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Bronchopulmonary Dysplasia and Perinatal Characteristics Predict One-Year Respiratory Outcomes in Extremely Low Gestational Age Newborns: A Prospective Cohort Study

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Abstract

Objective—To assess the utility of clinical predictors of persistent respiratory morbidity in extremely low gestational age newborns (ELGAN).

Study Design—We enrolled ELGAN (<29 weeks' gestation) at 7 postnatal days and collected antenatal and neonatal clinical data through 36 weeks' post-menstrual age. We surveyed caregivers at 3, 6, 9 and 12 months corrected age to identify post-discharge respiratory morbidity, defined as hospitalization, home support (oxygen, tracheotomy, ventilation), medications, or symptoms (cough/wheeze). Infants were classified as post-prematurity respiratory disease (PRD, the primary study outcome), if respiratory morbidity persisted over 2 questionnaires. Infants were classified with severe respiratory morbidity if there were multiple hospitalizations, exposure to systemic

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steroids or pulmonary vasodilators, home oxygen after 3 months or mechanical ventilation, or symptoms despite inhaled corticosteroids. Mixed effects models generated with data available at one day (perinatal) and 36 weeks' postmenstrual age were assessed for predictive accuracy.

Results—Of 724 infants (918±234g, 26.7±1.4 weeks' gestational age) classified for the primary outcome, 68.6% had PRD; 245/704 (34.8%) were classified as severe. Male sex, intrauterine growth restriction, maternal smoking, race/ethnicity, intubation at birth, and public insurance were retained in perinatal and 36-week models for both PRD and respiratory morbidity severity. The perinatal model accurately predicted PRD (c-statistic 0.858). Neither the 36-week model nor the addition of bronchopulmonary dysplasia (BPD) to the perinatal model improved accuracy (0.856, 0.860); c-statistic for BPD-alone was 0.907.

Conclusion—Both BPD and perinatal clinical data accurately identify ELGAN at risk for persistent and severe respiratory morbidity at one year.

Trial registration ClinicalTrials.gov: NCT01435187

Premature birth has a profound impact on postnatal pulmonary development. Fetal lung development is disrupted by early delivery, leading to lifelong morbidity and diminished pulmonary function (1). In particular, extremely low gestational age newborns (ELGAN) have substantial rates of persistent respiratory morbidity following hospital discharge. Bronchopulmonary dysplasia (BPD), defined at 36 weeks' post-menstrual age (PMA), has been used as both predictor and surrogate for this later morbidity (2–4). Various studies have identified male sex, degree of immaturity, and greater levels of respiratory support as important early predictors of BPD or death in ELGAN (5–7). Similarly, male sex, decreased intrauterine growth, singleton birth, exposure to young children, sociodemographic factors and a diagnosis of BPD have been associated with increased respiratory morbidity in early childhood (8, 9).

The primary aim of the Prematurity and Respiratory Outcomes Program (PROP) is to identify early predictors of later respiratory morbidity, allowing for prediction of ELGAN at risk for persistent respiratory morbidity, defined at one year corrected age. Epidemiological studies from term-born populations demonstrate that lower respiratory tract infection in early childhood increases the risk of later wheezing illness and impaired lung function (10–13). However, these types of studies are not available in more heterogeneous preterm populations. As preterm infants manifest respiratory illness both with and apart from infection, the PROP Steering Committee considered broader descriptors of infant respiratory morbidity, drawing from previously published markers of persistent respiratory morbidity in preterm infants (8, 14). Thus, the PROP Steering Committee chose primary and secondary outcomes that were felt to represent persistence (infants that were affected at least half of the first year, with unaffected infants likely to have limited manifestations of respiratory disease) and severity (graded intensity of care) of respiratory morbidity.

We hypothesized that perinatal (identified in the first day of life) and 36-week (describing infant status through 36 weeks' PMA) clinical factors would accurately predict the persistence and severity of respiratory morbidity in ELGAN. We used step-wise selection to develop perinatal and 36-week multivariate models from these clinical factors, assessed the accuracy of the models for the prediction of respiratory morbidity, and compared the models with the accuracy of BPD alone.

METHODS

The detailed design of the PROP Study (ClinicalTrials.gov: NCT01435187), including data collection forms and a CONSORT diagram, has been described (15, 16). Briefly, ELGAN 23 0/7–28 6/7 weeks' gestational age were enrolled by 7 postnatal days at 6 academic centers (13 hospitals) in the United States if they were without cardiopulmonary anomalies and deemed viable and available for follow up. Written parental consent was obtained following each institutional review board approval, with central oversight by an NIH-appointed Observational Safety Monitoring Board. Demographics, perinatal clinical information and daily respiratory, nutrition and growth data were collected to discharge or 40 weeks' PMA (term). Intrauterine growth was normalized to gestational age using contemporary, multi-national fetal reference curves (17). At discharge, caregivers were interviewed regarding potential exposures that might affect respiratory status, including anticipated daycare arrangements, young children and pets in the home, and smoking rules.

