I. INTRODUCTION

A. Nature of the research report: This report is for the secondary analysis grant, Longitudinal Analyses of the Psychosocial Sequelae of VLBW and BPD, Phases 1-3, R40MC08966. This study examined how bronchopulmonary dysplasia (BPD) and very low birthweight (VLBW), relative to other medical, neurologic and sociodemographic risk factors, impact cognitive, language, neuropsychological, pulmonary, and behavioral outcomes from birth through 14 years of age. VLBW and BPD births are on the rise in the United States, with more than 62,000 infants born with VLBW and more than 11,000 with BPD annually. Despite increased incidence of BPD and VLBW, there have been few comprehensive longitudinal studies of the health, psychosocial, and long term outcomes of such children. In addition, small sample sizes, the absence of adequate control groups, the lack of regional samples, the failure to control for drug exposure, and the lack of psychosocial assessments limit the conclusions that can be made from prior research.

These high risk conditions are significant predictors of major pediatric developmental problems and place a disproportionate burden of disability on educational and societal resources. The impact of this research and clinical knowledge gained from this study are sizeable, both theoretically and clinically. That is, the challenges faced by families of children with VLBW and BPD illness are not unlike those of other child chronic illnesses and disabilities and as such, information can be generalized to other chronic illnesses.

B. Purpose, scope and methods of the investigation: The study used the cohort of 329 children (122 BPD, 84 VLBW without BPD, 123 healthy, term) followed through 3 phases of research. The cohorts of BPD, VLBW, and term children to be studied have been well characterized in cross sectional comparisons on sociodemographic, family, behavioral, and medical characteristics at birth through 8 years of age. As all infants were born after the initiation of surfactant and steroid therapies in neonatal care, this cohort offered a unique opportunity to assess the impact of BPD relative to other complications of VLBW on long-term outcomes through adolescence.

The 3 specific Aims in this study were: 

Aim 1: To examine the differential stability of intelligence in cohorts of BPD, VLBW, and term children were examined three time points (3 years, 8 years and 14 years) of collected cognitive scores. Moderators of change were examined, including maternal IQ, gender, and SES.

Aim 2: To examine the differential stability of linguistic skills (receptive and expressive language) and how factors like chronic lung disease, very low birth weight, neurologic, and sociodemographic factors might differentially impact language skills.

Aim 3: To examine the impact that neonatal medical status and neurologic risk factors have on the trajectory of parenting stress, maternal mental health, and coping strategies.

C. Nature of the findings: The findings from the analyses done in this study indicate differential outcomes for children of VLBW with and without BPD and their families.

II. REVIEW OF THE LITERATURE

Very Low Birth Weight Birth. Over 67,000 infants with very low birth weight (VLBW; < 1500g) and over 11,000 infants with BPD are born annually in the U.S., with increasing numbers surviving due to recent advances in neonatology and biomedical technology. VLBW cohorts have more neurosensory abnormalities, and perform more poorly than full-term cohorts in growth, general cognitive abilities, specific neuropsychological functions, and behavioral competence. Differences in IQ increase with decreasing birth weight, and persist even when children with frank neurologic abnormalities are excluded. Epidemiological studies link VLBW birth to cerebral palsy and mental retardation in childhood. In a population-based study of infants born at 20–25 weeks of gestation, >50% had neurologic and developmental disabilities at 30 months corrected age. At preschool age, VLBW children lag behind term preschoolers in language development, even when other risk factors are controlled. Rivkin suggested that the neurodevelopmental deficits associated with VLBW become more apparent with increasing age of the child. Follow-up studies through adolescence and into adulthood revealed that preterm children encounter greater cognitive, psychological, neuropsychological and motor impairments, and are at greater risk for grade repetition, special education placement, and use of school-based services than full-term controls, with lower educational attainment in early adulthood.

