Published in final edited form as:

Pediatr Res. 2021 August ; 90(2): 359–365. doi:10.1038/s41390-020-01162-2.

Bronchopulmonary Dysplasia Precursors Influence Risk of White Matter Injury and Adverse Neurodevelopmental Outcome in Preterm Infants

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Abstract

Background—Cumulative supplemental oxygen (CSO) and cumulative mean airway pressure (CMAP) are associated with bronchopulmonary dysplasia (BPD) in preterm infants, but their relationships to white matter injury (WMI) and neurodevelopment have not been evaluated.

Methods—Preterm infants <32 weeks gestation were prospectively imaged with 3T-MRI near term. CSO and CMAP were retrospectively summed over the first 14 and 28 days. Neurodevelopment was assessed at 30-months adjusted using the Bayley-III. ROC and linear regression were used to evaluate the relationship between CSO, CMAP, and BPD with WMI and neurodevelopmental performance, respectively.

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Each author has met the *Pediatric Research* authorship requirements as follows:

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- Roberta Keller: Substantial contribution to design and interpretation of data; revising article critically for intellectual content; final approval of the version to be published.
- Elizabeth Rogers: Substantial contribution to acquisition of data; revising article critically for intellectual content; final approval of the version to be published.
- J. Colin Partridge: Substantial contribution to acquisition of data; revising article critically for intellectual content; final approval of the version to be published
- Duan Xu: Substantial contribution to acquisition of data and analysis; revising article critically for intellectual content; final approval of the version to be published.
- A. James Barkovich: Substantial contribution to acquisition of data and analysis; revising article critically for intellectual content; final approval of the version to be published.
- Dawn Gano: Substantial contribution to conception and design, acquisition of data, and analysis, and interpretation of data; revising it critically for intellectual content; final approval of the version to be published.

Disclosures/Conflicts of Interest: None

Category of study: Clinical

Statement regarding consent: Patient consent was not required for this retrospective analysis.

Informed consent was previously obtained for participation in the prospective cohort study.

Kimberly Grelli and Dawn Gano conducted the statistical analysis.

Results—Of 87 infants, 30 (34.5%) had moderate-to-severe BPD, which was associated with WMI (OR 5.5, 95% CI 1.1–34.9, p=0.012). CSO and CMAP predicted WMI as well as BPD (AUC 0.68–0.77). CSO was independently associated with decreased language and cognitive performance (mean difference at 14d: −11.0, 95% CI −19.8 to −2.2, p=0.015; −9.8, 95% CI −18.9 to −0.7, p=0.035, respectively) at 30-months adjusted.

Conclusions—BPD precursors predict WMI as well as BPD. Cumulative supplemental oxygen over the first 14 days of life is independently associated with lower language and cognitive performances. These data suggest that early respiratory status influences the risk of adverse neurodevelopment in preterm infants.

Introduction

Survival has increased among the most extremely premature infants with a subsequent increased incidence of bronchopulmonary dysplasia (BPD).(1) Following the original description of BPD by Northway and colleagues,(2) the definition of BPD has evolved as survival has improved due to broad use of antenatal steroids, exogenous surfactant, and application of positive end-expiratory pressure, allowing for decreased level and duration of mechanical ventilation and supplemental oxygen. A consensus conference held in 2000 at the National Institutes of Health (NIH) resulted in a severity-based definition of BPD, defined at 36 weeks' postmenstrual age (PMA) for infants born at less than 32 weeks' gestational age (GA), reflecting an evolution of the preterm population at risk for ongoing respiratory morbidity.(3–5)

This severity-based definition provides discriminatory criteria to evaluate rates and severity of BPD in various populations of former preterm infants, as well as associated later morbidity, such as adverse neurodevelopmental and pulmonary outcomes.(4, 6) Specifically, in the large cohort of 4866 preterm infants described by Ehrenkranz and colleagues, the majority (77%) had evidence of BPD, utilizing the NIH severity-based definition. Rates of severe intraventricular hemorrhage (IVH) and cystic white matter injury (WMI), also known as periventricular leukomalacia on cranial ultrasound and neurodevelopmental impairment (NDI) at 18–22 months corrected age all increased as severity of BPD increased.(4) Although the rates of cystic WMI and severe IVH have been decreasing in the preterm population, unfortunately, the rate of NDI in those with BPD has not.(1) Other studies similarly have observed a relationship between BPD and adverse neurodevelopmental outcomes.(7–10) While BPD is largely considered an independent risk factor for NDI,(11, 12) the underlying causes are not clear.

Respiratory precursors of bronchopulmonary dysplasia include both oxygen and mean airway exposure. More specifically, quantitative analysis of cumulative supplemental oxygen (CSO) over the first 28 days of life has been independently associated with BPD, and BPD or death at 36 week's PMA, with a plateau for the predictive potential of CSO at 14 days of life.(13) Cumulative mean airway pressure (CMAP) was similarly found to be an independent predictor of these outcomes, after adjustment for supplemental oxygen exposure.(13) The relationship between these respiratory precursors to BPD, WMI, and neurodevelopmental performance has not been previously described and may provide insight

into the underlying explanatory reasons for the association of BPD with WMI and adverse neurodevelopmental outcomes.