BPD status was determined at 36 0/7 weeks' PMA or earlier discharge from a modification of the proposed NIH workshop definition (3, 16). Infants receiving positive pressure respiratory support or prescribed FiO_2 0.30 were classified as severe, those receiving nasal cannula support and prescribed FiO_2 0.22–0.29 were classified as moderate, and those without respiratory support or nasal cannula flow with no supplemental oxygen were classified as no/mild.

Questionnaires were administered by research staff to parents/caregivers at 3, 6, 9 and 12 months corrected (for prematurity) age. All follow up was completed by August 2015. From initial hospital discharge (for first questionnaire) or prior interview (for subsequent questionnaires), we documented hospitalization for respiratory indication, home respiratory support (including tracheostomy and mechanical ventilation), respiratory medication administration (Table I; available at www.jpeds.com) and respiratory symptoms (cough without cold or wheeze at least once per week). Decisions regarding prescription of home respiratory support and medications were made by local clinicians.

The predetermined primary outcome for the PROP Study was termed post-prematurity respiratory disease (PRD) (15). An infant was classified with PRD if there were positive responses indicating respiratory morbidity on at least 2 caregiver questionnaires. Respiratory morbidity was defined as above: hospitalization for respiratory indication, home respiratory support, respiratory medication administration, and respiratory symptoms. PRD was chosen as a clinically relevant description of persistent respiratory morbidity. Similarly, the predetermined secondary outcome was a severity scale for respiratory morbidity for which specific markers of morbidity were placed, by consensus of the PROP Steering Committee,

into categories of respiratory morbidity severity (RMS) accounting for both the level of illness indicated by a particular marker and potential adverse effects associated with that marker. Infants were classified into one of three mutually exclusive, ordered categories of RMS as 1) severe, if there were 2 respiratory hospitalizations, home supplemental oxygen after 3 months or any home mechanical ventilation, systemic steroid exposure or pulmonary vasodilators at any time, or symptoms despite concurrent inhaled corticosteroids in 2 questionnaires, 2) moderate/mild, if one hospitalization, home oxygen <3 months corrected age or tracheostomy without ventilation, any inhaled corticosteroid exposure, or bronchodilator or symptoms in 2 questionnaires, and 3) minimal/none for all other cases. Infants who died secondary to a cardiopulmonary cause were classified with PRD and severe RMS.

Statistical analyses

The PROP Request for Applications specified a sample size of 750 infants available for follow up at 36 weeks' PMA. All analyses used SAS 9.4 (SAS Institute Inc., Cary NC). In univariate analyses, the relationship of clinical variables to PRD and RMS was evaluated in generalized linear mixed effects models to account for correlation between siblings, using the cumulative logit link and proportional odds model for RMS. The proportional odds assumption wasn't violated. Trends from ordered predictors were evaluated by treating these variables as continuous covariates. Multivariate predictive perinatal (considering only perinatal variables) and 36-week (considering perinatal variables and variables from the neonatal hospitalization describing infant status through 36 weeks) models were developed independently. Variables with P<0.05 in univariate analyses (Tables II and VI) were considered for inclusion in multivariate models. Gestational age was retained in all models. Other variables were retained if determined to have important contribution (P 0.2) by backward selection using residual maximum likelihood methods. Final models underwent sensitivity analyses to evaluate robustness of the results.

For PRD models, the receiver-operating-characteristic (ROC) curve and c-statistic (area under ROC curve) were generated from the best linear unbiased predictions, restricting the sample to infants with complete data to compare model accuracy across candidate models. We did not impute missing values. A priori, we omitted study center from our analyses, to increase generalizability; post-hoc addition of study center to PRD models increased c-statistics by only 0.008–0.013. Due to the three-level outcome for RMS models, we evaluated accuracy by generating predicted outcome probabilities from these models and comparing those with observed RMS classification.

