the 1991–92 and 1997 cohorts born ELBW or EP,[15] and for the 2005 cohort born EP only.[3] No data for the 1985–87 cohort have been previously reported.

Ethics statement

Ethical approval for all studies was obtained from the Human Research Ethics Committee at the Royal Women's Hospital, Melbourne. Follow-up assessments were considered to be part of routine clinical care for the earliest cohorts. Parents gave written informed consent for the children of the 2005 cohort to participate.

Statistical analysis

Data were analysed using Stata 17.0.[16] Participant characteristics and expiratory flow variables were described for each cohort using mean and standard deviation (SD) or number and percentage.

For the primary aim, the associations of expiratory flow outcomes with year of birth were examined by estimating differences in means of the expiratory flow variables for a one-year increase in birth year. For the secondary aim relating to BPD, the difference in mean expiratory flow outcomes between those with and without BPD were estimated. An interaction between BPD and year of birth was explored and the average changes over time were presented separately for those with and without BPD if there was strong evidence for an interaction. For the secondary aim related to differences in airflow between the pre- and post-surfactant eras, a model including an interaction between a dummy variable for pre-surfactant (births 1977–1987) vs. post-surfactant (births 1991–2005) eras and year of birth was fitted and the average changes over time were presented separately for pre- and post-surfactant eras if there was strong evidence for an interaction. Estimates were obtained from linear regression models, first without adjustment, and then with adjustment for potential confounders, as illustrated in a directed acyclic graph showing assumptions about casual and confounding paths (Fig. 1). Birthweight was included in models for BPD because changes in survival over the 28-year period resulted in more infants surviving at lower birthweights, who are at higher risk for BPD and adverse respiratory outcomes. Birthweight was not included in models for year of birth because it could be a mediator of any changes over time. Male sex was included in models for BPD only. Age at assessment was included because not all children were assessed at exactly the same age. All regression models were fitted using generalised estimating equations with an exchangeable correlation structure and reported with robust standard errors to allow for a lack of independence of data among multiples from the same family.

Since most studies today report data for cohorts selected by gestational age rather than by birthweight, we explored interactions between BPD and year of birth, restricted to just those <28 weeks' gestation in all of the cohorts in a supplementary analysis.

In addition, although we could not define BPD identically for all five eras, we could identify those with worse lung disease as being oxygen dependent for more than 28 days in all eras, so we repeated the analyses investigating changes over time in those with and without oxygen dependency for more than 28 days after birth.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. LWD and JLYC had full access to and verified all the data in the study and had final responsibility for the decision to submit for publication.

Results

The numbers of consecutive livebirths, survivors to 7–8 years, and who had valid data for expiratory flows at 7–8 years for each cohort are shown in Table 1, as are

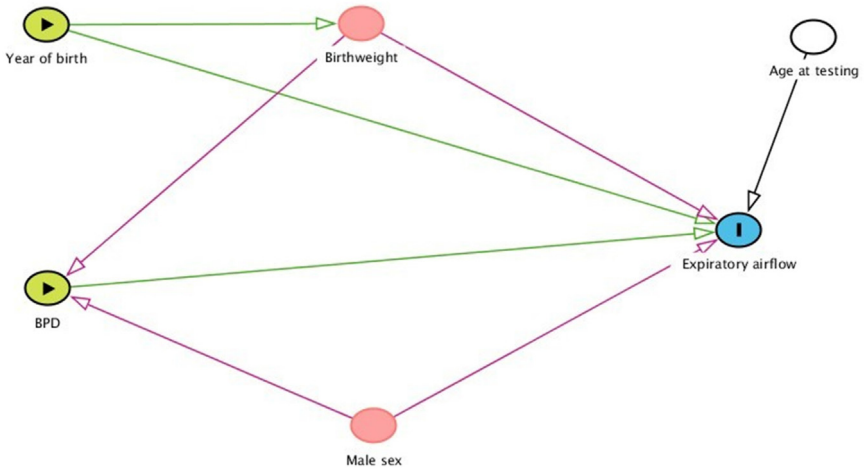

Fig. 1: Directed acyclic graph for expiratory airflow outcomes depicting assumed causal relationships between variables. BPD = bronchopulmonary dysplasia.