The aim of this study was to evaluate the association of CSO and CMAP over the first 14–28 days of life with WMI detected by magnetic resonance imaging (MRI) and to determine whether respiratory precursors to BPD improve the prediction for WMI compared to BPD alone. We secondarily evaluated the relationship of these respiratory parameters with Bayley-III composite scores at 30 months corrected age. We hypothesized that higher CSO and CMAP would be associated with increased risk of WMI as well as lower neurodevelopmental performance as measured by the Bayley-III.

Methods

We performed a retrospective secondary analysis of preterm infants <32 weeks at birth prospectively enrolled in the Prematurely Born Neonate MRI (PREMRI) study admitted to the University of California, San Francisco (UCSF) Benioff Children's Hospital Intensive Care Nursery between 2011–2016. Exclusion criteria for this cohort include congenital malformation, genetic syndrome, congenital infection, or instability for transport to MRI. Infants enrolled in the PREMRI cohort have an MRI performed as soon after birth as clinically feasible and, when possible, near term-equivalent age. Of the 108 infants enrolled in PREMRI over this timeframe, we excluded 7 infants with no MRI scans, 4 infants due to excessive motion artifact on MRI precluding ability to evaluate for WMI, and 10 infants with missing respiratory data. Complete data was available in 87 participants who comprised our final cohort. Three of the 87 infants died prior to discharge. The subjects in our final cohort were representative of the average intensive care nursery census at UCSF with regard to demographic data, such as GA and BPD status. The PREMRI study was conducted under oversight by the UCSF Institutional Review Board and signed parental consent for study participation was obtained.

Respiratory Parameters

A single investigator (KG) retrospectively collected the respiratory variables. CSO and CMAP were averaged over three standard daily time points (08:00, 16:00, and 00:00) and then summed over the first 28 days of life. CSO was calculated as a daily average of supplemental oxygen (recorded fraction of inspired oxygen [(FiO_2) – 0.21]) to estimate the overall supplemental oxygen exposure on a given day.(13) Utilizing the STOP-ROP guidelines, the recorded FiO_2 was converted to an effective FiO_2 when the infant was on nasal cannula.(14) CMAP was similarly calculated as a daily average and then summed over the first 28 days of life using data from both invasive and non-invasive support, as previously described.(15) For the current study, infants missing a complete day of oxygenation data were excluded. BPD was classified retrospectively utilizing the NIH consensus, severity-based definition reflecting the level of respiratory support and FiO_2 required at 36 weeks 0 days PMA.(3) Use of nasal cannula at any flow was classified as moderate BPD. Goal oxygen saturation values were 88–92% per unit protocol.

Magnetic Resonance Imaging

Clinical stability for MRI was at the discretion of the treating neonatologist. If an early and near-term scan were available, the scan closest to term corrected age was utilized. Upon review, there were no instances of changing WMI severity scores if infants received two scans. All MRI scans were acquired using a 3T-scanner (General Electric Discovery MR750; GE Medical Systems, Waukesha, Wisconsin) and included axial fast spin-echo T2-weighted images (repetition time, 5000 ms; echo time, 120 ms; field of view, 20 cm with 256 × 256 matrix; slice thickness, 2 mm; gap, 0 mm), sagittal volumetric 3-dimensional spoiled gradient echo T1-weighted images (inversion time, 450 ms; echo time, minimal; field of view, 18 mm; 1.0 mm isotropic), and SWI (TR, minimal; TE, 24.1 ms; FOV, 18 mm; slice thickness, 2.2 mm). One blinded pediatric neuroradiologist (AJB) evaluated all MRI scans and scored the severity of WMI on T1-weighted MRI according to our previously published criteria.(16) WMI was subsequently dichotomized as absent-mild or moderate-severe. IVH was classified on MRI by the Papile grading system and subsequently categorized as absent-mild (absent, Grade 1, and Grade 2) or moderate-severe (Grades 3 and 4).(17) The presence or absence of cerebellar hemorrhage (CbH) was evaluated on T2-weighted imaging and, when available, susceptibility-weighted imaging.(18)

Clinical Parameters

A trained clinical research nurse collected neonatal demographic and clinical variables, including GA at birth, birth weight, sex, prenatal steroid administration, maternal chorioamnionitis, surfactant administration, infection, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and neonatal surgery. Newborns with culture-positive sepsis, clinical signs of sepsis with negative blood culture, or meningitis were classified as having infection. Newborns with clinical signs of PDA (prolonged systolic murmur, bounding pulses, and hyperdynamic precordium), and evidence of left-to-right flow through the PDA on echocardiogram were classified as having a PDA. NEC was diagnosed according to Bell stage II criteria or higher.(19)

Neurodevelopmental Assessment

All infants were referred to the UCSF Intensive Care Nursery Follow-Up Program upon discharge for routine neurodevelopmental follow-up. Neurodevelopment was assessed using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III), which was performed by unblinded clinicians at 30 months corrected age. Follow-up was available in 64 of the 84 infants (76.2%) who survived to hospital discharge.

