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Author/s:
Doyle, LW;Ranganathan, S;Mainzer, RM;Cheong, JLY

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Relationships of Severity of Bronchopulmonary Dysplasia with Adverse Neurodevelopmental Outcomes and Poor Respiratory Function at 7-8 Years of Age

Lex W. Doyle, MD[1,2,3,4], Sarath Ranganathan, PhD[2,5], Rheanna M. Mainzer, PhD[2,4,6], and Jeanie L. Y. Cheong, MD[1,2,3,4], for the Victorian Infant Collaborative Study Group*

Objective To clarify the relationships of 3 definitions of severity of bronchopulmonary dysplasia (BPD) with adverse neurodevelopmental and respiratory outcomes at early school-age.

Study design Participants comprised 218 consecutive survivors to 7-8 years of age born either <28 weeks' gestation or weighing <1000 g in Victoria, Australia, in 2005. BPD was classified as none, grade 1 (mild), grade 2 (moderate), or grade 3 (severe), using 2 commonly accepted definitions: 1) Jobe2001, and 2) Higgins2018, and our own 3) Victorian Infant Collaborative Study (VICS) 2005, adapted from Jensen2019. Outcomes included major neurodevelopmental disability, low IQ and academic achievement, poor motor function, and poor respiratory function as assessed by spirometry. Outcomes for children with each grade of BPD were compared with children with no BPD.

Results Of the 218 survivors, 132 (61%) had BPD on Jobe2001 criteria, and 113 (52%) had BPD on both Higgins2018 and VICS2005 criteria. Grade 1 on any criteria was not associated with any adverse neurodevelopmental outcomes. Grade 1 on both Higgins2018 and VICS2005 was associated with reduced spirometry, grade 2 on both Higgins2018 and VICS2005, and grade 3 on all criteria were associated with increased risk for both adverse neurodevelopmental and respiratory outcomes.

Conclusions Compared with no BPD, receiving additional oxygen up to 29% but no positive pressure support at 36 weeks' postmenstrual age increased the risk of abnormal respiratory function but not adverse neurodevelopment. Receiving ≥30% oxygen or any positive pressure support at 36 weeks increased the risk of both adverse outcomes. *(J Pediatr 2024;269:114005)*.

Although bronchopulmonary dysplasia (BPD) is a common morbidity in infants born extremely preterm (EP) (<28 weeks' gestation) or extremely low birthweight (ELBW) (<1000 g birthweight), a diagnosis of BPD by itself is not as important as its consequences on long-term outcomes, such as adverse neurodevelopment or abnormal respiratory function. Children who have BPD in the newborn period, defined as oxygen dependency at 36 weeks' postmenstrual age (PMA), have reduced expiratory airflow[1,2] and more neurosensory problems, particularly motor dysfunction, and poorer performance on cognitive and academic function at school-age[3] compared with those who do not have BPD. How these outcomes are related to the severity of BPD is unclear, partly because of the different definitions of BPD and its severity that are in common use,[4-6] and partly because studies relating the severity of BPD with outcomes at school-age are sparse. The ability to identify more accurately children destined for long-term neurodevelopmental or respiratory dysfunction would help to target scarce

BPD	Bronchopulmonary dysplasia	IQ	Intelligence quotient
CI	Confidence interval	MABC-2	Movement Assessment Battery for Children–Second Edition
ELBW	Extremely low birth weight		
EP	Extremely preterm		
$FEF_{25-75\%}$	Forced expiratory flow from 25% to 75% of vital capacity	NA	Not applicable
		NCPAP	Nasal continuous positive airway pressure
FEV_1	Forced expiratory volume in 1 second	NIPPV	Non-invasive intermittent positive pressure ventilation
FiO_2	Fractional inspired oxygen concentration	PMA	Postmenstrual age
		RR	Risk ratio
FVC	Forced vital capacity	SD	Standard deviation
GMFCS	Gross Motor Function Classification System	VICS	Victorian Infant Collaborative Study
IPPV	Intermittent positive pressure ventilation	WRAT4	Wide Range Achievement Test–4th Edition

From the [1]Department of Obstetrics, Gynaecology and Newborn Health, The Royal Women's Hospital, Melbourne, Australia; [2]Department of Paediatrics, University of Melbourne, Melbourne, Australia; [3]Newborn Services, The Royal Women's Hospital, Melbourne, Australia; [4]Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Australia; [5]Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Australia; and [6]Clinical Epidemiology and Biostatistics, Murdoch Children's Research Institute, Melbourne, Australia

*Members listed in **Supplementary Material** (available at www.jpeds.com).