perinatal characteristics of those with expiratory flow data in each era. Rates of antenatal corticosteroids and caesarean birth both rose over time. Exogenous surfactant was first used in March 1991, but was initially restricted by government regulations relating to the severity of lung disease after birth required to receive treatment. By 1997 these restrictions had been lifted, and surfactant use rose. Postnatal corticosteroids to prevent or treat BPD were not prescribed until the 1990s. Rates of BPD fluctuated between eras, but were highest in 1985–87, before surfactant was available. The mean ages at assessment of expiratory flow were close to 8 years for each cohort and was lowest for the 2005 cohort. Overall, there were 596 ELBW participants with expiratory flow data from the five cohorts, 280 (47%) of whom had BPD. Most of the participants were from different families (n = 523), however 30, 3 and 1 families had 2, 3 and 4 children, respectively, who contributed data to the final analysis.

Mean Z-scores for expiratory flows were substantially below zero for all expiratory airflow variables overall, as well as within individual cohorts for most variables (Table 2). Those who had BPD had lower z-scores than those without BPD overall, and for most variables for most cohorts (Supplementary Table S1). Notably, those who did not have BPD still had mean z-scores substantially below zero overall, and for most individual cohorts (Supplementary Table S1).

	1977–1982	1985–1987	1991–92	1997	2005
Livebirths free of lethal anomalies—n	262[a]	187[a]	423[b]	226[b]	257[b]
Survived to 8–9 years—n (% livebirths)	86 (33)	92 (49)	241 (57)	170 (75)	171 (67)
Expiratory airflow data—n (% survivors)	72 (84)	80 (87)	195 (80)	126 (74)	123 (72)
Antenatal corticosteroids—n (%)	38 (53)	37 (46)	151 (77)	110 (87)	111/122 (91)
Multiple birth—n (%)	15 (21)	12 (15)	64 (33)	33 (26)	36 (29)
Cesarean birth– n (%)	18 (25)	37 (46)	79 (41)	84 (67)	84 (68)
Birthweight (g)—mean (SD)	863 (100)	855 (88)	836 (116)	789 (133)	808 (128)
Gestational age (completed weeks)—mean (SD)	27.4 (2.1)	27.4 (1.9)	26.7 (2.1)	26.5 (2.0)	26.6 (2.2)
Male—n (%)	34 (47)	33 (41)	89 (46)	56 (44)	48 (39)
Surfactant—n (%)	0	0	76 (39)	107 (85)	92/119 (77)
Postnatal corticosteroids—n (%)	0	0	70 (36)	46 (37)	22/122 (18)
Bronchopulmonary dysplasia[c]—n (%)	31 (43)	68 (85)	76 (39)	42 (33)	63 (51)
Age at assessment[d] (years)—mean (SD)	8.3 (0.4)	8.1 (0.2)	8.7 (0.3)	8.4 (0.3)	7.6 (0.4)

Data are n (% with expiratory airflow data), unless otherwise specified. [a]Born in the Royal Women's Hospital only. [b]Born in the state of Victoria. [c]Defined before 1990 on chest X-ray and oxygen requirement for at least 28 days after birth, and by oxygen dependency at 36 weeks' postmenstrual age from 1991 onwards. [d]Corrected for prematurity.