Statistical Analysis

Statistical analysis was performed using Stata 15 (Stata Corporation, College Station, Texas). A cross-sectional analysis of baseline characteristics of newborns enrolled in the prospective cohort was performed. Clinical characteristics were compared between newborns with no-mild versus moderate-to-severe BPD using Fisher exact test or χ^2 test for categorical variables and Student's t-test and Kruskal-Wallis test for parametric and non-parametric continuous variables, respectively. The association of CSO and CMAP with BPD and WMI was evaluated using Kruskal-Wallis test. To evaluate the predictive

potential of respiratory precursors to BPD over the first 28 days of life, only infants in whom an MRI was obtained ≥28 days of life were included (N=75). Receiver operating characteristic (ROC) curves were utilized for the prediction of WMI, and the area under the curve (AUC) was compared using non-parametric ROC analysis. Linear regression was used to evaluate the relationship of CSO, CMAP, and BPD severity with motor, language, and cognitive scores on the Bayley-III (N=64) in univariate and multivariate models. CSO and CMAP were analyzed across the first 14 and 28 days of life in two separate multivariate models. Multivariate linear regression model assumptions for normality and linearity were confirmed. No significant collinearity was observed. Influential points were assessed, and when removed from the model (N=7), similar results were obtained (data not reported). Mean difference for CSO is the effect for a one-unit change, while for CMAP, it is the effect for a 10 unit change. One unit CSO over 14 and 28 days is ~7% and ~3.5% difference per day, respectively, in FiO_2. Ten units CMAP over 14 and 28 days corresponds to ~0.7 cmH_20 and ~0.35 cmH_20 difference per day, respectively. No adjustment for multiple comparisons was performed. For all analyses, a p value < 0.05 was considered significant.

Results

Clinical Characteristics and Imaging Findings by BPD Status

Among the cohort of 87 preterm infants, 42 (48.3%), 15 (17.2%), 20 (23.0%), and 10 (11.5%) had no, mild, moderate, and severe BPD, respectively. The average GA at birth was 28.2 ±2.2 weeks and the median postmenstrual age at MRI was 36.1 weeks (IQR 34.9, 37.7). Infants with moderate-to-severe BPD were more likely to be of younger GA and lower birth weight with increased rates of neonatal comorbidities, including surgery, PDA, and infection (Table 1).

There were significantly more infants with WMI (OR 5.5, 95% CI 1.1–34.9, p=0.012) and IVH (OR 11.2, 95% CI 1.1–538.8, p=0.009) in the moderate-to-severe BPD group compared to the no-mild BPD group. Using ordinal logistic regression, increasing severity of BPD, classified as a 4-level variable, was associated with increased odds of WMI (OR 2.4, 95% CI 1.2–4.7, p=0.011) and IVH (OR 3.3, 95% CI 1.4–7.6, p=0.005).

$CSO_{D1–14}$ and $CMAP_{D1–14}$ were significantly higher in the moderate-to-severe BPD group compared to the no-mild BPD group (Table 2). A similar pattern was seen with $CSO_{D1–28}$ and $CMAP_{D1–28}$. The results confirm that these measures at both time points are precursors to BPD in our cohort. In comparing infants with no-mild WMI to those with moderate-severe WMI, there was no statistically significant difference in $CSO_{D1–14}$. In contrast, $CMAP_{D1–14}$ was statistically significantly elevated in the moderate-severe WMI group (126.4 vs. 60.8, p=0.038). Over the first 28 days, although the median CSO and CMAP were higher in the moderate-severe WMI group, there were no statistically significant differences between infants with and without WMI.

BPD, CSO, and CMAP for the Prediction of WMI

In evaluation of AUC for the prediction of WMI, BPD, $CSO_{D1–14,}$ and $CMAP_{D1–14}$ demonstrated similar moderate-to-good prediction (Table 3). Although a multivariate model

with all of these variables resulted in a higher AUC, there was no statistically significant difference between the AUC of the univariate and multivariate models (p=0.30). Using additional data to 28 days, $CSO_{D1–28}$ and $CMAP_{D1–28}$ had similar AUC to $CSO_{D1–14}$ and $CMAP_{D1–14,}$ respectively, which was the same pattern seen previously for prediction of BPD. There also was no statistically significant difference in AUC between univariate and multivariate (BPD, $CSO_{D1–28,}$ and $CMAP_{D1–28}$) models including the data to 28 days (p=0.36), although the AUC from the multivariate model was higher than the univariate models. When compared directly, there was no difference between the multivariate models including CSO and CMAP over days 1–14 versus days 1–28 for the prediction of WMI (p= 0.51).

Respiratory Precursors to BPD and Motor, Language, and Cognitive Performance

Follow-up was obtained as part of standard clinical care and available in 64/84 surviving infants (76.2%) at a median corrected age of 28.8 months (IQR 14.7, 31.6). Infants with follow-up had similar GA at birth (28.0 ±2.2 vs. 28.8 ±2.4 weeks, p=0.17) and a similar rate of moderate-to-severe BPD (34.4% vs. 25.0%, p=0.59) as those without follow-up. There were only 5 infants with moderate-severe WMI at follow-up, and all had non-cystic WMI. Rate of moderate-severe WMI was higher in those lost to follow-up (25.0% vs. 7.8%, p=0.053).

