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Bronchopulmonary Dysplasia and Neurobehavioral Outcomes at Birth and Two Years in Infants Born Before 30 Weeks

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Abstract

Objectives: To identify neurobehavioral risks in preterm infants with bronchopulmonary dysplasia (BPD) prior to hospital discharge.

Design and patients: Longitudinal study of 676 newborns born before 30 weeks gestation.

Setting: Nine university NICUs affiliated with 6 universities. All were Vermont Oxford Network (VON) participants.

Patients and interventions: Infants were enrolled in The Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) Study from April 2014 through June 2016. Prospective medical record reviews, VON definitions and criteria, and maternal interviews were used to collect maternal and neonatal medical variables and socio-environmental data.

Main Outcome Measures: NICU Network Neurobehavioral Scale (NNNS) at the time of hospital discharge; Bayley-III and Gross Motor Function Classification System (GMFCS) at two years corrected age.

Results: Infants with moderate/severe BPD were less attentive (Wald chi-square 9.68, p=0.008), more lethargic (Wald chi-square 9.91, p=0.007), with poor quality of movement (Wald chi-square 10.15, p=0.006) and increased non-optimal reflexes (Wald chi-square 7.37, p=0.025). Infants with moderate/severe BPD were more likely to have Bayley-III language and motor scores < 85 (aOR 1.74; 95% CI: 1.06, 2.85 and aOR 2.06; 95% CI: 1.10, 3.85). Infants with both moderate/severe and mild BPD were more likely to have a CP diagnosis (aOR 2.96; 95% CI: 1.34, 6.54 and aOR 2.81; 95% CI: 1.32, 5.99).

Conclusions: BPD severity presents risks for poor neurodevelopment at NICU discharge and at age two years. Early identification of poorly regulated behavior can provide critical information for early preventive and targeted interventions with potential to improve long term outcomes.

Introduction

Prematurity accounts for approximately 10% of all births in the United States. An increased number of extremely premature newborns are surviving secondary to medical advances. However, infants born at <30 weeks postmenstrual age (PMA) are at highest risk of neurodevelopmental impairment.(1–4) Contributing to these outcomes are conditions such as perinatal brain injuries, necrotizing enterocolitis (NEC), sepsis, and bronchopulmonary dysplasia (BPD),(1, 5–9) where BPD has been found to develop in up to 40% of infants born <30 weeks.

Though severity of BPD often correlates with degree of neurodevelopmental impairment, predicting which infants are at highest risk remains challenging.(10–11) Given the importance of early intervention to optimize long term outcomes for these children,

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identifying the risk for neurodevelopmental deficits at Neonatal Intensive Care Unit (NICU) discharge may enhance the effectiveness of prevention efforts. Behavior problems in low birthweight and preterm infants are also of clinical concern because these behaviors persist and can have an impact on school achievement as well as psychiatric and attention problems. (12)

We conducted this study to determine if the presence and severity of BPD is associated with specific neurobehavioral characteristics reflected in neurobehavioral measures at NICU discharge and at two years of age.

Methods

The Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) Study enrolled infants from April 2014 through June 2016 at 9 university affiliated NICUs that were also Vermont Oxford Network (VON) participants. Enrollment and consent procedures were completed in accordance with each of the following center's Institutional Review Board *[Children's Mercy Hospital IRB in Kansas City, MO (IRB00004750), Western Institutional Review Board in Puyallup, WA (WIRB20131387), John F. Wolf Human Subjects Committee in Los Angeles, CA (IRB00000389), Spectrum Health Systems, Inc. in Grand Rapids, MI (IRB00009435), Women & Infants Hospital in Providence, RI (IRB00000746), and Wake Forest University Health Sciences in Winston-Salem, NC (IRB00000212)].* Inclusion criteria were: 1) birth at <30 weeks PMA 2) parental ability to read and speak English or Spanish 3) residence within 3 hours of the NICU follow-up clinic. Determination of birth PMA was based on the Extremely Low Gestational Age Newborns (ELGAN) Study criteria.(13) Exclusion criteria included maternal age < 18 years, cognitive impairment, and death, and infant major congenital anomalies(14) or NICU death. Parents of eligible infants were invited to participate in the study when survival was deemed likely by the attending neonatologist.