Table 1: **Numbers of livebirths free of lethal anomalies, survivors, and survivors with expiratory flow data at 7–8 years of age, and perinatal characteristics of those with expiratory flow data across five cohorts of children born weighing 500–999 g.**

Expiratory airflow variables	Era (years of birth)					
	1977–1982	1985–1987	1991–92	1997	2005	Total
	N = 72	N = 80	N = 195	N = 126	N = 123	596
$zFEV_1$	−1.01 (1.24)	−0.65 (1.31)[a]	−0.85 (1.04)	−0.61 (1.31)	−0.89 (1.13)[b]	−0.80 (1.20)[c]
zFVC	−0.65 (1.38)	−0.41 (1.42)	−0.84 (1.19)	−0.37 (1.24)	−0.49 (1.16)	−0.59 (1.26)
$zFEV_1$/FVC	−0.51 (1.42)	−0.40 (1.37)[a]	0.20 (1.52)	−0.35 (1.32)	−0.74 (1.24)[b]	−0.27 (1.43)[c]
$zFEF_{25–75\%}$	−0.98 (1.12)	−1.02 (1.04)[d]	−1.27 (1.14)[e]	−1.37 (1.09)[d]	−1.18 (1.10)[f]	−1.20 (1.11)[g]

Data are mean (standard deviation). FEV_1 = forced expired volume in 1 s, FVC = forced vital capacity. $FEF_{25–75\%}$ = flow between 25% and 75% of vital capacity. [a]n = 5 missing. [b]n = 2 missing. [c]n = 7 missing. [d]n = 1 missing. [e]n = 6 missing. [f]n = 14 missing. [g]n = 22 missing.

Table 2: **Expiratory airflow z-scores at 7–8 years of age across five cohorts of children born weighing 500–999 g.**

Concerning the primary outcome, there was little evidence that z-scores for FEV_1 or FVC differed over the 28-year period, but there was some evidence for declines over time in z-scores for FEV_1/FVC and $FEF_{25–75\%}$ (Table 3). After adjustment for age at assessment, the evidence for a decline in FEV_1/FVC by year of birth largely disappeared, but the evidence for a decline in $FEF_{25–75\%}$ increased (Table 3).

Concerning the secondary outcomes, there was strong evidence that children who had BPD in the newborn period had substantially reduced expiratory airflow over all eras combined compared with those who did not have BPD, exceeding a mean of −0.5 SD for FEV_1 (Table 3). Adjustment for male sex, birthweight and age at assessment somewhat reduced the evidence for lower airflow in those who had BPD (Table 3).

There was evidence for interactions between BPD and year of birth for FEV_1, FVC, and $FEF_{25–75\%}$ (Table 4; Fig. 2). Within the BPD subgroup, there was evidence for declines over time in FEV_1 and $FEF_{25–75\%}$, whereas in the no-BPD subgroup there was evidence for increases over time in both FEV_1 and FVC (Table 4, Fig. 2). Adjustment for covariates had minimal effects on the strength of these relationships (Table 4).

There was little evidence that the slopes over time differed between the pre- and post-surfactant eras for variables reflecting expiratory airflow, except for FEV_1/FVC (Supplementary Table S2); the mean change in $zFEV_1$/FVC per year of birth was 0.034 (95% CI −0.029, 0.097) P = 0.29, for the pre-surfactant era, and was −0.071 (95% CI −0.095, −0.048) P < 0.001 for the post-surfactant era.

In the supplementary analyses restricted to those with gestational ages <28 weeks, there were substantially fewer participants with data at 7–8 years for the cohorts born before 1990 than there were when the cohorts were selected by birthweight only, but there were smaller reductions in the sample size for the cohorts born after 1990 where the original selection criteria for the cohorts were by birthweight <1000 g or gestational age <28 weeks (Supplementary Table S3). Notably, all but one child in the 1985–87 cohort had BPD when selected by gestational age <28 weeks. Those who had BPD had lower z-scores for expiratory airflow than those without BPD for most variables for most individual cohorts, as well as overall (Supplementary Table S3). The findings regarding BPD and interactions between BPD and year of birth in the supplementary analyses restricted to just those <28 weeks' gestation (Supplementary Table S4, Supplementary Figure S2) were similar to the findings in the main analyses for those 500–999 g birthweight.