The mean Bayley-III composite scores for the cohort in motor, language, and cognitive domains were 99.8 ±15.0, 98.8 ±16.6, and 105.2 ±16.5, respectively, similar to population-level means for the Bayley-III.(20) Univariate and multivariate analyses of the association of respiratory precursors to BPD with neurodevelopmental outcomes were performed (Table 4). In univariate analysis, severe BPD was associated with lower motor performance (mean difference −15.6, 95% CI −29.9 to −1.2, p=0.03), but not language or cognitive performance. Higher $CSO_{D1–14}$ was associated with lower motor scores, although this relationship did not reach statistical significance (mean difference −4.2, 95% CI −8.6 to 0.2, p=0.06). Higher $CMAP_{D1–14}$ was significantly associated with higher language and cognitive scores, but the effect size was very small. Higher $CSO_{D1–28}$ was also associated with decreased motor performance (mean difference −2.5, 95% CI −4.6 to −0.4, p=0.023), while $CMAP_{D1–28}$ was not significantly associated with performance in any domain.

In a 14 day model adjusting for $CSO_{D1–14,}$ $CMAP_{D1–14,}$ WMI, moderate-severe IVH, and GA, severe BPD was independently associated with lower language scores (mean difference −23.1, 95% CI −45.4 to −0.7, p=0.043) but findings were not significant for motor or cognitive scores. Higher $CSO_{D1–14}$ was significantly associated with lower language and cognitive scores (Language mean difference −11.0, 95% CI −19.8 to −2.2, p=0.015; Cognitive mean difference −9.8, 95% CI −18.9 to −0.7, p=0.035) while higher $CMAP_{D1–14}$ was independently associated with higher language and cognitive scores (Language mean difference 3.2, 95% CI 1.5 to 4.8, p<0.001; Cognitive mean difference 2.4, 95% CI 0.7 to 4.1, p=0.008). In a similar 28 day model, severity of BPD was not significantly associated with any neurodevelopmental domain. Higher $CSO_{D1–28}$ continued to have a small, significant effect on language and cognitive scores; there was no significant relationship between $CSO_{D1–28}$ and motor performance. WMI was not associated with performance in

any domain for both univariate and multivariate analyses including respiratory precursors over days 1–14 or days 1–28.

Discussion

To our knowledge, neither cumulative supplemental oxygen nor cumulative mean airway pressure has been utilized previously to study white matter injury or neurodevelopmental outcomes in infants with BPD.(13) We found that CSO and CMAP, precursors of BPD, were, in fact, associated with the later determination of BPD. They both also moderately predicted the risk of WMI, as did BPD, and there was no difference in the strength of these predictions across days 1 to 14 or days 1 to 28. Respiratory precursors to BPD were independently associated with both language and cognitive performance on the Bayley-III at 30 months corrected age. While the relationship between CMAP and language and cognitive performance was statistically significant, the effect size is small and unlikely to be of clinical significance. In contrast, higher cumulative oxygen exposure was independently associated with decreased language and cognitive performance, with a clinically meaningful effect size.

From previous research, it is well known that BPD is associated with adverse neurodevelopmental outcomes, and to date, there are no known modifiable predictors of adverse neurodevelopmental performance associated with BPD.(21) Although we hypothesized that WMI served as an important mediator between BPD and adverse neurodevelopmental performance, in our study, neurodevelopmental performance was not associated with WMI in either univariate or multivariate analysis. This may be due to low power for this analysis, but our data do suggest that CSO may serve as a plausible biological marker to identify high-risk subgroups of preterm infants with BPD who are at risk of both WMI and NDI.

Given BPD is a diagnosis that is assigned at 36 weeks PMA, precursor respiratory parameters, such as CSO and CMAP over the first 2–4 weeks of life, offer early predictive potential to identify infants who are at greatest risk for BPD, as well as both WMI and poorer neurodevelopmental performance. CSO and CMAP over the first 2 weeks of life perform as well as over the first 4 weeks of life for the prediction of WMI. The tradeoff of sensitivity versus specificity must be considered in future investigations of cut-offs for these respiratory parameters as biomarkers in consideration of interventions to interrupt the pathophysiology. Taken together, these respiratory precursors may offer an early tool to implement in future studies to optimize neurodevelopment and prevent BPD and its sequalae.