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early intervention resources towards those with the highest risk and provide more accurate counseling for families of children related to the varying severity of BPD in the newborn period. In addition, because BPD is a common endpoint for many perinatal and neonatal randomized controlled trials, its longer-term health implications need to be understood.

The aim of this study of children born EP/ELBW was to describe the relationships of severity of BPD with neurodevelopment and respiratory function at early school-age, and how these relationships varied with 3 different definitions of BPD.

Methods

Participants comprised consecutive survivors to 7-8 years of age born EP/ELBW (n = 218) in the state of Victoria, Australia, in 2005. Contemporaneous healthy term-born (37-42 weeks' gestational age) and normal birthweight (>2499 g) infants (n = 218) were also recruited at birth, and were matched for sex, expected date of birth, the mother's health insurance status (private or public, as a proxy for social class), and the primary language spoken in her country of birth (English or other). The purpose of the term-born, normal birthweight group in this study was to compute *z* score cut-offs on psychological tests for EP/ELBW participants, as described below.

Perinatal data, including gestational age and birthweight, were collected prospectively in the newborn period. BPD and its severity were classified into 4 categories of 1) no BPD, 2) grade 1 (mild), 3) grade 2 (moderate), and 4) grade 3 (severe), using 3 definitions. The first (Jobe2001) followed the criteria of Jobe and Bancalari reported in 2001.[4] The second (Higgins2018) followed criteria reported in 2018.[5] The third (Victorian Infant Collaborative Study [VICS] 2005, our own as applied to the cohort in the current study) was adapted from the criteria of Jensen et al, reported in 2019.[6] Since nasal high flow was not used in 2005 in Victoria, we adapted the Jensen criteria by replacing nasal high flow with fractional inspired oxygen concentration (FiO_2) at 36 weeks' PMA (**Table I**). Noninvasive intermittent positive pressure ventilation (NIPPV), used in both Higgins2018 and Jensen2019 criteria, was not used in our cohort and hence was not considered in our definition.

Children were assessed at 7-8 years of age, corrected for prematurity. Assessors were blinded to knowledge of birth group.

Measurements

Neurodevelopmental Outcomes. IQ was assessed using the Differential Ability Scales, Second Edition,[7] and academic achievement with the Wide Range Achievement Test—fourth Edition[8] from which scores for Reading, Spelling, and Arithmetic were obtained. Results were adjusted for social risk, and *z* scores were computed relative to the mean score (SD 15) for the contemporaneously-assessed infants born at term, as described elsewhere.[9] Poor performance on IQ and academic assessments was defined as a *z* score < -2 SD relative to the term-born, normal birthweight group.

Major neurosensory disability was defined as having 1 or more of the following: moderate or severe cerebral palsy

Table I. Criteria for severity of bronchopulmonary dysplasia for Jobe2001, Higgins2018, and VICS2005

	Bronchopulmonary dysplasia severity			
Criteria (y)	**Nil**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
1. Jobe2001[4]	Oxygen duration for <28 d after birth	Oxygen ≥28 d but not at 36 wk' PMA; and no other respiratory support at 36 wk	Oxygen ≥28 d and FiO_2 >0.21-<0.30 at 36 wk with no other respiratory support	Oxygen ≥28 d and FiO_2 ≥0.30 at 36 wk or other respiratory support
2. Higgins2018[5]*	No assessment of oxygen duration No oxygen or other respiratory support at 36 wk	At 36 wk: NCPAP, NIPPV, or nasal cannula ≥3 l/min and FiO_2 0·21; or nasal cannula <3-≥1 l/min and FiO_2 0.22-0.29; or hood FiO_2 0.22-0.29; or nasal cannula <1 l/min and FiO_2 0.22-0.70	At 36 wk: Invasive IPPV and FiO_2 0.21; or NCPAP, NIPPV, or nasal cannula ≥3 l/min and FiO_2 0.22-0.29; or nasal cannula <3-≥1 l/min and FiO_2 ≥0.30; or hood FiO_2 ≥0.30; or nasal cannula <1 l/min and FiO_2 >0.70	At 36 wk: Invasive IPPV and FiO_2 >0.21; or NCPAP, NIPPV, or nasal cannula ≥3 l/min and FiO_2 ≥0.30
3. VICS2005	No assessment of oxygen duration. No oxygen or other respiratory support at 36 wk	At 36 wk: FiO_2 >0.21-0.29 into incubator; or nasal cannula 100% oxygen <100 ml/min (or equivalent); and no other respiratory support	At 36 wk: FiO_2 ≥0.30 into incubator; or nasal cannula 100% oxygen ≥100 ml/min (or equivalent); or NCPAP at 36 wk regardless of FiO_2	At 36 wk: Invasive IPPV regardless of FiO_2.
Jensen[6]† 2019	No assessment of oxygen duration No oxygen or other respiratory support at 36 wk	At 36 wk: Nasal cannula ≤ 2 l/min regardless of FiO_2 and no other respiratory support	At 36 wk: Nasal cannula >2 l/min or NCPAP or NIPPV, regardless of FiO_2	At 36 wk: Invasive IPPV regardless of FiO_2