Measures

Maternal prenatal and intrapartum variables from the infant medical record were collected by NOVI research personnel with oversight by study neonatologists. These included validated maternal medical risk factors for preterm birth (15) such as infection and hypertension. Maternal age, education, race/ethnicity, and economic resources were obtained during standardized maternal interviews.

Neonatal medical data

The VON (16) neonatal medical variables were collected using standardized criteria and methods for infections, retinopathy of prematurity (ROP), respiratory, gastrointestinal and central nervous system complications. BPD was stratified using an adaptation of Jensen et al.'s criteria:(11) mild (supplemental oxygen, or high flow nasal cannula with FiO_2=0.21), moderate (supplemental oxygen via high flow nasal cannula, nasal continuous positive airway pressure, or nasal positive airway pressure ventilation), or severe (mechanical ventilation via endotracheal tube) at <=36 weeks.

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Brain injury

Brain injury diagnoses were based on routinely collected site ultrasonograms at days 3–14 and again between 36 weeks PMA and discharge. NOVI neuroradiologists were trained to reliability as masked centralized second readers for classifying injuries according to ELGAN study criteria.(17) A third tie-breaker reading by a different study neuroradiologist was performed if the initial and second readings disagreed about the presence of following: intraventricular hemorrhage, parenchymal echodensity, parenchymal echolucency, or moderate-to-severe ventricular enlargement.(9)

Neurobehavioral Assessments

NNNS.—The NNNS is a standardized measure of tone, primitive reflexes, physical maturity, social and behavioral functioning, including visual and auditory tracking, cuddling, consolability, with stress signs organized by organ system.(18–19) Exams were conducted during the week of NICU discharge by site examiners trained to reliability and certified by central NNNS trainers. Although examiners were not able to be masked to visible nasal cannula, examiners were masked to all study hypotheses, including relationships with BPD and other neonatal complications. Individual items were converted to 13 summary scores: habituation, attention, handling, regulation, arousal, excitability, lethargy, hypertonia, hypotonia, non-optimal reflexes, asymmetric reflexes, quality of movement, and stress abstinence. A higher summary score reflects a higher level of the construct. Habituation was omitted from analyses, as 50% of infants were not in the requisite sleep state at the initiation of exam.(20)

Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III).—The Bayley-III is a developmental assessment of cognitive, language, and motor domains.(21) The Bayley-III has demonstrated validity in similar samples of premature infants.(22–23)

CP diagnosis.—A neuromotor examination was performed along with the Gross Motor Function Classification System (GMFCS). Diagnosis of CP was determined based on the GMFCS and/or abnormal neurological exam.(24)

Statistical analysis

BPD severity was analyzed as a 3 level categorical variable – no BPD, mild BPD, and moderate/severe BPD. Differences in BPD severity by neonatal medical data, prenatal, perinatal maternal, and infant risk was examined using chi-square (or Fisher's exact test) and one-way ANOVA as appropriate. P values were considered significant at <0.05.

Latent profile analysis (LPA, Mplus version 8.1) of all 12 NNNS summary scores was used to group infants into mutually exclusive categories that represent heterogeneous subgroups. LPA models with different numbers of profiles were fitted and the model containing the optimal number of profiles identified.(25) In this NOVI sample six distinct NNNS profiles were identified. Infants in profile 6 had scores that reflect the most extremely poor functioning in multiple domains, compared to the other 5 profiles. Profiles can indicate which infants are most at risk, which behaviors are problematic, and have been shown to predict long term developmental outcomes.(20,22–23)

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Generalized estimating equations (GEEs) accounted for mothers with multiple infants by nesting infants within families. Analyses examined associations between BPD and NNNS summary scores and risk profiles, Bayley-III, and CP. Models adjusted for site and the following covariates: PMA at NNNS exam (NNNS models only), maternal hypertension, infection during pregnancy, infant NEC or sepsis, infant brain injury, use of antenatal steroids, and infant birthweight < 950 grams (yes/no). Less than 950 grams was selected using the curve from a receiver operating characteristic (ROC) analysis, which illustrated that particular weight had 80% sensitivity to moderate/severe BPD. Covariates selected have been reported previously in the literature as being associated with various neurodevelopmental outcomes and BPD. Interactions between BPD severity and model covariates were explored further when p-values were < 0.10 to explore further important interactions. Interactions between model covariates and BPD severity were not tested in the model for NNNS summary profile due to small cell sizes.