In the supplementary analyses investigating changes over time in those with oxygen dependency >28 days compared with those who did not have oxygen dependency for >28 days across all eras, the patterns of change over time for the two groups in Supplementary Figure S2 were similar to those in Fig. 2 in the main document. Of note there was no positive slope over time for any expiratory variable in the "Oxygen >28 days" group.

Expiratory airflow variables	Per year of birth		Bronchopulmonary dysplasia	
	Mean difference (95% CI); P	Adjusted mean difference[a] (95% CI); P	Mean difference (95% CI); P	Adjusted mean difference[b] (95% CI); P
$zFEV_1$	0.003 (−0.010, 0.015) 0.67	0.003 (−0.011, 0.017) 0.65	−0.52 (−0.71, −0.33) <0.001	−0.43 (−0.63, −0.24) <0.001
zFVC	0.007 (−0.006, 0.020) 0.29	0.003 (−0.012, 0.018) 0.67	−0.40 (−0.60, −0.20) <0.001	−0.33 (−0.54, −0.13) 0.001
$zFEV_1$/FVC	−0.014 (−0.028, 0.001) 0.06	−0.001 (−0.017, 0.014) 0.88	−0.24 (−0.47, −0.02) 0.036	−0.18 (−0.42, 0.06) 0.13
$zFEF_{25–75\%}$	−0.011 (−0.022, 0.001) 0.08	−0.015 (−0.028, −0.003) 0.019	−0.35 (−0.52, −0.17) <0.001	−0.29 (−0.48, −0.10) 0.002

CI = confidence interval; FEV_1 = forced expired volume in 1 s, FVC = forced vital capacity. $FEF_{25–75\%}$ = flow between 25% and 75% of vital capacity. [a]Adjusted for age at assessment. [b]Adjusted for age at assessment, birthweight and male sex.

Table 3: **Mean differences in expiratory airflow z-scores at 7–8 years of age for a) year of birth and b) bronchopulmonary dysplasia in children born weighing 500–999, with and without adjustment for covariates.**

Expiratory airflow variables	Interaction coefficient, (95% CI); P[a]	Change per year of birth			
		Bronchopulmonary dysplasia		No bronchopulmonary dysplasia	
		Mean difference (95% CI); P	Adjusted mean difference (95% CI); P[b]	Mean difference (95% CI); P	Adjusted mean difference (95% CI); P[b]
$zFEV_1$	−0.040 (−0.063, −0.017) <0.001	−0.020 (−0.037, −0.001) 0.035	−0.016 (−0.035, 0.003) 0.10	0.021 (0.006, 0.037) 0.007	0.022 (0.004, 0.039) 0.014
zFVC	−0.034 (−0.059, −0.009) 0.008	−0.011 (−0.030, 0.007) 0.23	−0.010 (−0.029, 0.010) 0.32	0.023 (0.005, 0.040) 0.011	0.020 (0.001, 0.040) 0.041
$zFEV_1/FVC$	−0.007 (−0.033, 0.019) 0.62	[c]	[c]	[c]	[c]
$zFEF_{25-75\%}$	−0.027 (−0.048, −0.006) 0.011	−0.026 (−0.043, −0.009) 0.003	−0.028 (−0.047, −0.010) 0.003	0.001 (−0.013, 0.015) 0.85	−0.004 (−0.018, 0.011) 0.63

CI = confidence interval; FEV_1 = forced expired volume in 1 s, FVC = forced vital capacity. $FEF_{25-75\%}$ = flow between 25% and 75% of vital capacity. [a]P-value for interaction between BPD and year of birth. [b]Adjusted for male sex, birthweight, and age at assessment. [c]Subgroups not reported because of insufficient evidence for an interaction between year of birth and BPD.