IPPV, intermittent positive pressure ventilation (via an endotracheal tube); *NCPAP*, nasal continuous positive airway pressure; *VICS*, Victorian Infant Collaborative Study.
Criteria from Jensen2019 provided for comparison. No infant received NIPPV, or high-flow nasal cannula oxygen/air; hence these criteria not used for severity of BPD on Higgins2018 criteria.
*Requires radiographic confirmation of parenchymal lung disease, but postnatal age and criteria for parenchymal lung disease not stated.
†Criteria with highest predictive value from Jensen et al.

(Gross Motor Function Classification System[10] levels 2-5), blindness (visual acuity <6/60 in the better eye), deafness (hearing impairment needing amplification or a cochlear implant, or worse), or an IQ *z* score of < −2 SD. Motor function was assessed using the Movement Assessment Battery for Children–Second Edition.[11] Children who were unable to perform the test due to severe motor impairment were given a centile of 1. Poor motor function was defined as having either cerebral palsy or motor impairment on the Movement Assessment Battery for Children–Second Edition (≤fifth centile).

Respiratory Function. 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 ($FEF_{25-75\%}$) were measured by spirometry according to American Thoracic Society guidelines,[12] as described previously.[2] Results were converted into *z* scores for age, height, sex, and ethnicity.[13] Poor respiratory function was defined as a *z* score < −1.645 (<fifth percentile).

Statistical Analysis

Data were analyzed using Stata 18.0 (Stata Corp).[14] For each set of criteria for BPD, risk ratios (RRs) were used to describe the relative risks of major neurosensory disability, poor performance on developmental tests, poor motor function, and poor respiratory function, given exposure to grade 1, 2, or 3 BPD, relative to no BPD. RRs were estimated using log-binomial regression, with the no BPD group the basis for each comparison. All regression models were fitted using Generalized Estimating Equations with robust standard errors to account for clustering within multiple births from the same family. Estimates were presented with 95% CIs and *P* values. Results were interpreted based on the magnitude of differences and their 95% CIs, and not just on *P* values alone.

Ethical approval for this study was obtained from the Human Research Ethics Committees at the Royal Women's Hospital, Mercy Hospital for Women, Monash Children's Hospital, and the Royal Children's Hospital, Melbourne. Parents gave written informed consent for their children to participate.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Lex Doyle and Jeanie Cheong 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 perinatal characteristics of the cohort were as expected of EP/ELBW survivors born in 2005 in Australia; most had received antenatal corticosteroids and exogenous surfactant (Table II). Of the 218 survivors to 8 years of age, 132 (61%) had BPD on Jobe2001 criteria, and 113 (52%) had

Table II. Perinatal data, including 3 classifications of bronchopulmonary dysplasia, and school-age outcome data for survivors born EP/ELBW at age 7-8 years