Results

The sample included 676 infants with NNNS and maternal and infant data available for analysis (Figure 1). Moderate/severe BPD was present in 177 (26.2%) infants, mild BPD in 163 (24.1%) infants and no BPD in 336 (49.7%) infants. Among the three groups, there were no differences in maternal demographics or maternal medical risk, except for higher rates of maternal infection in the no BPD group (Table 1). Nearly two-thirds of infants in the moderate/severe BPD group and in the mild BPD group were born <27 weeks PMA at birth. Infants without BPD were more likely to be born >27 weeks compared to those with any type of BPD, and age at NNNS exam was highest in the moderate/severe BPD group. Infant birthweight and length of hospital stay also differed by BPD group, with birthweight averages less than 950 grams and length of hospital stays up to 4 months for those with BPD. NEC/sepsis, ROP, and brain injury were more prevalent in infants with moderate/severe or mild BPD, whereas infants without BPD had higher rates of antenatal steroid use.

BPD severity did not differ significantly on the NNNS risk profiles (p=0.147). However, BPD severity did differ on several NNNS summary scores in adjusted models (Table 2). BPD severity was associated with decreases in attention (Wald chi-square 9.68, p=0.008) and quality of movement (Wald chi-square 10.15, p=0.006) and increases in nonoptimal reflexes (Wald chi-square 7.37, p=0.025) and lethargy (Wald chi-square 9.91, p=0.007). (Table 2). The decrease in attention was significantly lower in the moderate/severe BPD group vs. the no BPD group (mean difference = −.584, 95 % CI −0.953, −0.216, p=0.002). The increase in nonoptimal reflexes was significantly higher in the moderate/severe BPD group vs. the no BPD group (mean difference=0.69, 95% CI 0.19, 1.19, p=0.007) and the increase in lethargy was significantly higher in the moderate/severe BPD group as compared to the mild (mean difference=0.73. 95% CI 0.26, 1.2, p=0.003) and no BPD groups (mean difference=0.72, 95% CI 0.20, 1.24, p=0.007). Quality of movement scores were significantly lower in the no BPD group vs. the mild BPD group (mean difference= −.188, 95% CI −0.31, −0.06, p=0.003)

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Interaction testing between BPD group and model covariates was conducted (Supplemental Table A). The interaction between BPD and birth weight less than 950 grams was associated with attention (p=0.007) and handling (p=0.033). Chronic or pregnancy induced HTN and BPD group interactions were found for handling (p=0.029), self-regulation (0.050) and excitability (p=0.002). The interaction between the BPD group and maternal infection during pregnancy was stronger for non-optimal reflexes (p=0.065). Infant NEC/Sepsis BPD group interactions were found for handling (p=0.071) and hypertonicity (p=0.047). Interactions between model covariates and BPD severity were not tested in the model for NNNS summary profile due to small cell sizes.

Further analysis was stratified on specific covariate levels to explore the BPD severity interactions for several NNNS summary scores (Table 3). Infants with birthweight ≤950 grams exhibited decreasing attention scores with increasing BPD severity (p=0.004). In infants of mothers without infection, nonoptimal reflex scores increased with increasing BPD severity (p=0.007). Decreasing excitability scores across increasing BPD severity were seen in infants born to mothers who had hypertension (HTN) (p=0.022). Infants in the mild BPD group who also experienced NEC or sepsis were significantly more hypertonic (p=0.002).

At two years, 553 infants diagnosed with BPD at birth were available for follow-up. Of those, the Bayley-III was administered to 530 infants and the GMFCS to 542 infants. Moderate/severe BPD was associated with an increased odds of Bayley-III language and motor scores < 85 (aOR 1.74; 95% CI: 1.06, 2.85 and aOR 2.06; 95% CI: 1.10, 3.85) and both moderate/severe and mild BPD was associated with an increased odds of CP diagnosis (aOR 2.96; 95% CI: 1.34, 6.54 and aOR 2.81; 95% CI: 1.32, 5.99) (Table 4).

NNNS summary scores that significantly predicted BPD severity (see Table 2) were added to adjusted models to examine their association with Bayley-III and CP. Cognitive composite scores <85 were associated with increased nonoptimal reflexes (Wald chi-square 4.14, p=0.042). Motor composite scores <85 and cerebral palsy were associated with increases in nonoptimal reflexes (Wald chi-square 10.42, p<0.001; Wald chi-square 10.70, p<0.001). Cerebral palsy was also associated with increased lethargy (Wald chi-square 7.72, p=0.005) and decreased attention (Wald Chi-Square 4.63, p=0.032) (Supplemental Table B).