VLBW, a major predictor of pediatric disabilities, also impacts societal resources. Given variation in the
sequelae associated with VLBW, delineation of the longitudinal impact that VLBW has on cognitive, linguistic, and familial outcomes is critical. While many factors play a prominent role in the problems experienced by VLBW cohorts, the added impact that BPD has on a VLBW birth has been the primary focus of our work. **Bronchopulmonary Dysplasia.** BPD has emerged in the past 15 years as the leading chronic lung disease in infancy in the U.S. Although medical and technological advances have reduced mortality and severity for VLBW infants, a consequence has been an increase in survivors with BPD. The incidence of BPD climbs with decreasing birth weight, with approximately 22% of infants weighing 1,000 – 1,500 grams and 71% of infants weighing <1,000 grams having BPD. First described by Northway in 1967, diagnostic criteria for BPD used in this study included the sustained need for oxygen supplementation >28 days and radiologic evidence of lung abnormalities related to premature birth, respiratory failure, oxygen toxicity, and barotraumas.

**Outcomes Associated with BPD: Central Nervous System, Cognitive and Language Functioning.** BPD usually occurs in the third intrauterine trimester, when cerebellar growth is rapid and neural development is vulnerable to the alterations in blood gases and malnutrition. Central nervous system pathology in infants with BPD shows brain atrophy and gliosis compatible with chronic hypoxia. Prolonged ventilator and oxygen dependence results in repeated episodes of hypoxia and acidosis leading to hypoxic-ischemic cerebral injury and increased mortality and morbidity. Clinically, unsuspected hypoxia during sleep, sleep apnea and hypoxic airway constriction have been reported in infants with moderate to severe BPD. Also, recurrent oxygen desaturation has been observed during and immediately after feedings.

BPD affects children’s cognitive, language and neuropsychological development at school age and adolescence, as well as rate of learning disabilities. School age and adolescent differences included lower IQ, receptive language, visual motor integration, academic achievement, physical stature, and pulmonary function. While not all of these studies addressed the issue of BPD, the relatively small samples and the lack of adequate controls limit conclusions about the long term impact of BPD. Also, since most of these reports were cross sectional, it is possible that differences observed at preschool and school ages are solely due to differences observed at an earlier time point. Longitudinal examination of the developmental trajectories will clarify the impact that BPD has on long-term functioning.

**Parenting Stress.** Child risk/illness status affects maternal psychological distress, family functioning, and child outcomes. VLBW populations are more vulnerable to the negative impact of early maternal depressive symptoms for several reasons. First, the birth and parenting of a VLBW child is related to higher maternal psychological distress postpartum. Second, VLBW infants may be affected by maternal care giving differences. Third, transactional models suggest that infant characteristics/behaviors may be negatively affected by preterm birth and medical complications, as well as caregiver psychological distress with each reciprocally modifying the other over time. In this cohort through 3 years, sociodemographic and family factors were related to child risk status and outcomes, especially maternal psychological distress, coping mechanisms and social supports. The increased health problems and adverse developmental outcomes associated with BPD compounds stressors associated with VLBW birth. Compared to term controls, families of BPD infants reported that their child’s health was a significant burden, impacting their work, education, and pastimes, far beyond the neonatal period.

**III. STUDY DESIGN AND METHODS**

**A. Study design:** This study was a prospective, longitudinal quasi-experimental design with prior measures administered from birth to 14 years. Measures can be summarized as sets of independent, dependent, and control variables. The major independent variables are lung disease status, prematurity, i.e. the presence of BPD and/or VLBW and time (repeated measures). Dependent variables include cognitive, school achievement, neuropsychological, language, behavioral and parental outcomes. Control variables include race, socioeconomic status, and multiple birth status, as those factors contribute independently to differences in the dependent variables. Within group variance among the combined VLBW cohorts is also of interest, using multiple birth status, length of hospitalization, severity of
BPD (total days of oxygen supplementation), presence of medical problems, neurologic risk score, severity of IVH, and parental stress/coping variables as either independent or control variables.