Variable	n = 218
Perinatal characteristics	
Antenatal corticosteroids	192 (88%)
Multiple birth	50 (23%)
Cesarean birth	141 (65%)
Gestational age (completed wk)	26.5 (1.9)
Birthweight (g)	867 (178)
Male	101 (46%)
Birthweight <10th percentile	49 (22%)
Exogenous surfactant	170 (78%)
Necrotizing enterocolitis	18 (8%)
Postnatal corticosteroids	42 (19%)
Bronchopulmonary dysplasia	
Jobe2001	
No BPD	86 (39%)
Grade 1	24 (11%)
Grade 2	52 (24%)
Grade 3	56 (26%)
Higgins2018	
No BPD	105 (48%)
Grade 1	63 (29%)
Grade 2	25 (11%)
Grade 3	25 (11%)
VICS2005	
No BPD	105 (48%)
Grade 1	55 (25%)
Grade 2	52 (24%)
Grade 3	6 (3%)
School-age outcomes	
Assessed at 7-8 y	191 (88%)
Corrected age when assessed—y	7.7 (0.4)
Neurodevelopmental outcomes	n = 189
Blind	0 (0%)
Deaf	7 (4%)
Cerebral palsy—GMFCS level >1	13 (7%)
Major neurodevelopmental disability	30 (16%)
IQ	n = 188
z score	−0.66 (1.14)
<−2 SD	20 (11%)
Reading	n = 181
z score	−0.72 (1.18)
<−2 SD	26 (14%)
Spelling	n = 179
z score	−0.71 (1.22)
<−2 SD	23 (13%)
Arithmetic	n = 181
z score	−0.83 (1.27)
<−2 SD	36 (20%)
Poor motor function*	71/175 (41%)
Respiratory function	
FEV_1	n = 157
z score	−1.10 (1.19)
<5th centile	44 (28%)
FVC	n = 159
z score	−0.70 (1.19)
<5th centile	32 (20%)
FEV_1/FVC	n = 157
z score	−0.74 (1.19)
<5th centile	36 (23%)
$FEF_{25-75\%}$	n = 140
z score	−1.23 (1.06)
<5th centile	51 (36%)

GMFCS, Gross Motor Function Classification System; *NA*, not applicable.
Data are n (%) or mean (SD), unless otherwise stated.
*Either cerebral palsy or ≤fifth centile on the Movement Assessment Battery for Children—second Edition.

Table III. Rates of adverse school-age outcomes by different classifications of severity of BPD

Outcome	Criteria	Bronchopulmonary dysplasia severity			
		Nil	Grade 1	Grade 2	Grade 3
Neurodevelopment					
Major disability	Jobe2001	8/75 (11%)	2/20 (10%)	2/44 (5%)	18/50 (36%)
	Higgins2018	10/91 (11%)	3/53 (6%)	6/22 (27%)	11/23 (48%)
	VICS2005	10/91 (11%)	2/46 (4%)	14/47 (30%)	4/5 (80%)
IQ < −2 SD	Jobe2001	2/75 (3%)	0/20 (0%)	2/44 (5%)	16/49 (33%)
	Higgins2018	2/91 (2%)	3/53 (6%)	4/21 (19%)	11/23 (48%)
	VICS2005	2/91 (2%)	2/46 (4%)	12/46 (26%)	4/5 (80%)
Reading < −2 SD	Jobe2001	8/74 (11%)	0/20 (0%)	4/44 (9%)	14/43 (33%)
	Higgins2018	7/90 (8%)	5/53 (9%)	6/20 (30%)	8/18 (44%)
	VICS2005	7/90 (8%)	5/46 (11%)	11/41 (27%)	3/4 (75%)
Spelling < −2 SD	Jobe2001	7/73 (10%)	0/20 (0%)	4/44 (9%)	12/42 (29%)
	Higgins2018	6/89 (7%)	6/53 (11%)	5/19 (26%)	6/18 (33%)
	VICS2005	6/89 (7%)	5/46 (11%)	9/40 (22%)	3/4 (75%)
Arithmetic < −2 SD	Jobe2001	10/74 (14%)	0/20 (0%)	7/44 (16%)	19/43 (44%)
	Higgins2018	10/90 (11%)	9/53 (17%)	7/20 (35%)	10/18 (56%)
	VICS2005	10/90 (11%)	7/46 (15%)	16/41 (39%)	3/4 (75%)
Poor motor function*	Jobe2001	23/73 (32%)	6/19 (32%)	14/41 (34%)	28/42 (67%)
	Higgins2018	28/88 (32%)	19/50 (38%)	11/19 (58%)	13/18 (72%)
	VICS2005	28/88 (32%)	15/43 (35%)	26/42 (62%)	2/2 (100%)
Respiratory function					
FEV_1 <5th centile	Jobe2001	5/62 (8%)	2/17 (12%)	13/40 (32%)	17/38 (45%)
	Higgins2018	7/75 (9%)	15/49 (31%)	5/17 (29%)	10/16 (62%)
	VICS2005	7/75 (9%)	13/42 (31%)	14/37 (38%)	3/3 (100%)
FVC <5th centile	Jobe2001	8/63 (13%)	1/17 (6%)	10/41 (24%)	13/38 (34%)
	Higgins2018	8/76 (11%)	13/50 (26%)	3/17 (18%)	8/16 (50%)
	VICS2005	8/76 (11%)	11/43 (26%)	11/37 (30%)	2/3 (67%)
FEV_1/FVC <5th centile	Jobe2001	14/62 (23%)	2/17 (12%)	12/40 (30%)	12/38 (32%)
	Higgins2018	16/75 (21%)	13/49 (27%)	4/17 (24%)	7/16 (44%)
	VICS2005	16/75 (21%)	12/42 (29%)	11/37 (30%)	1/3 (33%)
$FEF_{25-75\%}$ <5th centile	Jobe2001	16/57 (28%)	5/17 (29%)	18/34 (53%)	12/32 (38%)
	Higgins2018	20/70 (29%)	19/42 (45%)	6/16 (38%)	6/12 (50%)
	VICS2005	20/70 (29%)	19/36 (53%)	11/32 (34%)	1/2 (50%)