When considering whether CSO and/or CMAP could be potentially useful biomarkers or modifiable exposures, the interaction between brain and lung health must be considered. Studies have shown that BPD is associated with WMI,(22) in addition to abnormalities in white matter microstructure and volume, as well as delayed brain maturation.(23, 24) Hyperoxia is known to be detrimental in the pathogenesis of retinopathy of prematurity, and our data suggest that hyperoxia in the setting of chronic lung disease is associated with adverse neurodevelopmental outcomes independent of non-cystic WMI and IVH. This is supported by data from newborn rodents in which exposure to hyperoxia at a stage in brain

development analogous to preterm humans leads to widespread apoptosis in the cortex, basal ganglia, hypothalamus, hippocampus, and white matter.(25) Hyperoxia also leads to hypoxic chemosensitivity ablation and decreased carotid body afferents in rats, further contributing to impairment of the cerebral autoregulation mechanism of the developing brain.(26) In preterm infants, hyperoxia leads to reduced cerebral blood flow, an effect that can last two hours, even after a brief exposure to hyperoxia.(27) We suggest that future studies evaluating associations between BPD and white matter microstructure, as well as connectivity, in preterm infants, incorporate cumulative oxygen exposure as a potential mediator of these relationships.

In addition to oxygen management, which, depending on an infant's oxygen saturation and underlying lung disease severity may not be immediately modifiable, lung ventilation strategies should be considered as potential modifiable interventions. The early application of non-invasive ventilation to provide continuous positive airway pressure has been shown to modestly reduce the combined outcome of death or BPD.(28) Invasive ventilation, in contrast, is known to cause significant pulmonary inflammation and lead to worsening lung disease.(29) This pulmonary inflammatory cascade can lead to systemic inflammation either with or without an underlying infection, which may contribute to preterm brain injury.(22) Maintaining adequate mean airway pressure, both invasively and non-invasively, is crucial to avoid ventilation-perfusion mismatch and to maintain appropriate cerebral perfusion. Too little mean airway pressure leads to ventilation-perfusion mismatch, atelectotrauma, hypoxia-hyperoxia swings, and worsening inflammation. Too much mean airway pressure can negatively impact the vulnerable preterm cerebrovascular autoregulation system, leading to decreased cerebral blood flow.(30) The differing roles of airway pressure may explain the small but significant positive effect size associated with language and cognitive performance and may provide an argument for continuous cerebral tissue oxygenation monitoring to titrate ventilation effect. Lastly, it is possible that CSO and CMAP are not themselves modifiable exposures that result in brain injury but instead are clinical biomarkers that reflect greater underlying illness severity and generalized immaturity.

Our investigation of the association of BPD and WMI with neurodevelopmental performance revealed an association of severe BPD with lower motor performance in the univariate, but not multivariate model, and of CSO with adverse language and cognitive performance at 30 months corrected age, independent of WMI and IVH on conventional MRI. These results are likely multifactorial. First, our results are consistent with other studies in which the sensitivity of MRI-detected WMI for motor and cognitive outcomes is relatively low.(31, 32) Our sample size is also small and only 5 babies had moderate-severe WMI (and no cases of cystic WMI) at follow-up, which limited our power to detect associations with neurodevelopmental outcome. However, the small number of WMI cases may have allowed the statistical models to better discriminate additional contributing variables, such as CSO, since the models were not overwhelmed by the magnitude of the effects of WMI. Other authors have also shown that the volume and topology of WMI as well as grey matter injury are important determinants of outcome; however, we did not evaluate these parameters as the focus of our study was on the influence of respiratory precursors to BPD.(33) Given that cognitive and behavioral deficits far outnumber functional motor deficits due to cerebral palsy in the preterm population (25–

50% vs. 5–10%), we may have been underpowered to detect associations of CSO with adverse motor outcome.(34) Finally, infants with abnormal MRIs may be more likely to receive early intervention services, mitigating the potential impact of WMI on observed neurodevelopmental performance.

Limitations to our study include a small sample size and relatively short follow-up period of 30 months corrected age. Although there was variability in the timing of imaging obtained, WMI was assessed on MRI images obtained via standardized imaging protocols and all were reviewed by the same pediatric neuroradiologist. We focused on MRI images obtained ≥ 4 weeks of age to standardize CSO exposure through 28 days of life. Although respiratory data were collected retrospectively, complete data were available in the electronic medical record and we used standardized time points for daily collection of respiratory parameters, which limited the bias of our data collection. It is important to note that while CSO reflects the amount of oxygen exposure delivered to the infant, it is unknown whether the increased CSO exposure was due to periods of hypoxia leading to increased FiO_2 or periods of hyperoxemia as oxygen saturation and arterial partial pressure of oxygen values were not collected. Additionally, caffeine, the drug of choice to treat apnea of prematurity, is known to reduce exposure to positive pressure ventilation and supplemental oxygen(35), but information on the dose and duration of treatment was not collected for this study. Our unit standard is routine, early administration of caffeine, limiting concern for differential rates of exposure by BPD severity. Given the observational study design however, residual confounding cannot be excluded. Because of the sample size, we were unable to conduct subgroup analyses by clinical characteristics, such as small for gestational age or postnatal steroid exposure. Lastly, follow-up data, which was collected by unblinded clinicians, was missing for 23.8% of our cohort. Infants missing follow-up had similar GA and similar rates of moderate-to-severe BPD. Though it did not reach statistical significance, there were higher rates of moderate-severe WMI in those lost to follow-up, suggesting that the potential impact of loss to follow-up is an underestimation of the effect size of CSO and CMAP in this cohort.