RESULTS

Of 765 infants enrolled from August 2011-October 2013 who remained in the study at 36 weeks' PMA, 18 subsequently expired; 13 secondary to cardiopulmonary disease. We were able to determine the presence or absence of PRD in 724 infants (94.6%) and the severity of morbidity (RMS) in 704 infants (92.0%) (Figure 1; available at www.jpeds.com). Infants with follow up had similar characteristics to those alive at 36 weeks' PMA (Table II) (16). Infants that died prior to 36 weeks' PMA tended to be smaller and less mature at birth (birth

weight 709±200 grams, 25.2±1.5 weeks' gestation), although those with follow up were extremely preterm with early lung disease: 86% were exposed to antenatal steroids, 83.3% (603/724) received surfactant therapy for neonatal respiratory distress syndrome, 89.9% (651/724) were intubated during the hospitalization, and 51 % (369/724) were intubated for at least 7 days.

Questionnaires were completed at 3.2±0.6 (n=695), 6.4±1.3 (n=700), 9.2±0.7 (n=683), and 12.3±1.4 (n=688) months corrected age. Of the 497 (68.6%) infants who were classified as having PRD, 13 (2.6%) died due to a cardiopulmonary cause, with remaining infants reporting four, three or two positive questionnaires in equal proportions: 32.0% (n=159), 32.6% (n=162), and 32.8% (n=163) of infants, respectively. For those infants with PRD based on two positive questionnaires, 53 (10.7% of those with PRD) had morbidity only reported in the first half of the year, on the 3 and 6 month questionnaires. The proportion of infants classified with PRD varied across centers (range 46.9% to 78.8%). Four centers had rates of PRD higher than the overall proportion of infants with PRD and 2 centers had rates lower than the overall proportion.

RMS was classified as severe in 245 (34.8%), moderate/mild in 264 (37.5%), and minimal/none in 195 (27.7%) infants (see Table III, available at www.jpeds.com for comparison of distributions of PRD and RMS). By design, some infants with severe RMS met more than one criterion. Overall, similar proportions of infants with severe RMS had persistent supplemental oxygen use (110/245, 44.9%) and systemic steroid exposure (106/245, 43.3%). Eighteen infants with follow up had undergone tracheostomy and 17 (6.9% of severe) had home ventilation, although all infants with tracheostomy met criteria for severe RMS. Sixty-four (26.2%) infants had at least two hospitalizations for respiratory indications, and only 8 infants (3.3%) reported pulmonary vasodilator exposure. The proportion of infants with severe RMS varied across centers (range 22.9% to 50.9%), with higher rates than the overall proportion of severe RMS in half of the 6 centers and lower rates in the other half of the centers.

For all univariate analyses, the relationship of potential predictors to PRD and RMS was in the same direction with similar P-values, so only PRD results are shown (Table II). Univariate analyses of potential perinatal predictors related to degree of prematurity, initial severity of illness and other clinical descriptors, and infant race/ethnicity, socioeconomic indicators and family history, revealed many significant associations with PRD. Both PRD and RMS had an inverse association with gestational age; advancing gestational age was associated with decreased morbidity (Table IV; available at www.jpeds.com). Multiple variables describing the neonatal respiratory course were significantly associated with PRD (Table V; available at www.jpeds.com), although these were not used in model development as we expected to capture these variables in other summary variables from later in the hospitalization, at 36 weeks' PMA or discharge (Table VI). BPD and additional clinical descriptors were associated with PRD, but growth velocity in the 4 weeks prior to 36 weeks was similar between infants with and without PRD.

Multivariate models for PRD (n=697) and RMS (n=679), restricted to infants with complete data to directly compare c-statistics for perinatal and 36-week models with different subsets

of predictors, are shown (Table VII). For PRD, all perinatal predictors except parental history of asthma were retained in the independently-developed 36-week model. Gestational age and birth weight were not significant in most models, with birth weight generally excluded when gestational age was retained. Male sex and intrauterine growth restriction were important risk factors for morbidity in all models, with increased odds of morbidity for male infants ranging from 1.7–3.1, depending on the model. Similarly, public insurance status was associated with increased odds of morbidity and retained in all models, but smoking in pregnancy was retained only in PRD models and parental asthma was more important in RMS models. Infant race/ethnicity remained in all models, with increased odds of morbidity for infants of Black race (compared with the reference group of White, non-Hispanic infants), and BPD was an important predictor of morbidity in both 36-week models. Low breast milk exposure (<28 days) had similar effects in both PRD and RMS models, but growth failure at 36 weeks' PMA (<10th percentile) had greater influence in predicting severity of morbidity.