Data are n/N (%).
*Either cerebral palsy or ≤fifth centile on the Movement Assessment Battery for Children—second Edition.

BPD on both the Higgins2018 and VICS2005 criteria (Table II). There were more infants classified as grade 2 or 3 on Jobe2001 criteria than on Higgins2018 and VICS2005 criteria (Table II). There were only 6 (3%) children with grade 3 on VICS2005 criteria, far fewer than on both Jobe2001 and Higgins2018 criteria.

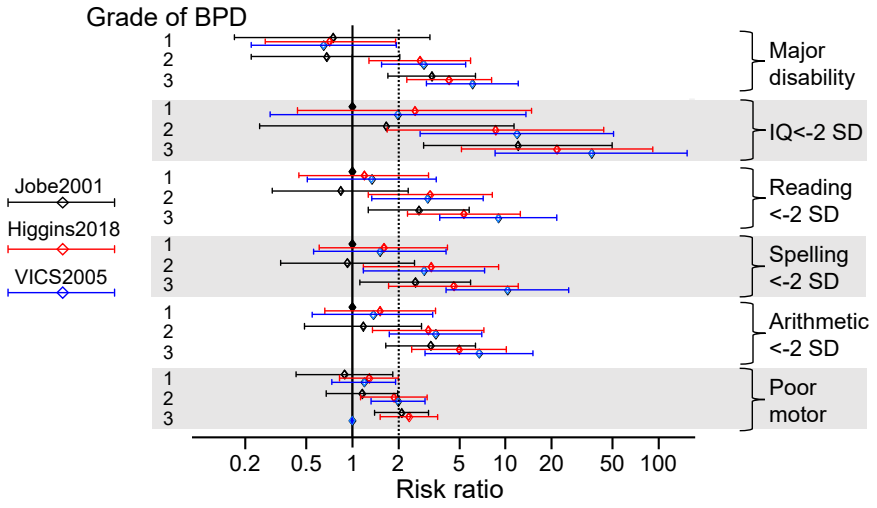


Figure 1. Risk ratios (*diamonds*) and 95% CIs (*error bars*) among infants born EP/ELBW for major neurodevelopmental disability, poor performance in cognitive scores, and poor motor function for each grade of BPD compared with no BPD, for each set of criteria for BPD. Risk ratios for several comparisons could not be calculated due to no events for grade 1 for Jobe2001 (*solid black diamonds*), and perfect prediction of the outcome related to small sample size (n = 2) for grade 3 for VICS2005 (*solid blue diamond*).