When included in multivariable models examining the association between BPD and two-year outcomes, attention (aOR 2.86; 95% CI: 1.31,6.22 and aOR 3.26; 95% CI: 1.42, 7.46) and lethargy (aOR 3.15; 95% CI: 1.46, 6.78 and aOR 3.20; 95% CI: 1.42, 7.20) increased the magnitude of the association between both mild and moderate/severe BPD and CP (Table 4).

Discussion

Our study demonstrates differences in neurobehavior associated with BPD severity at NICU discharge and two-year follow-up in infants born <30 weeks gestation. Specifically, infants with moderate/severe BPD severity exhibited increased lethargy and more nonoptimal reflexes, as well as less regulated attention and quality of movement compared to

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infants with mild or no BPD. They also were more likely to have language and motor deficits and a CP diagnosis. Neurobehavior at discharge increased the magnitude of the association between 2-year neurobehavioral outcomes and BPD severity. This is consistent with previous findings demonstrating subsequently worse neurodevelopmental outcomes in infants with BPD.(5–8) However, to our knowledge this is the first study to identify specific NNNS abnormalities at NICU discharge in this vulnerable population, and to relate them to outcomes at two-years adjusted age.

BPD is a recognized risk factor for neurodevelopmental impairment.(10) NNNS characteristics have previously been correlated with developmental outcomes at and beyond 2 years of age.(3, 26) In preterm samples, NNNS scores for poor regulation, suboptimal reflexes, hypertonicity, and increased handling were associated with poor Bayley outcomes at 18 months.(22) The present study's specific NNNS findings of lethargy and low movement quality were previously reported to predict two-year Bayley scores and CP(23) and increased suboptimal reflexes and stress signs on the NNNS were associated with sensory processing disorders at age 4 to 6 years.(27)

NNNS summary scores revealed significant differences in multiple domains between infants with and without BPD. More poorly regulated neurobehavior was associated with increasing severity of BPD suggesting a possible continuity in these specific BPD severity-related patterns. These findings are consistent with previously published studies of profile patterns that subsequently were associated with poor neurodevelopmental outcomes.(5–8)

The development of BPD is a multifactorial process, with inflammation considered to be a major contributor.(28) As expected, infants with the most severe BPD were also the most likely to have severe ROP, NEC, sepsis, and brain injury, all of which are known to be associated with pro-inflammatory mechanisms. Interestingly, though antenatal infection is associated with BPD,(29) our cohort demonstrated the highest rate of maternal infection in the group without BPD. These findings may explain why the differences in nonoptimal reflexes among BPD severity groups were seen in infants of mothers without maternal infection. Further, significantly higher rates of hypertonicity in the presence of NEC or sepsis were found in the mild BPD group. These collective findings suggest that neonatal BPD and infections may modulate neuromotor tone, which is a more sensitive metric in demonstrating the effects of a pro-inflammatory process than other components of the NNNS.

We continue to follow this cohort long term to evaluate developmental trajectories sequentially and to further examine correlates of NNNS and later outcomes. Our own and previous studies have consistently demonstrated what is now an increased range of risk identification using early and later neurobehavioral exams. These exams show promise as tools to identify a wide range of early neurobehavioral regulation and dysregulation in infants with BPD at NICU discharge and 2-year follow-up. By identifying these differences early, targeted therapeutic interventions may begin in the NICU, continuing through discharge and into the transition to the home community.

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Our study strengths included the use of masked and highly trained examiners, several validated and standardized neonatal and outcome assessments, prospective data on maternal and infant characteristics and exposures, and centralized CUS diagnostics. The inclusion of outborn infants to increase generalizability may be a weakness due to reliance on infant labor and delivery summaries to standardize maternal data collection across sites that included children's hospitals.