Sensitivity analyses suggested our models were relatively robust (Table VIII; available at www.jpeds.com). As the reporting of respiratory symptoms in infancy has not been broadly validated, we derived a secondary PRD outcome that excluded symptoms, decreasing the outcome prevalence to 46%. Using a threshold of 20% change in the odds ratio, we found diminished influence of race/ethnicity, with increased influence of male sex and intubation at birth in both perinatal and 36-week models. For the second sensitivity analysis, because smoking in pregnancy might capture different effects than exposure to environmental tobacco smoke, we substituted responses from discharge questions regarding potential environmental tobacco smoke exposure (focused narrowly on rules regarding smoking in the home and vehicle) and questions at 6 months (which added report of smokers in the home and parental smoking) for intrauterine exposure, but found no substantive changes in odds ratios. Finally, for the RMS models, we evaluated the alternative dichotomous outcome of severe versus not severe, changing the outcome from three to two levels, requiring us to rely on changes in P-values for individual predictors to evaluate effects of these analyses. In both perinatal and 36-week models, intrauterine growth restriction lost statistical significance, as did insurance status and infant race/ethnicity in the 36-week model. Intubation at birth became significant in the perinatal model and gestational age became significant in the 36-week model. The direction of effect was unchanged through multiple sensitivity analyses.

C-statistics for PRD models showed little variation in model predictive accuracy (Figure 2, A). For perinatal and 36-week models, the c-statistics were 0.858 and 0.856, respectively, with minimal change after the addition of BPD to the perinatal model. An analogous model with BPD- alone had a c-statistic of 0.907. To assess accuracy of RMS models, predicted probabilities generated from perinatal and 36-week models were plotted against each observed level of RMS (Figure 2, B-E). This demonstrated minimal overlap between classes for the model-based predictions, consistent with high accuracy.

DISCUSSION

In this large prospective multicenter cohort of ELGAN <29 weeks' gestational age surviving to 36 weeks' PMA, we found that perinatal factors (identified in the first day of life)

accurately predicted both persistence and severity of respiratory morbidity to one year corrected age, similar to the strong prediction demonstrated by BPD alone. As BPD is not substantively better than prediction based on the perinatal models, we suggest that genetic factors and prenatal exposures (which can be assessed shortly after birth), greatly influence the clinical trajectories of children born prematurely and thus can be used for early identification of infants at high risk of late respiratory morbidity.

Prospective cohort studies in term-born children have shown that decrements in lung function in the first month of life are associated with later symptomatic lung disease (18, 19). Factors implicated in early reduced lung function in both term and preterm infants include decreased fetal growth, maternal diet, intrauterine tobacco exposure and male sex, with some modifiable effects (20–24). Further, worse neonatal outcomes (including BPD) are associated with preterm placental characteristics and assays of perinatal biological samples (25–29). These findings suggest that the intrauterine environment is a strong determinant of postnatal outcomes in ELGAN, consistent with the predictive accuracy demonstrated with our perinatal models, and prior data showing that ELGAN at greatest risk for developing adverse neurodevelopmental outcomes can be identified very early in life (30, 31). However, as much of the human and experimental data implicate impaired lung and vascular development, supplemental oxygen, and inflammation in the pathobiology of early adverse pulmonary outcomes (23), these areas should be the focus of tailored interventions to mitigate the persistence of early impaired lung function in infants identified as being at highest risk for later adverse outcomes.

The contemporary use of BPD as a predictor of later respiratory outcome is based on retrospective work by Shennan et al, which demonstrated that supplemental oxygen at 36 weeks PMA improved prediction of later respiratory outcome, compared with 28 days (2). However, the definition of abnormal respiratory outcome in the Shennan study was broad, including oxygen requirement at 40 weeks, and use of medications, hospitalizations, abnormal radiographic findings, and adverse neurodevelopmental outcomes at one year. In a systematic review, various definitions of BPD were associated with poorer lung function at follow up (1). The later definition of severity of BPD that incorporates level of support at 36 weeks (similar to our definition), was subsequently validated retrospectively by correlation with report of respiratory hospitalizations and medication use (3, 4). Yet many children with severe BPD had no reported respiratory morbidity and at least 25% of infants without BPD had morbidity. Similarly, in the current study, although moderate and severe BPD were associated with PRD, 21% of these infants had no PRD, and 40% of those who were classified as no/mild BPD had PRD. Risk of BPD is related to severity of neonatal lung disease, yet there are multiple other factors involved (5, 6, 32, 33). These "mismatches" between BPD and later outcomes may be due to a variety of factors related to the heterogeneity of lung disease in ELGAN, the socioeconomic factors that influence symptomatic respiratory disease in infancy, and the inherent limitations in using supplemental oxygen alone as a marker for lung disease (8, 16). For instance, the use of high-flow nasal cannula (without supplemental oxygen) as an alternative to positive airway pressure, and the application of supplemental oxygen to mitigate the effects of dysmature respiratory control, may result in misclassification of BPD (16, 34). Interestingly, although the addition of BPD and other 36-week variables did not substantially alter the specific

perinatal variables selected for 36-week models, the effects of gestational age, male sex, intrauterine growth restriction and parental history of asthma decreased in the 36-week PRD model, but the effect of Black race increased. These changes suggest that the biological vulnerability of some ELGAN is captured by the 36-week variables, whereas the effects of race/ethnicity are independent of these factors.