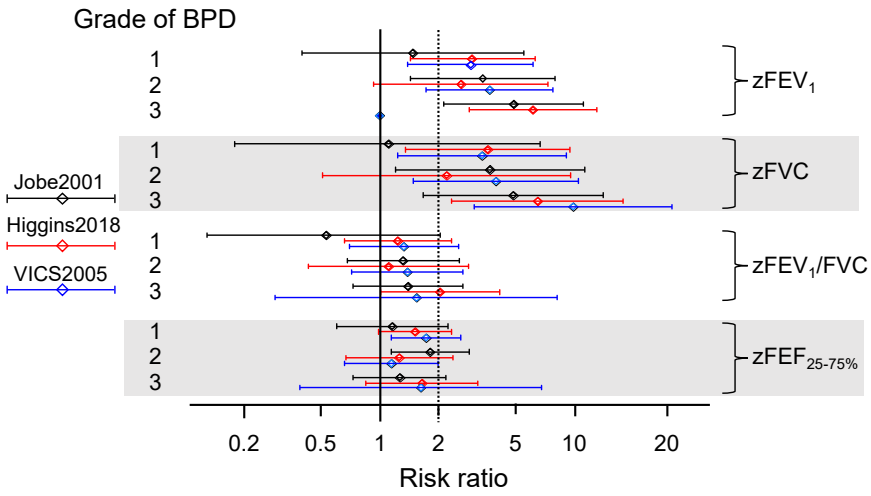


Figure 2. Risk ratios (*diamonds*) and 95% CIs (*error bars*) among infants born EP/ELBW for poor expiratory airflow for each grade of BPD compared with no BPD, for each set of criteria for BPD. Risk ratios for 1 comparison could not be calculated due to perfect prediction of the outcome related to small sample size (n = 3) for grade 3 for VICS2005 (*solid blue diamond*).

Overall, 88% of the cohort was assessed at 7-8 years of age, with some variation in the numbers with outcomes available across the different domains assessed (**Table II**). Of those assessed, 16% (30/189) children had major neurodevelopmental disability. The rates of other adverse neurodevelopmental outcomes were substantial, ranging from 11% to 41%, as were rates of poor respiratory function, ranging from 20% to 36%. Generally, the lowest rates apply to the no-BPD group and the highest rates relate to grade 3 BPD.

There was evidence that risks of adverse neurodevelopmental outcomes and poor respiratory function increased with worsening severity of BPD compared with no BPD, regardless of the criteria for BPD (**Table III**; **Figures 1** and **2**).

Looking more closely at individual levels of severity on the different criteria, there was little difference in the risks of any poor neurodevelopmental outcome between grade 1 BPD and no BPD on any criteria (**Figure 1**). There was little evidence that grade 1 on Jobe2001 criteria was associated with any respiratory variable, whereas there was some evidence for higher risks of poor FEV_1, FVC, and $FEF_{25-75\%}$ for those with grade 1 BPD relative to no BPD using Higgins2018 and VICS2005 criteria (**Figure 2**). Of clinical relevance, the point estimates for the RR for poor FEV_1 on grade 1 on both Higgins2018 and VICS2005 criteria were more than doubled.

There was little evidence that grade 2 on Jobe2001 was related to the risks of any adverse neurodevelopmental outcomes, whereas there was evidence that grade 2 on Higgins2018 and VICS2005 were both related to higher rates of all adverse neurodevelopmental outcomes, with the point estimates for the RR for adverse neurodevelopmental outcomes on grade 2 on both Higgins2018 and VICS2005 criteria being more than doubled for most outcomes (**Figure 1**). There was evidence that grade 2 on Jobe2001 was related to higher risks for poor FEV_1, FVC, and $FEF_{25-75\%}$, and for grade 2 on VICS2005 with higher risks for poor FEV_1 and FVC, but no strong evidence for relationships of grade 2 on Higgins2018 with any respiratory variable (**Figure 2**). Of clinical relevance, the point estimates for the RR for poor FEV_1 on grade 2 on all criteria were more than doubled.

Where calculable, there was evidence that grade 3 on all criteria was associated with higher risks of all adverse neurodevelopmental outcomes and higher risks of low FEV_1 and FVC, with the point estimates for the RRs well in excess of 2 for all of these associations. The point estimates of the RRs for Grade 3 on VICS2005 were generally the largest of all, but with the widest CIs, related to the small sample size of that subgroup.

Discussion

The major findings from our cohort study of children born EP/ELBW were that worse neurodevelopmental and respiratory outcomes at school-age were generally associated with increasing severity of BPD in the newborn period. However, the strength of the associations differed between the criteria for BPD because different children were identified with the same level of severity of BPD across the classifications. There was little evidence for differences in any neurodevelopmental or respiratory outcomes between grade 1 BPD and no BPD using Jobe2001 criteria, whereas there was some evidence that grade 1 BPD was associated with worse respiratory function compared with no BPD on both Higgins2018 and VICS2005 criteria. Adverse neurodevelopmental outcomes were similar between those with grade 2 BPD and those with no BPD using Jobe2001 criteria, whereas grade 2 on both Higgins2018 and VICS2005 was associated with more than a doubling of the risk of adverse neurodevelopmental outcomes compared with no BPD. Grade 3 BPD was