Table 4: **Evidence for an interaction between year of birth and bronchopulmonary dysplasia, and changes in expiratory airflow z-scores per year of birth in bronchopulmonary dysplasia and no-bronchopulmonary dysplasia subgroups where evidence exists for an interaction, with and without adjustment for covariates, in children born weighing 500–999 g.**

Discussion

The major findings from the current study of individual participant data from five discrete cohorts born ELBW are that not only is expiratory airflow at 7–8 years of age substantially lower than expected, but it has not improved over a 28-year period despite improvements in perinatal care including an increased use of antenatal corticosteroids as well as the introduction of exogenous surfactant in the middle of the time-period. Compared with those who did not have BPD, those who had BPD had substantial reductions in expiratory airflow overall, and deterioration in expiratory airflow over time. There was little evidence for a difference in trajectories over time between the pre- and post-surfactant eras, except for FEV_1/FVC.

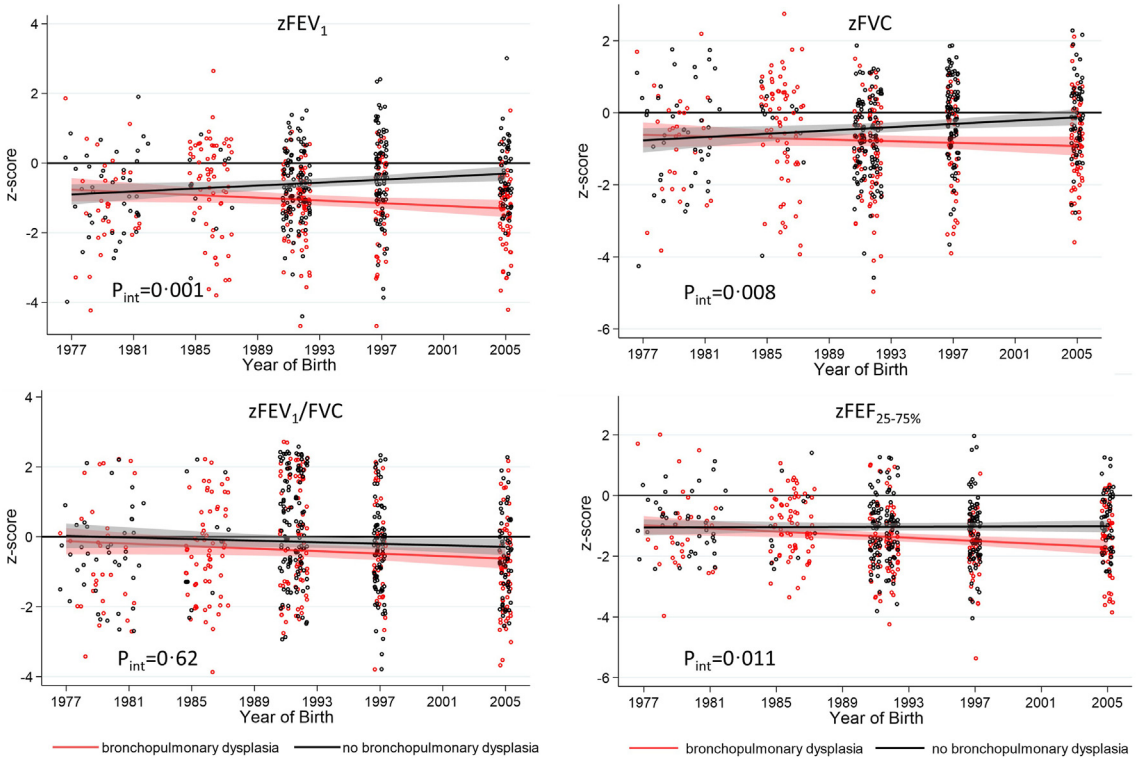

Fig. 2: Z-scores for variables reflecting expiratory airflow at 7–8 years of age by year of birth for children born 500–999 g birthweight; bronchopulmonary dysplasia (BPD) in red; no bronchopulmonary dysplasia in black. P-value for interaction (P_{int}) between bronchopulmonary dysplasia and year of birth, and individual regression lines and their 95% confidence intervals for bronchopulmonary dysplasia (red) and no bronchopulmonary dysplasia (black) groups are shown. $zFEV_1$ = z-score for forced expired volume in 1 s; zFVC = z-score for forced vital capacity; $zFEV_1/FVC$ = z-score for forced expired volume in 1 s/forced vital capacity; $zFEF_{25-75\%}$ = z-score for forced expired volume between 25% and 75% of vital capacity.