In summary, specific patterns of poorly regulated neurobehavior at NICU discharge and differences in neurodevelopmental outcomes at age 2 years were associated with BPD severity. These findings support the potential use of NNNS exam findings prescriptively in infants with BPD for preventive and targeted interventions. Our findings are consistent with previous findings of cognitive and motor impairments at 24 months associated with BPD severity.(30–31)

Further, we have identified the earliest targets that may be amenable to NICU interventions--those related to poorly regulated attention, handling, and tone. These findings support the addition of neurobehavioral assessments during the NICU stay and again at the week of discharge to inform community referrals and discharge care plans as well as continued follow-up. These targeted referrals include physical therapy, occupational therapy, and speech therapy that can be provided prior to and after discharge.(32–34)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

NICU	Neonatal intensive care unit
PMA	Postmenstrual age
BPD	Bronchopulmonary Dysplasia
NICU	Neonatal Intensive Care Unit
NNNS	NICU Network Neurobehavioral Scale
NOVI	Neonatal Neurobehavior and Outcomes in Very Preterm Infants
VON	Vermont Oxford Network

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ELGAN	Extremely Low Gestational Age Newborns
ROP	Retinopathy of prematurity
CNS	Central nervous system
IVH	Intraventricular hemorrhage
LPA	Latent profile analysis
BIC	Bayesian information criteria
GEE	Generalized estimating equations
NEC	Necrotizing enterocolitis
GMFCS	Gross motor function classification system

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What is already known on this topic:

Bronchopulmonary Dysplasia is a significant risk factor for developmental delays in children born prematurely.

What this study adds:

To our knowledge, this is the first study to demonstrate specific neurobehavioral patterns associated with severity of BPD at the time of hospital discharge.

How this study might affect research, practice, or policy:

Neurobehavioral assessments during the NICU stay and at discharge can inform designs for the implementation of preventive and targeted interventions. This can potentially improve long term neurodevelopment for premature newborns.

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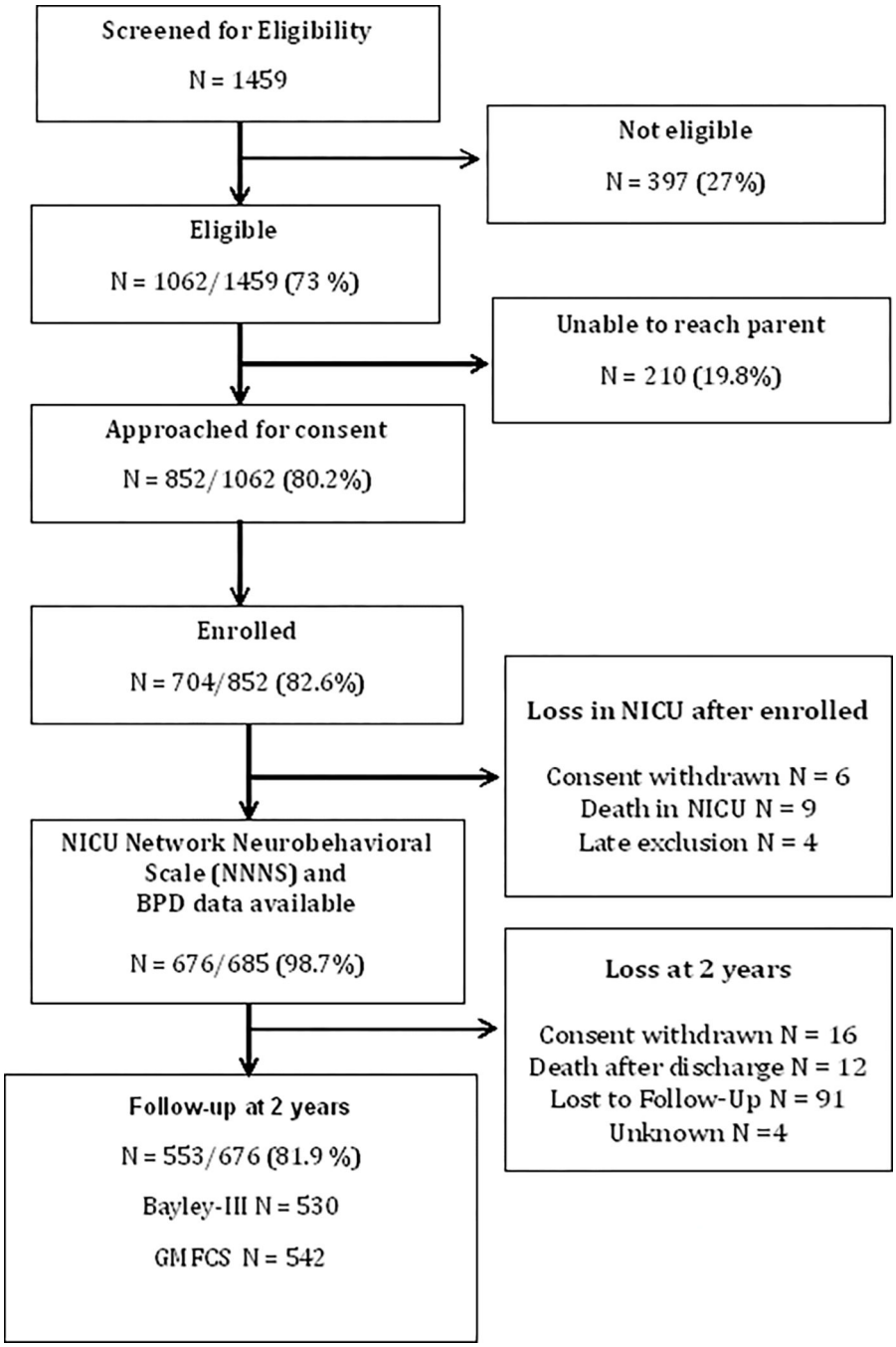