We chose to retain gestational age in our models as it is an important predictor for many preterm outcomes, including BPD (4, 5, 7, 32, 33). However, it was not an important independent predictor in multivariate models of these later pulmonary outcomes. We might expect this with 36-week models, as the predictors retained could capture the severity of the neonatal course; yet, this is the case even in perinatal models. Similar to our findings, Laughon et al described a significant relationship of gestational age to severity of initial respiratory illness in infants enrolled in the ELGAN Study (<28 weeks' gestational age) (32), but the relationship of gestational age to BPD was only significant among the sickest of these infants (33). Thus, in both of these cohorts of ELGAN surviving to 36 weeks' PMA (with high rates of antenatal steroid exposure), the relationship of gestational age to later pulmonary outcomes is likely related to underlying lung immaturity as well as the severity of initial lung disease.

The specific outcomes explored in the PROP Study have not been previously used as infant respiratory outcomes. Although they both represent a spectrum of infant respiratory disease, PRD is consistent with persistence of morbidity and RMS identifies infants receiving more intensive therapy. In general, research on pulmonary outcomes at 1–2 years in former preterm infants has focused on separate aspects of respiratory morbidity or lung function (4, 8, 14, 35–38). More recently, Gage et al proposed a respiratory morbidity scoring system for former preterm infants at 4–9 months corrected age (39). From this, they determined low, moderate and severe categories of morbidity, which, when compared with no morbidity were consistently associated with neonatal systemic steroid use, with less consistent relationships with gestational age, male sex, race/ethnicity, initial resuscitation and severity of respiratory illness. Stevens et al identified consistent univariate relationships of multiple outcomes, including respiratory symptoms, hospitalizations and medications, with a diagnosis of BPD (37). Similarly, Greenough et al found BPD and male sex were associated with increased risk of pulmonary morbidity (symptoms and medications), and multiple birth with decreased risk, in multivariate analyses (8). In a subset of this cohort, frequent wheeze was associated with lower indices of lung function at one year corrected age (40).

The strength of this study is demonstrated by the consistency of the variables retained across four independently-generated models, with only modest alterations following the sensitivity analyses; both persistence and severity of respiratory morbidity are influenced by similar factors in the perinatal period and at 36 weeks' PMA. Multiple academic centers enrolled infants in this study, with a diversity of racial and ethnic backgrounds and socioeconomic status, enhancing generalizability, which might otherwise be limited by the nature of this study and its requirement for informed consent. However, these findings may be less applicable to the ELGAN population outside of academic centers as clinical practices reflected in the variables under consideration, including delivery room management, early nutritional strategies and oxygen saturation targets, are important in interpretation of the

final models. In addition, components of these outcomes that depend on prescribing practices likely vary across centers, as previously shown for home oxygen use (41). Regardless, the addition of study center added little to the predictive ability of the final models, possibly due to the selection of some patient characteristics that vary by center. Finally, due to our cohort size, we used the entire cohort for model derivation, without an independent validation cohort. Thus, these findings need to be externally validated prior to application of a prediction model in clinical practice. Although the contemporary definition of BPD as determined at 36 weeks PMA was developed to predict later respiratory outcomes, our perinatal model (once externally validated) provides a framework for identifying those infants in the first day of life who will go on to develop important subsequent respiratory morbidity.

In conclusion, we have utilized unique composite outcomes of persistent and severe respiratory morbidity to build accurate perinatal and 36-week models in ELGAN. Although the diagnosis of BPD strongly predicts respiratory outcomes in this cohort, the utility of information obtained in the first day of life implicates fetal environmental and genetic factors as critical influences on later respiratory outcomes, providing opportunity to identify and study targeted interventions in high-risk infants soon after birth, if these factors can be confirmed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

BPD	bronchopulmonary dysplasia
ELGAN	extremely low gestational age newborn
PMA	post-menstrual age
PROP	Prematurity and Respiratory Outcomes Program
PRD	post-prematurity respiratory disease
RMS	respiratory morbidity severity