Lower than expected expiratory flow rates overall in children born ELBW are consistent with reports from most other studies comparing children born preterm with controls born at term, which have been systematically reviewed.[5,6] In the systematic reviews, Kotecha et al. reported that children born preterm who had BPD had larger reductions in expiratory airflow than those who did not have BPD, and that both groups were worse than controls born at term.[5,6] Where our results differ from those of Kotecha et al. is that we found evidence for a worsening of expiratory airflow over time in children who had BPD, whereas Kotecha et al. reported an improvement in airflow in children with BPD born between the mid-1960s and mid-1990s,[5] and subsequently into the 2010s[6] compared with controls born at term. One explanation for our different conclusions might be that the earliest participants in the studies in Kotecha et al.'s systematic reviews were born in the late 1960s and early 1970s, comprising survivors from the first attempts at assisted ventilation when survival rates were low, and when BPD was first described. The oldest studies (earliest years of birth) in the systematic reviews were largely convenience samples with small sample sizes, with mean birthweights well above 1000 g, and had some of the lowest mean values for FEV_1 compared with controls. The results from the earliest studies hold down the lower end of the regression line, and hence contribute to the positive linear slope in FEV_1 over time in the systematic reviews. However, low values from the earliest studies from the 1960s and 1970s are not the entire explanation because the positive slope in FEV_1 over time in those who had BPD in Kotecha et al.'s latest study[6] applied to BPD defined both by oxygen dependency at 28 days, which comprised cohorts born as early as the 1960s, and by oxygen dependency at 36 weeks, which comprised cohorts born from the mid-1980s onwards. In contrast to Kotecha et al.'s systematic reviews,[5,6] we studied complete cohorts of survivors, albeit the first two cohorts were from the one hospital, all with birthweights 500–999 g, and over a narrower span of years of birth, excluding the earliest years of using assisted ventilation in neonatal intensive care. Kotecha et al. speculated that the introduction of exogenous surfactant may have contributed to the improvements in expiratory airflows over time in those with BPD.[6] Our study straddled the 14 years before and the 14 years after the introduction of exogenous surfactant into clinical practice. We did not find conclusive evidence that surfactant has improved expiratory airflows in children born 500–999 g birthweight in our region, and particularly not in those who had BPD.

The strengths of the current study include reporting on outcomes from consecutive survivors born over a period of similar duration before and after exogenous surfactant was introduced into clinical practice. We also had expiratory flow data at 7–8 years on high proportions of all survivors. There are limitations, however. It would have been preferable if we had studied complete cohorts derived from the state of Victoria selected by gestational age <28 weeks from well before surfactant was introduced until well after, which would exclude participants who were more mature but growth restricted. However, in the 1970s and 1980s ascertainment of gestational age was largely by menstrual history as antenatal ultrasound dating was uncommon in clinical practice. Hence, the Victorian cohorts in 1979–80 and 1985–87 were selected by birthweight <1000 g only. Also, the initial design of these cohort studies did not include respiratory function at school-age or later as an outcome. Thus, expiratory airflow was only assessed in children from one of the four major hospitals involved in the statewide follow-up program in the early years encompassed by our current report. The results from our supplementary analyses restricted to participants with gestational age <28 weeks were similar to those of cohorts selected by birthweight in the main analyses, which is not surprising, since 69% (411/596) of the cohort in the main analysis had both birthweight <1000 g and gestational age <28 weeks. The supplementary data are, however, reassuring with respect to the applicability of our results to cohorts selected by gestational age. We acknowledge the limitation of not having complete cohorts born <28 weeks' gestation for the 1977–82 and 1985–87 cohorts. We also did not have expiratory airflow data available for term-born controls for the first two cohorts at 8 years of age. Where we have obtained data from controls at 7–8 years of age for the last three cohorts, the mean z-scores are close to zero (e.g., for 532 controls combined from the last three cohorts; mean $zFEV_1$ = 0.18; mean zFVC = 0.11). Comparing our results with controls when the mean for controls is close to zero would have little effect on our overall results, or on our conclusions concerning differences between those with or without BPD within the ELBW group. A limitation common to all long-term follow-up studies is the lag time from birth to reporting outcomes; neonatal intensive care has continued to evolve since our last cohort was born in 2005, but our data are still among the most contemporary reports of expiratory airflows in childhood. We had different definitions for BPD for those born before 1990 than for those born after 1990, which is a limitation of the study but is unlikely to have had much effect on our conclusions since Kotecha et al. have shown that regardless of the definition of BPD based either predominantly on oxygen dependence over 28 days after birth, which applied to our pre-1990 cohorts, or on oxygen dependency at 36 weeks' postmenstrual age, which applied to our cohorts born after 1990, results for preterm children with BPD compared with controls born at term were similar.[6] Moreover, in the supplementary analyses investigating changes over time in those receiving oxygen for more than 28 days with those who did not, the overall patterns of change over time were similar to