Figure 1. Study Flow Chart

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Table 1.

Maternal and Infant Characteristics

N (%) or Mean (SD)	No BPD(n=336)		Mild BPD (n=163)		Moderate/Severe BPD (n=177)		P
Maternal age at childbirth	29.0	6.3	30.0	6.9	28.4	6.1	0.324
Pre-pregnancy BMI	28.0	7.7	28.5	7.3	27.1	7.0	0.376
SES Hollingshead index, neonatal	35.2	12.9	37.1	13.0	35.3	12.7	0.938
PMA at Birth	28.0	1.5	26.2	1.8	26.0	1.9	**<0.001**
PMA at Birth group							**<0.001**
27+ weeks	260	76.5%	63	37.5%	64	33.9%	
<27 weeks	80	23.5%	105	62.5%	125	66.1%	
PMA at NNNS Exam	37.3	2.4	40.0	2.6	42.5	3.1	<0.001
Minority race or ethnicity	190	57.8%	94	57.7%	92	52.9%	0.541
Sex of Infant							0.809
Female	148	44.0%	70	42.9%	82	46.3%	
Male	188	56.0%	93	57.1%	95	53.7%	
Birth Weight (grams)	1087.7	264.0	846.1	227.5	797.8	230.4	**<0.001**
Fetal Growth Restriction (SGA)	20	6.0%	13	8.0%	17	9.7%	0.299
Total Length of Stay (days)	70.6	25.0	102.8	25.4	123.6	48.3	**<0.001**
Maternal medical risks							
Maternal Hypertension, Chronic or Pregnancy-Induced	75	22.3%	44	27.2%	51	29.0%	0.208
Diabetes mellitus	27	8.1%	9	5.5%	9	5.1%	0.350
Infection, pregnancy	46	13.7%	8	4.9%	15	8.5%	**0.006**
Asthma	24	7.2%	14	8.6%	15	8.5%	0.804
Neonatal medical risks							
NEC or Sepsis	38	11.3%	33	20.2%	46	26.0%	**<0.001**
Severe ROP: stage 4 or 5 or surgery	4	1.2%	15	9.2%	21	11.9%	**<0.001**
Antenatal Steroids	309	92.0%	141	86.5%	146	83.0%	**0.008**
Brain Injury	29	8.7%	20	12.3%	39	22.0%	**<0.001**

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Table 2.

NNNS Outcomes by BPD Severity *

NNNS Summary Scores	No BPD (n=336)	Mild BPD (n=163)	Moderate/Severe BPD (n=177)	Wald Chi-Square	P
	Group 0	Group 1	Group 2		
Attention	5.33 (0.17)^	5.08 (0.17)	4.75 (0.17)^	9.68	0.008
Handling	0.45 (0.03)	0.46 (0.03)	0.44 (0.03)	0.31	0.857
Quality of Movement	4.42 (0.07)^	4.61 (0.08)^	4.46 (0.08)	10.15	0.006
Self-Regulation	5.53 (0.08)	5.55 (0.09)	5.58 (0.09)	0.34	0.842
Nonoptimal Reflexes	5.45 (0.23)^	5.71 (0.25)	6.14 (0.25)^	7.37	0.025
Stress Abstinence	0.13 (0.01)	0.13 (0.01)	0.14 (0.01)	0.93	0.629
Arousal	3.78 (0.07)^	3.74 (0.08)	3.59 (0.08)^	5.25	0.072
Excitability	2.88 (0.24)	2.62 (0.24)	2.35 (0.25)	3.48	0.175
Lethargy	4.68 (0.24)+	4.67 (0.26)^	5.40 (0.28)^,+	9.91	0.007
Hypertonicity	0.40 (0.09)	0.38 (0.09)	0.31 (0.08)	1.09	0.588
Hypotonicity	0.29 (0.06)	0.31 (0.07)	0.38 (0.10)	0.95	0.622
Asymmetrical Reflexes	0.72 (0.12)	0.83 (0.13)	0.95 (0.15)	2.85	0.241
NNNS Profiles					
Poorly Regulated Atypical Profile 6 **	25 (7.4)	9 (5.5)	12 (6.8)	2.49	0.287