associated with even worse neurodevelopmental and respiratory outcomes than lesser grades on all 3 different criteria. In clinical terms, compared with children born EP/ELBW without BPD, those who received oxygen for more than 28 days but who did not receive oxygen or other respiratory support at 36 weeks' PMA (11% of our cohort) were not at increased risk for adverse neurodevelopmental or respiratory outcomes at school-age, those who received only additional oxygen up to <30% at 36 weeks' PMA but no positive pressure support (25% of our cohort) were at increased risk of reduced spirometry, but not adverse neurodevelopment, and it was only those who received at least 30% oxygen or any positive pressure respiratory support at 36 weeks' PMA (27% of our cohort) who were at increased risk for both adverse neurodevelopmental and respiratory outcomes.

A major difference between the 3 different criteria is that most children with grade 1 on Jobe2001 criteria have no BPD on Higgins2018 and VICS2005 criteria. Another important difference is that of grade 3 BPD; the VICS2005 criteria, being identical to grade 3 of Jensen2019, encompass only invasive intermittent positive pressure ventilation, regardless of FiO_2. Grade 3 on Jobe2001 includes FiO_2 ≥0.30, regardless of how it is administered, as well as other forms of noninvasive respiratory support, and grade 3 on Higgins2018 includes other noninvasive respiratory support with FiO_2 ≥0.30; hence both Jobe2001 and Higgins 2018 have more infants categorized into grade 3 compared with VICS2005. Grade 3 BPD on VICS2005 identifies the most severe form of BPD, which explains the larger point estimates but with greater uncertainty for most outcomes than grade 3 on the other 2 criteria because of the smaller sample size.

Increasing severity of BPD has been related to worse health outcomes in preschool-aged children. In almost 4000 infants with birthweight <1000 g, Ehrenkranz et al reported that there was little difference between no BPD and grade 1 on Jobe2001 criteria in requirements for pulmonary medications or rehospitalizations for pulmonary causes up to 18-22 months' corrected age, whereas grade 2 and grade 3 had progressively higher odds compared with no BPD for these 2 outcomes.[15] They also reported progressively higher rates of neurodevelopmental impairment with increasing severity of BPD. In 790 children born <30 weeks' gestation, Katz et al reported that the overall risk of neurodevelopmental impairment at either 2 or 5 years rose with increasing severity of BPD for each of grade 1, 2, and 3 BPD on Jobe2001 criteria compared with no BPD.[16] In another study using the Jensen2019 criteria, increasing severity of BPD was associated with more withdrawn behavior and pervasive developmental problems, but with fewer sleep problems and less aggressive behavior at 2 years.[17]

Studies of neurodevelopmental outcomes in school-age children related to severity of BPD are uncommon. Similar to the results of our study, Sriram et al reported that IQ, academic achievement, executive function and language performance at 10 years of age in children born <28 weeks' gestation were all progressively worse with increasing severity of BPD at 36 weeks' PMA.[18] However, they defined BPD differently to any of the criteria described in the current study in 3 categories: no to mild (no oxygen), moderate (oxygen but no ventilator assistance), and severe (oxygen and ventilator assistance); moderate BPD in their classification would be closest to grades 1 and 2 BPD combined on VICS2005 criteria. Severe BPD on their criteria would identify the same children as grade 3 on VICS2005; 9% of their cohort had severe BPD compared with only 3% of our cohort. Unlike our study they did not report results of respiratory function in relationship to BPD severity.

It is well known that expiratory airflow is lower in children who had BPD compared with term-born infants, regardless of whether the definition is based on determining BPD at 28 days or at 36 weeks.[1] Moreover, expiratory airflow is lower among survivors born preterm who had BPD compared with those without BPD.[19-22] What is less well reported is the relationship between severity of BPD and expiratory airflow, although several small studies have reported worse expiratory airflow with increasing severity of BPD in survivors born preterm.[23,24] In contrast with only grades 2 and 3 BPD on newer criteria being associated with adverse neurodevelopmental outcomes, the current study confirms that all grades of BPD on newer criteria are associated with reduced spirometry.

In contrast with the results of our study, Katz et al concluded that rates of neurodevelopmental impairment and of respiratory morbidity over the first 5 years of life were worse with increasing severity of BPD but differed little between Jobe2001, Higgins2018, and Jensen2019 criteria, and that Higgins2018 was less discriminatory than Jobe2001 for neurologic outcome at 2 years.[25] The reason for their different findings to ours for neurodevelopmental outcomes may be explained by our ability to assess a broader range of neurodevelopmental domains at a later age (7-8 years) which are not possible in earlier childhood. Such broad neurodevelopmental domains at school-age may have enabled more important clinical differences related to the different criteria for severity of BPD to emerge.