Appendix

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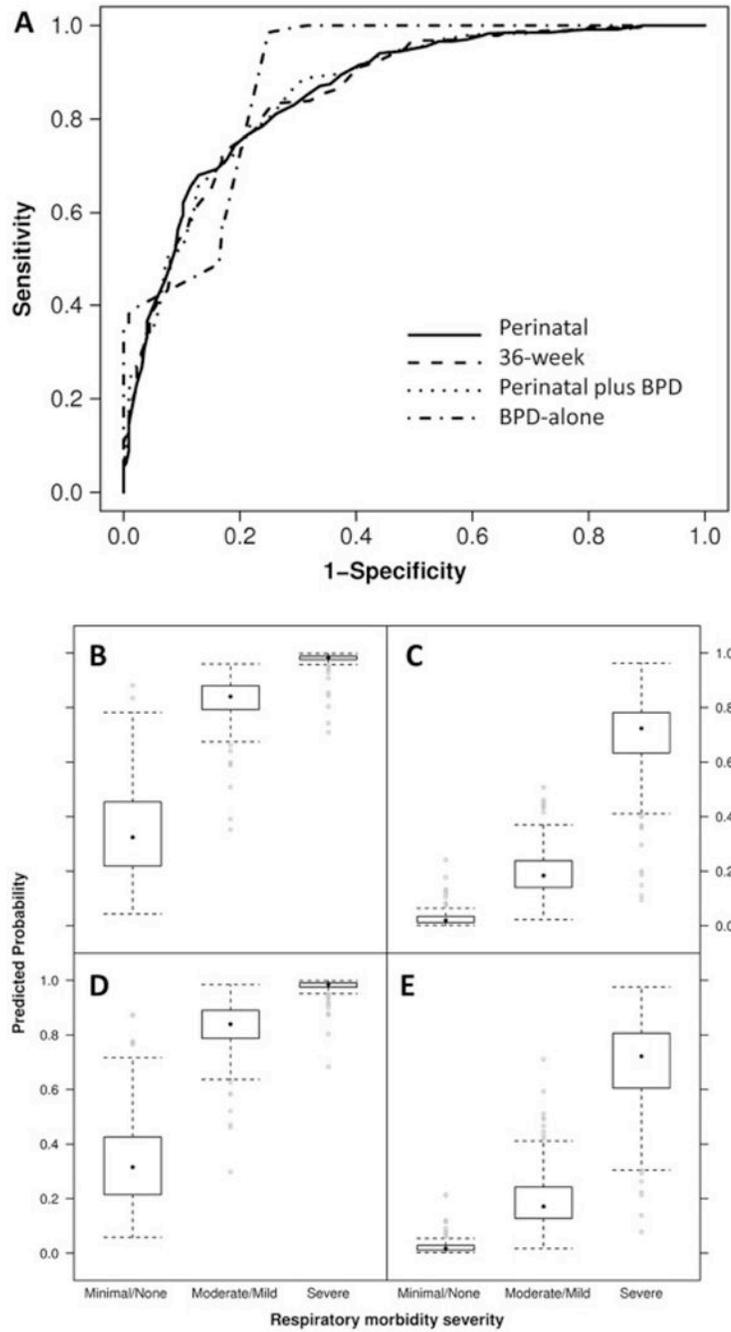
Figure 2.
Accuracy of perinatal (including only factors identified in the first day of life) and 36-week (including perinatal variables and variables describing infant status through 36 weeks' post-menstrual age or discharge) multivariate models for post-prematurity respiratory disease (PRD) and respiratory morbidity severity (RMS). **A**. Receiver operator characteristic curves, generated by plotting sensitivity versus 1-specificity, for prediction of PRD. Area under the curve, for various PRD models: perinatal (0.858), 36-week (0.856), perinatal with the addition of BPD (0.860), and BPD-alone (0.907). BPD was classified as No/Mild, Moderate,

or Severe. **B-E**. Predicted probability of outcome for respiratory morbidity severity (RMS) from multivariate models versus observed level of RMS classification. **B**. Probability of mild-to-severe (versus minimal/none) RMS classification for perinatal model. **C**. Probability of severe (versus not severe) RMS classification for perinatal model. **D**. Probability of mild-to-severe (versus minimal/none) RMS classification for 36-week model. **E**. Probability of severe (versus not severe) RMS classification for 36-week model.