* Multivariable models adjusted for study site, PMA at NNNS exam, infant birthweight < 950 grams (yes/no), maternal hypertension, infection during pregnancy, infant NEC or sepsis, infant brain injury, and use of antenatal steroids

** frequency and percentage

^ or + Post-hoc pairwise comparisons were also conducted and groups whose means were significantly different From one another are noted(P>0.5)

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Table 3.

Associations between BPD and NNNS summary scores

			NNNS Means by BPD Group			
NNNS Summary Scores	**Covariate**	**Level**	**None**	**Mild**	**Mod/Severe**	**p-value**
NNNS Attention	Birthweight	> 950 grams	5.30 (0.24)	5.63 (0.41)	5.33 (0.34)	0.504
		≤ 950 grams	5.25 (0.24)	5.01 (0.38)	4.45 (0.26)	0.004
NNNS Handling	Birthweight	> 950 grams	0.46 (0.04)	0.46 (0.08)	0.43 (0.07)	0.156
		≤ 950 grams	0.45 (0.04)	0.57 (0.07)	0.40 (0.05)	0.052
	Maternal Hypertension	No	0.42 (0.04)	0.47 (0.07)	0.45 (0.05)	0.883
		Yes	0.49 (0.04)	0.55 (0.09)	0.38 (0.06)	0.223
	NEC/Sepsis	No	0.43 (0.04)	0.47 (0.07)	0.45 (0.05)	0.764
		Yes	0.48 (0.05)	0.56 (0.09)	0.38 (0.06)	0.093
NNNS Self-Regulation	Maternal Hypertension	No	5.47 (0.10)	5.71 (0.13)	5.65 (0.14)	0.645
		Yes	5.40 (0.12)	5.55 (0.17)	5.88 (0.17)	0.339
NNNS Non Optimal Reflexes	Infection during pregnancy	No	5.29 (0.26)	5.47 (0.37)	6.42 (0.29)	0.007
		Yes	5.53 (0.39)	5.43 (0.80)	5.53 (0.44)	0.752
NNNS Excitability	Maternal Hypertension	No	2.75 (0.32)	2.23 (0.41)	2.54 (0.35)	0.204
		Yes	3.15 (0.37)	3.03 (0.51)	1.79 (0.46)	0.022
NNNS Hypertonicity	NEC/Sepsis	No	0.32 (0.10)	0.44 (0.18)	0.39 (0.11)	0.761
		Yes	0.32 (0.14)	1.04 (0.51)	0.33 (0.12)	0.002

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Table 4.

2 Year Outcomes by BPD Severity with NNNS summary scores

	Mild BPD aOR (95% CI)	Moderate/Severe BPD aOR (95% CI)
Bayley-III *	**N=134**	**N=144**
Cognitive composite <85	1.08 (0.60, 1.94)	1.56 (0.89, 2.73)
Language composite <85	1.15 (0.71, 1.85)	1.74 (1.06, 2.85)
Motor composite <85	1.14 (0.61, 2.15)	2.06 (1.10, 3.85)
Cerebral Palsy Diagnosis *	**N=132**	**N=137**
	2.81 (1.32, 5.99)	2.96 (1.34, 6.54)
with NNNS attention added to the model	2.86 (1.31, 6.22)	3.26 (1.42, 7.46)
with NNNS lethargy added to the model	3.15 (1.46, 6.78)	3.20 (1.42, 7.20)

* Multivariable models adjusted for study site, infant birthweight < 950 grams (yes/no), maternal hypertension, infection during pregnancy, infant NEC or sepsis, infant brain injury, and use of antenatal steroids

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