The strengths of our study include the population-based cohort, a high follow-up rate at early school-age, and assessments of neurodevelopment and respiratory function at 7-8 years by health professionals blinded to knowledge of birth group. Although the study was relatively small it was still large enough to observe progressively worse neurodevelopment and respiratory function as the severity of BPD increased. A limitation is that since nasal high-flow and NIPPV were not used in 2005 in any of our centers, we could not define grades 2 and 3 BPD as per Jensen2019. However, the modified criteria we used for VICS2005 are relevant to centers that do not have nasal high-flow or NIPPV data with which to categorize the severity of BPD, which particularly relates to cohorts born more than a decade ago and which will apply to ongoing and future studies where nasal high-flow and NIPPV are not used. A limitation is that we were unable to obtain valid spirometry data from 100% of survivors in our complete geographical cohort; 12% of the survivors were not assessed at 7-8 years of age, and 16% of the survivors who were assessed at 7-8 years were not able

to provide valid spirometry data. Given the strict requirements of the American Thoracic Society to obtain adequate spirometry there will never be a complete cohort of school-age children with valid data from 100% of participants.

A limitation of grade 3 BPD on VICS2005 criteria in the current study is that few children were in this category, being derived from Jensen2019 criteria which only comprise children receiving invasive ventilation, whereas the Higgins2018 criteria did result in more children being identified with grade 3 BPD, because it included criteria related to noninvasive ventilation, and not just invasive ventilation alone. Since both grade 2 and grade 3 BPD are associated with worse neurodevelopmental and respiratory outcomes compared with no BPD on VICS2005 criteria, distinguishing between the grades 2 and 3 may not be useful to cohorts that are similar to ours where few are categorized with grade 3 BPD. As more noninvasive modes of respiratory support are used, the proportion of infants who require invasive ventilation beyond 36 weeks could well diminish to the point where there is limited value in distinguishing between grade 2 and grade 3 on Jensen2019 criteria.

We have not aimed to establish the causal effect of BPD on later neurodevelopment or expiratory airflow, and thus have not adjusted for potential confounders, such as cerebral injury or postnatal corticosteroids to prevent or treat BPD. However, our descriptive analysis has identified those with more than a doubling of risk of adverse neurodevelopmental outcomes or reduced spirometry at school-age compared with no BPD. Being at more than double the risk for a particular adverse outcome identifies those who would benefit most from increased surveillance and early intervention to try to avoid later cognitive or academic problems, or respiratory ill-health. Early developmental intervention over the first year of life is effective at improving cognitive and motor outcomes of survivors born preterm.[26] Although there may not be any proven early interventions known to improve later respiratory function, avoidance of passive smoke exposure in early childhood seems sensible advice to discuss with families of children who had BPD. In a recent randomized controlled trial in children born <32 weeks' gestation studied at 6-12 years of age, there was an improvement in spirometry 12 weeks after a course of inhaled corticosteroids compared with placebo.[27] However, it is unknown if such changes are sustained, or if inhaled corticosteroids are disease-modifying.

In conclusion, in our cohort of infants with extremely prematurity, neurodevelopmental and respiratory outcomes at early school-age were generally worse with increasing severity of BPD for survivors born EP/ELBW, regardless of the criteria for defining BPD. However, only those receiving oxygen or pressure support at 36 weeks were at increased risk compared with no BPD, and the risk rose with increasing requirements for oxygen and pressure support at 36 weeks. As long-term follow-up studies continue to increase their focus on school-age and older children, it will be important to incorporate BPD severity into their analyses. ■

CRediT authorship contribution statement

Lex W. Doyle: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sarath Ranganathan:** Writing – review & editing, Methodology. **Rheanna M. Mainzer:** Writing – review & editing, Methodology, Formal analysis. **Jeanie L.Y. Cheong:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

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Reprint requests: Lex W. Doyle MD, Department of Obstetrics and Gynaecology, The Royal Women's Hospital, 20 Flemington Rd, Parkville, 3052, Australia. E-mail: lwd@unimelb.edu.au

Data Statement

Data sharing statement available at www.jpeds.com.

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