In summary, respiratory precursors to BPD perform as well as BPD for the prediction of WMI in preterm infants, and increased cumulative supplemental oxygen exposure over the first 14–28 days is associated with worse language and cognitive performance. These data suggest that respiratory status importantly influences risk of adverse neurodevelopmental outcomes, independent of WMI, with effects potentially as early as 14 days of age. Future studies are needed to better understand the influence of respiratory status on brain health, and whether interventions to improve respiratory status may improve neurodevelopment in the vulnerable preterm population.

Acknowledgments

Funding Sources: National Institutes of Health (NS035902 and EB009756 to AJB and DX) and the UCSF California Preterm Birth Initiative funded by Marc and Lynne Benioff (DG).

References

1. Stoll BJ, et al.Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA314, 1039–1051 (2015). [PubMed: 26348753]
2. Northway WH Jr., Rosan RC, Porter DYPulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med276, 357–368 (1967). [PubMed: 5334613]
3. Jobe AH, Bancalari EBronchopulmonary dysplasia. Am J Respire Crit Care Med163, 1723–1729 (2001).
4. Ehrenkranz RA, et al.Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics116, 1353–1360 (2005). [PubMed: 16322158]
5. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EMAbnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics82, 527–532 (1988). [PubMed: 3174313]
6. Keller RL, et al.Bronchopulmonary dysplasia and perinatal characteristics predict 1-year respiratory outcomes in newborns born at extremely low gestational age: a prospective cohort study. J Pediatr187, 89–97 e83 (2017). [PubMed: 28528221]
7. Majnemer A, et al.Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Dev Med Child Neurol42, 53–60 (2000). [PubMed: 10665976]
8. Short EJ, et al.Developmental sequelae in preterm infants having a diagnosis of bronchopulmonary dysplasia: analysis using a severity-based classification system. Arch Pediatr Adolesc Med161, 1082–1087 (2007). [PubMed: 17984411]
9. Vohr BR, et al.Neurodevelopmental and medical status of low-birthweight survivors of bronchopulmonary dysplasia at 10 to 12 years of age. Dev Med Child Neurol33, 690–697 (1991). [PubMed: 1717327]
10. Skidmore MD, Rivers A, Hack MIncreased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Dev Med Child Neurol32, 325–332 (1990). [PubMed: 2332123]
11. Walsh MC, et al.Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. J Pediatr146, 798–804 (2005). [PubMed: 15973322]
12. Trittmann JK, Nelin LD, Klebanoff MABronchopulmonary dysplasia and neurodevelopmental outcome in extremely preterm neonates. Eur J Pediatr172, 1173–1180 (2013). [PubMed: 23644648]
13. Wai KC, et al.Early cumulative supplemental oxygen predicts bronchopulmonary dysplasia in high risk extremely low gestational age newborns. J Pediatr177, 97–102 e102 (2016). [PubMed: 27470692]
14. The STOP-ROP Multicenter Study Group Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics105, 295–310 (2000). [PubMed: 10654946]
15. Ballard PL, et al.Inhaled nitric oxide increases urinary nitric oxide metabolites and cyclic guanosine monophosphate in premature infants: relationship to pulmonary outcome. Am J Perinatol32, 225–232 (2015). [PubMed: 24968129]
16. Miller SP, et al.Comparing the diagnosis of white matter injury in premature newborns with serial MR imaging and transfontanel ultrasonography findings. AJNR Am J Neuroradiol24, 1661–1669 (2003). [PubMed: 13679289]
17. Papile LA, Burstein J, Burstein R, Koffler H, Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr92, 529–534 (1978). [PubMed: 305471]
18. Gano D, et al.Antenatal exposure to magnesium sulfate is associated with reduced cerebellar hemorrhage in preterm newborns. J Pediatr178, 68–74 (2016). [PubMed: 27453378]
19. Bell MJ, et al.Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg187, 1–7 (1978). [PubMed: 413500]
20. Bayley NBayley Scales of Infant and Toddler Development: Screening Test. (Psychological Corporation, San Antonio, TX, 2006).