Table 2

Perinatal characteristics (identified in the first day of life) and univariate associations with post-prematurity respiratory disease

		Whole cohort (n=724)	Post-prematurity respiratory disease (n=497)	No Post-prematurity respiratory disease (n=227)	P value*
Gestational age (weeks)		26.7 ± 1.4	26.6 ± 1.4	26.9 ± 1.3	0.009
Gestational age group (weeks)					0.005**
	23–24	102 (14.1)	81 (16.3)	21 (9.3)	
	25	106 (14.6)	79 (15.9)	27 (11.9)	
	26	154 (21.3)	105 (21.1)	49 (21.6)	
	27	183 (25.3)	117 (23.5)	66 (29.1)	
	28	179 (24.7)	115 (23.1)	64 (28.2)	
Birth weight (grams)		918 ± 234	899 ± 232	960 ± 233	0.003
Intrauterine growth restriction†		36 (5.0)	32 (6.4)	4 (1.8)	0.02
Male sex		369 (51.0)	273 (54.9)	96 (42.3)	0.005
Multiple gestation		187 (25.8)	111 (22.3)	76 (33.5)	0.006
Antenatal steroids		625 (86.3)	429 (86.3)	196 (86.3)	0.95
Smoking during pregnancy		139/723 (19.2)	111/496 (22.4)	28/227 (12.3)	0.004
Stabilization at birth					
	Intubation	564 (77.9)	405 (81.5)	159 (70.0)	0.003
	Chest compressions	81 (11.2)	65 (13.1)	16 (7.0)	0.03
Infant race					0.002
	White, Non-hispanic	359 (49.6)	231 (46.5)	128 (56.4)	
	Black/African-American	261 (36.0)	205 (41.2)	56 (24.7)	
	White, Hispanic	69 (9.5)	40 (8.0)	29 (12.8)	
	Multiple/ Other	35 (4.8)	21 (4.2)	14 (6.2)	
Maternal age (years)		28.0 ± 6.2	27.7 ± 6.1	28.8 ± 6.5	0.07
Maternal education					0.007**
	High school graduate or	389 (53.7)	283 (56.9)	106 (46.7)	

		Whole cohort (n=724)	Post-prematurity respiratory disease (n=497)	No Post-prematurity respiratory disease (n=227)	P value [*]
	Pearsrtial college	143 (19.8)	100 (20.1)	43 (18.9)	
	College graduate or beyond	192 (26.5)	114 (22.9)	78 (34.4)	
Public insurance		470/721 (65.2)	348/494 (70.4)	122/227 (53.7)	<0.001
Parent with asthma		173/712 (24.3)	129/485 (26.6)	44/227 (19.4)	0.04

Data are mean ± standard deviation or n (%).

Data are presented as column percentages.

[*] P value by generalized linear mixed effect models, unless otherwise noted.

[**] P value by trend test, treating ordered covariates as continuous variables.

[†] Intrauterine growth restriction defined as < 10th percentile from gestational age-specific fetal growth curves by Fenton (12).

Table 6

Clinical characteristics at 36 weeks' post-menstrual age or discharge and univariate associations with post-prematurity respiratory disease

		Whole cohort	Post-prematurity respiratory disease (n=497)	No Post-prematurity respiratory disease (n=227)	P value [*]
Low breast milk exposure [†]		70/721 (9.7)	57/494 (11.5)	13/227 (5.7)	0.03
Growth velocity (g/kg/d) [††]		16 ± 3.4	16 ± 3.5	16 ± 3.2	0.43
Growth failure at 36 weeks [†]		297/716 (41.1)	217/489 (44.4)	77/227 (33.9)	0.01
BPD [††]					<0.001 [**]
	No/Mild	401/709 (56.6)	241/484 (49.8)	160/225 (71.1)	
	Moderate	91/709 (12.8)	65/484 (13.4)	26/225 (11.6)	
	Severe	217/709 (30.6)	178/484 (36.8)	39/225 (17.3)	
Potential environmental tobacco smoke exposure [#]		69/710 (9.7)	54/483 (11.2)	15/227 (6.6)	0.09
> 6 people in home		74 (10.4)	55 (11.3)	19 (8.4)	0.24
Older child < 5 years in home		475 (66.4)	324 (66.4)	151 (66.5)	0.92
Daycare anticipated		305 (42.7)	215 (44.1)	90 (39.6)	0.31
Discharge month					0.11
	January-February	99 (13.7)	76 (15.3)	23 (10.1)	
	March-April	113 (15.6)	80 (16.1)	33 (14.5)	
	May-June	103 (14.2)	74 (14.9)	29 (12.8)	
	July-August	140 (19.3)	101 (20.3)	39 (17.2)	
	September-October	132 (18.2)	79 (15.9)	53 (23.3)	
	November-December	137 (18.9)	87 (17.5)	50 (22.0)	

Data are mean ± standard deviation or n (%)

Data are presented as column percentages.

[*] P value by generalized linear mixed effect models, unless otherwise noted.

[**] P value by trend test, treating ordered covariates as continuous variables.