those for the BPD and no BPD groups. It is important to note that our definition of BPD in those born prior to 1990 was based not only on the requirement for oxygen for more than 28 days but also on the need for an abnormal chest X-ray consistent with stage 3 or 4 BPD as defined by Northway.[7] Our pre-1990 definition differs from the 2001 classification of mild BPD based on only oxygen requirement for more than 28 days and not the additional need for an abnormal chest X-ray.[10]

As survivors born preterm are not reaching their full airway growth potential by their early 20s,[17] they are at high risk of developing chronic obstructive pulmonary disease earlier in life than would otherwise be expected. Rather than relaxing our efforts to improve respiratory support for tiny babies because expiratory airflow is improving over time, our findings of deterioration in airflow in those who had BPD suggest that we need more strategies to support infants born ELBW or EP in the newborn period that minimise injury to their developing lungs, and to improve their long-term expiratory airflow. The trend to using more non-invasive respiratory support in the 2000s was accompanied by an increase in the diagnosis of BPD and worse expiratory airflows in our Victorian cohort born EP in 2005 compared with births in 1991–92 and 1997.[3] However, in our next Victorian cohort born EP in 2016–17 where there has been a further increase in non-invasive respiratory support we have seen a drop in the rate of BPD, which is encouraging.[18] Whether a decrease in BPD is accompanied by an improvement in expiratory airflow at school-age in our 2016–17 cohort remains to be determined.

In conclusion, children born ELBW have substantially reduced airflow at 7–8 years of age, particularly those who had BPD in the newborn period. Overall, airflow values have not clearly improved with the introduction of surfactant and appear to be worse in those who had BPD, conclusions that differ from those obtained from recent systematic reviews on expiratory airflow from cohorts born preterm.

Contributors

Lex Doyle–conception and design of the study, data analysis and interpretation, drafting and revising the article; and approval of the final manuscript as submitted.

Sarath Ranganathan–conception and design of the study, drafting and revising the article, and approval of the final manuscript as submitted.

Alicia Spittle–conception and design of the study, drafting and revising the article, and approval of the final manuscript as submitted.

Gillian Opie–conception and design of the study, drafting and revising the article, and approval of the final manuscript as submitted.

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Jeanie Cheong–conception and design of the study, data analysis and interpretation, drafting and revising the article; and approval of the final manuscript as submitted.

Data sharing statement

De-identified data used in this study can be requested by contacting the corresponding author. Data will be shared with researchers who provide an ethically approved and methodologically sound proposal. Data requestors will be required to sign a Data Access Agreement.

Declaration of interests

Dr Cheong reports receiving additional grants from the National Health and Medical Research Council of Australia (Leadership Fellowship #2016390), and non-industry support for airfare and accommodation as an invited speaker.

Dr Mainzer reports no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102115.

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