21. Alvarez-Fuente M, et al.Preventing bronchopulmonary dysplasia: new tools for an old challenge. Pediatr Res85, 432–441 (2019). [PubMed: 30464331]
22. Albertine KHBrain injury in chronically ventilated preterm neonates: collateral damage related to ventilation strategy. Clin Perinatol39, 727–740 (2012). [PubMed: 22954278]
23. Ball G, et al.An Optimised tract-based spatial statistics protocal for neonates: applications to prematurity and chronic lung disease. Neuroimage53, 94–102 (2010). [PubMed: 20510375]
24. Boardman JP, et al.Early growth in brain volume is preserved in the majority of preterm infants. Ann Neurol62, 185–192 (2007). [PubMed: 17696128]
25. Felderhoff-Mueser U, et al.oxygen causes cell death in the developing brain. Neurobiol Dis17, 273–282 (2004). [PubMed: 15474364]
26. Reich B, Hoeber D, Bendix I, Felderhoff-Mueser UHyperoxia and the immature brain. Dev Neurosci38, 311–330 (2016). [PubMed: 28152539]
27. Brew N, walker D, Wong FYCerebral vascular regulation and brain injury in preterm infants. Am J Physiol Regul Integr Comp Physiol306, R773–786 (2014). [PubMed: 24647591]
28. Schmolzer GM, et al.Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ347, f5980 (2013). [PubMed: 24136633]
29. Albertine KHProgress in understanding the pathogenesis of BPD using the baboon and sheep models. Semin Perinatol37, 60–68 (2013). [PubMed: 23582959]
30. Mirro R, Karanth S, Armstead WM, Shibata M, Leffler CWAlterations in cerebrovascular reactivity after positive pressure ventilation. Pediatr Res32, 114–117 (1992). [PubMed: 1635836]
31. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TENeonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med355, 685–694 (2006). [PubMed: 16914704]
32. Vanť Hooft J, et al.Predicting developmental outcomes in premature infants by term equivalent MRI: systematic review and meta-analysis. Syst Rev4, 71 (2015). [PubMed: 25982565]
33. Guo T, et al.Quantitative assessment of white matter injury in preterm neonates: association with outcomes. Neurology88, 614–622 (2017). [PubMed: 28100727]
34. Volpe JJBrain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol8, 110–124 (2009). [PubMed: 19081519]
35. Schmidt B, et al.Caffeine therapy for apnea of prematurity. N Engl J Med354, 2112–2121 (2006). [PubMed: 16707748]

Impact

- Respiratory precursors to bronchopulmonary dysplasia (BPD), cumulative supplemental oxygen and mean airway pressure, over the first 14–28 days performed as well as BPD for the prediction of white matter injury on MRI in preterm infants.
- Cumulative supplemental oxygen was independently associated with lower language and cognitive performance on the Bayley-III at 30-months adjusted.
- These data suggest that early respiratory status may help explain why BPD is independently associated with adverse neurodevelopmental outcomes in the preterm population and highlights the importance of interventions targeting respiratory status as a potential avenue to improve neurodevelopmental outcomes.

Table 1:

Neonatal Cohort Demographics and Clinical Characteristics by BPD Status

Neonatal Characteristics	No-Mild BPD (n=57) n (%)	Moderate-to-Severe BPD (n=30) n (%)	p-value
Gestational Age (wks ±SD)	28.9 ±2.0	26.7 ±2.0	<0.001
Birth Weight (g ±SD)	1220 ±347	781 ±257	<0.001
Male	31 (54.4)	11 (36.7)	0.116
Prenatal Steroids	47 (82.5)	21 (70.0)	0.181
Maternal Chorioamnionitis	7 (12.3)	2 (6.7)	0.713
Surfactant	20 (35.1)	26 (86.7)	<0.001
Neonatal Surgery	2 (3.5)	11 (36.7)	<0.001
NEC	1 (1.8)	4 (13.3)	0.046
PDA	23 (40.4)	24 (80.0)	<0.001
Infection	22 (38.6)	21 (70.0)	0.005
WMI	3 (5.3)	7 (23.3)	0.028
IVH Grade 3 or 4	1 (1.8)	5 (16.7)	0.017
CbH	17 (29.8)	12 (40.0)	0.339

BPD: bronchopulmonary dysplasia; SD: standard deviation; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; WMI: white matter injury; IVH: intraventricular hemorrhage; CbH: cerebellar hemorrhage

Table 2:

CSO and CMAP from Days 1–14 and Days 1–28 by BPD and WMI Status

	No-Mild BPD (n=57)	Moderate-to-Severe BPD (n=30)	p-value	Absent-Mild WMI (n=67)	Moderate-Severe WMI (n=8)	p-value
CSO 1–14	0.03 (0, 0.3)	0.8 (0.4, 1.5)	<0.001	0.20 (0, 0.9)	0.7 (0.3, 0.9)	0.11
CMAP 1–14	31.3 (10.0, 59.7)	125.7 (78.5, 143.7)	<0.001	60.8 (19.3, 115.0)	126.4 (64.6, 141.8)	0.04
CSO 1–28	0.06 (0, 0.5)	2.0 (0.7, 3.5)	<0.001	0.4 (0.02, 1.8)	2.0 (0.4, 2.6)	0.10
CMAP 1–28	36.3 (10.0, 90.7)	251.7 (153.5, 270.8)	<0.001	90.7 (25.7, 235.3)	253.3 (75.3, 262.8)	0.07

Data displayed as median (IQR)

BPD: bronchopulmonary dysplasia; WMI: white matter injury; IQR: interquartile range; CSO: cumulative supplemental oxygen; CMAP: cumulative mean airway pressure

Table 3:

AUC of BPD, CSO, and CMAP for the Prediction of WMI

	AUC	95% CI
BPD	0.77	0.64–0.91
CSO 1–14	0.68	0.52–0.83
CMAP 1–14	0.73	0.57–0.88
Multivariate Model 1–14[a]	0.83	0.70–0.95
CSO 1–28	0.68	0.51–0.85
CMAP 1–28	0.70	0.54–0.86
Multivariate Model 1–28[b]	0.77	0.59–0.95