[†] Low breast milk exposure defined as < 28 days of any breast milk feed prior to 36 weeks' post-menstrual age.

[††]Growth velocity over last 28 days prior to 36 weeks' post-menstrual age defined as (weight 36 weeks –weight 32 weeks)/[(weight 36 weeks - weight 32 weeks)/2/(days 36 weeks - days 32 weeks)].

[+]Growth failure defined as weight < 10th percentile based on anticipated fetal growth from gestational age-specific fetal growth curves by Fenton (12).

[++]BPD classification modified from NIH workshop proposed definition (3, 11)

[#]Potential environmental tobacco smoke exposure at discharge based on positive responses to allowing smoking in the home or infant traveling in a vehicle where smoking occurs.

Table 7

Multivariate perinatal (identified in the first day of life) and 36-week models for post-prematurity respiratory disease and respiratory morbidity severity, showing adjusted odds ratios.

		Perinatal		36-week	
		Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Post-prematurity respiratory disease (n=697)					
Gestational age	per week	0.90 (0.79, 1.04)	0.15	1.00 (0.86, 1.16)	0.99
Intrauterine growth restriction *		2.57 (0.82, 8.09)	0.11	2.32 (0.70, 7.63)	0.16
Male sex		1.96 (1.36, 2.83)	<0.001	1.74 (1.20, 2.54)	0.004
Smoking during pregnancy		1.70 (1.01, 2.89)	0.047	1.66 (0.97, 2.84)	0.07
Intubation at birth		1.47 (0.95, 2.29)	0.09	1.36 (0.87, 2.14)	0.18
Infant race			0.03		0.01
	White, Non-hispanic	1.00 (REF)		1.00 (REF)	
	Black/ African-American	1.59 (1.01, 2.50)		1.83 (1.15, 2.91)	
	White, Hispanic	0.62 (0.32, 1.19)		0.69 (0.35, 1.33)	
	Multiple/ Other	0.84 (0.37, 1.88)		0.88 (0.38, 2.02)	
Public insurance		1.57 (1.03, 2.40)	0.04	1.47 (0.95, 2.26)	0.08
Parent with asthma		1.40 (0.89, 2.21)	0.14		
Low breast milk exposure **				2.21 (1.08, 4.51)	0.03
Growth failure at 36 weeks *				1.32 (0.88, 1.99)	0.18
BPD					<0.001
	No/Mild			1.00 (REF)	
	Moderate			1.73 (0.98, 3.08)	
	Severe			2.70 (1.68, 4.33)	

		Perinatal		36-weeK	
Respiratory morbidity severity (n=679)					
Gestational age	per week	0.85 (0.64, 1.13)	0.27	0.83 (0.67, 1.02)	0.08
Birth weight	per 100g	0.82 (0.68, 0.99)	0.04		

Post-prematurity respiratory disease (n=697)

	Odds ratio (95% confidence interval) Perinatal	P value	Odds ratio (95% confidence interval) 36-week	P value
Intrauterine growth restriction *	3.82 (0.91, 16.10)	0.07	4.55 (1.15, 17.97)	0.03
Male sex	3.11 (1.74, 5.58)	<0.001	2.25 (1.31, 3.84)	0.004
Multiple gestation	0.62 (0.31, 1.25)	0.18		
Intubation at birth	1.73 (0.90, 3.34)	0.10	1.54 (0.81, 2.96)	0.19
Infant race		0.02		0.03
White, Non-hispanic	1.00 (REF)		1.00 (REF)	
Black/ African-American	1.19 0.64, 2.22)		1.60 (0.85, 3.00)	
White, Hispanic	0.25 (0.09, 0.71)		0.37 (0.14, 0.99)	
Multiple/ Other	0.35 (0.09, 1.30)		0.40 (0.11, 1.46)	
Public insurance	1.96 (1.05, 3.68)	0.04	1.86 (1.00, 3.45)	0.049
Parent with asthma	1.93 (1.00, 3.71)	0.049	1.72 (0.91, 3.27)	0.10
Low breast milk exposure **			2.62 (1.07, 6.40)	0.04
Growth failure at 36 weeks *			1.97 (1.11, 3.48)	0.02
BPD				<0.001
No/Mild			1.00 (REF)	
Moderate			2.10 (0.99, 4.48)	
Severe			6.90 (3.20, 14.91)	

*
Intrauterine growth restriction and growth failure defined as < 10 percentile for anticipated growth from gestational age-specific fetal growth curves by Fenton (12).

**
Low breast milk exposure defined as < 28 days of any breast milk feed prior to 36 weeks' post-menstrual age.