AUC: area under the curve; WMI: white matter injury; BPD: bronchopulmonary dysplasia; CSO: cumulative supplemental oxygen; CMAP: cumulative mean airway pressure

[a]Multivariate Model: BPD, CSO_{1to14}, and $CMAP_{1to14}$

[b]Multivariate Model: BPD, CSO_{1to28}, and $CMAP_{1to28}$

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Table 4:

Univariate and Multivariate Analysis of Predictors with Neurodevelopmental Performance

	Motor			Language			Cognitive		
	Mean Difference	**95% CI**	**p-value**	**Mean Difference**	**95% CI**	**p-value**	**Mean Difference**	**95% CI**	**p-value**
Univariate									
BPD Severity									
None	Ref			Ref			Ref		
Mild	−2.9	−12.8 to 7.0	0.56	3.5	−7.4 to 14.5	0.52	7.1	−3.7 to 17.9	0.19
Moderate	−2.8	−11.8 to 6.3	0.54	8.5	−1.5 to 18.5	0.094	9.2	−0.7 to 19.0	0.068
Severe	−15.6	−29.9 to −1.2	0.034	−5.9	−21.8 to 10.0	0.46	−4.7	−20.4 to 10.9	0.55
CSO 1–14	−4.2	−8.6 to 0.2	0.060	−0.4	−5.4 to 4.5	0.87	−0.5	−5.4 to 4.5	0.86
CMAP 1–14[a]	−0.3	−1.0 to 0.4	0.40	0.9	0.1 to 1.6	0.027	0.8	0.01 to 1.6	0.047
CSO 1–28	−2.5	−4.6 to −0.4	0.023	−0.4	−2.8 to 2.0	0.74	−0.5	−2.9 to 1.9	0.71
CMAP 1–28[a]	−0.2	−0.6 to 0.1	0.20	0.3	−0.07 to 0.7	0.11	0.3	−0.1 to 0.7	0.14
WMI	−2.0	−16.1 to 12.1	0.78	6.0	−9.4 to 21.5	0.44	7.3	−8.0 to 22.7	0.34
Multivariate[b]									
BPD Severity									
None	Ref			Ref			Ref		
Mild	−4.7	−18.7 to 9.3	0.50	−11.2	−25.4 to 3.0	0.12	−2.5	−17.3 to 12.2	0.73
Moderate	−7.5	−22.0 to 7.0	0.31	−12.0	−26.8 to 2.7	0.11	−6.0	−21.3 to 9.2	0.43
Severe	−15.1	−37.1 to 7.0	0.18	−23.1	−45.4 to −0.7	0.043	−15.3	−38.5 to 7.9	0.19
CSO 1–14	−5.0	−13.6 to 3.7	0.26	−11.0	−19.8 to −2.2	0.015	−9.8	−18.9 to −0.7	0.035
CMAP 1–14[a]	1.6	−0.09 to 3.2	0.064	3.2	1.5 to 4.8	<0.001	2.4	0.7 to 4.1	0.008
WMI	−0.4	−15.6 to 14.8	0.96	6.7	−8.7 to 22.2	0.39	8.5	−7.5 to 24.6	0.29
Multivariate[c]									
BPD Severity									
None	Ref			Ref			Ref		

	Motor			Language			Cognitive		
	Mean Difference	**95% CI**	**p-value**	**Mean Difference**	**95% CI**	**p-value**	**Mean Difference**	**95% CI**	**p-value**
Mild	−4.1	−17.9 to 9.7	0.56	−9.4	−23.7 to 4.8	0.19	−1.7	−16.2 to 12.8	0.81
Moderate	−7.6	−22.5 to 7.3	0.31	−10.9	−26.3 to 4.5	0.16	−5.5	−21.2 to 10.1	0.48
Severe	−13.2	−36.3 to 9.9	0.26	−20.2	−44.2 to 3.7	0.095	−12.7	−37.0 to 11.7	0.30
CSO 1–28	−4.0	−8.9 to 0.9	0.11	−7.2	−12.3 to −2.1	0.006	−6.7	−11.8 to −1.5	0.012
CMAP 1–28[a]	0.9	−0.08 to 1.9	0.071	1.7	0.7 to 2.8	0.001	1.4	0.3 to 2.4	0.011
WMI	3.3	−12.1 to 18.7	0.67	12.9	−3.1 to 28.8	0.11	13.6	−2.6 to 29.8	0.099

BPD: bronchopulmonary dysplasia; CSO: cumulative supplemental oxygen; CMAP cumulative mean airway pressure; WMI: white matter injury

[a] CMAP 1–14 and CMAP 1–28 divided by 10

[b] Multivariate Model: BPD severity, CSO_{1to14}, $CMAP_{1to14}$, WMI, IVH, and GA

[c] Multivariate Model: BPD severity, CSO_{1to28}, $CMAP_{1to28}$, WMI, IVH, and GA