**B. Population studies:** NA

**C. Sample selection:** 329 children (122 BPD, 84 VLBW without BPD, 123 healthy, term) were prospectively recruited from three independent Cleveland hospitals whose NICU treated all infants with BPD in the greater Cleveland, Ohio region. Survivors were followed at seven time points from birth to early adolescence (i.e. 1, 8, 12, 24, 36 months and 8 & 14 years). The eligibility criteria for BPD infants included birth weight < 1,500 grams, oxygen dependence >28 days, and radiologic evidence of chronic lung disease. VLBW infants without BPD weighed <1,500 g. birth weight. Term infants had no diagnosed medical illnesses at birth, were >36 weeks gestational age, and >2,500 g. birth weight for singleton infants. Infants were excluded for: major congenital malformations, cocaine exposure, positive HIV, or mothers with psychiatric illness, mental retardation or severe medical illnesses. The large sample has allowed for multivariate analyses of the impact of medical, sociodemographic, and parenting variables on outcomes in infancy through adolescence. Retention at 14 years was 89%, 83%, and 80% of the total sample for BPD, VLBW, and term groups.

**D. Instruments used:** Neonatal Medical and Demographic Characteristics. Medical and demographic characteristics available at birth included race, sex, gestational age, birth weight, social class, birth order, maternal/paternal education, marital status, perinatal medical complications, and multiple birth status. Neurologic complications at birth include neurologic malformations, seizures, porencephaly, hydrocephalus, ventriculoperitoneal shunt, meningitis, IVH, periventriculo-leukomalacia; other complications include necrotizing enterocolitis, retinopathy of prematurity, patent ductus arteriosus, abnormal hearing, peak bilirubin, and septicemia. VLBW infants were classified based on the total number of days of supplemental oxygen, grade of IVH, the presence/absence of neurologic/illness findings, and postnatal surfactant/steroid therapies. Drug (cocaine/marijuana) exposure, assessed through urinanalysis at birth and maternal screening interviews, allowed for exclusion of drug and alcohol exposed infants. Available information included presence/absence of cerebral palsy, autism, sensory-motor deficits, significant illness, total number of days hospitalized, and type/amount of interventions received, as well as longitudinal data on numerous outcome measures.

For parents, identical measures were employed at each time point, allowing for longitudinal analyses such as mixed linear or generalized estimating equation models. Measures included the Brief Symptom Inventory (BSI),76 the Parenting Stress Index (PSI)77 or Stress Index of Parents of Adolescence (SIPA),78 the Multidimensional Perceived Social Support Scale (MSPSS),79 the COPE,80 and the FILE.81 Child measures administered correspond to several critical domains, including physical status,82 pulmonary (Spirometry),83 growth (weight, height, & head circumference), general cognitive abilities (Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID-II)84, Wechsler Intelligence Scales for Children (WISC-III/IV)85,86), motor abilities (Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development,86 Bruininks-Oseretsky Test of Motor Proficiency (BOTMP),87 Tactile Performance Test (TPT),88 Purdue Pegboard (Purdue89), emotional-behavioral (Child Behavior Checklist – parent & teacher (CBCL-P, CBCL-T, YSR),90-92 depression (Children’s Depression Inventory (CDI),93 language (Battelle Developmental Inventory, Communication Domain (BDI-Comm)),94 Clinical Evaluation of Language Fundamentals (CELF-3),95 Comprehensive Assessment of Spoken Language (CASL)96 articulation and oral motor skills (Goldman Fristoe Test of Articulation (GFTA),97 Test of Oral Structures and Functions (TOSF)98, Comprehensive Test of Phonological Processing (CTOPP),99 Speech Repetition Tasks (SRT)100, neuropsychological and attention abilities (Conner’s Continuous Performance Test (CPT),101 Cambridge Neuropsychological Test Automated Battery (CANTAB),102 Brown Attention-Deficit Disorder Scale (ADS),103 Connors Rating Scale (CRS-P, CRS-E, CRS-T)),104 memory (CANTAB and TPT), standardized achievement (Woodcock Johnson Tests of Achievement (WITA-R/III)),105 and maternal-child interaction (Affective Rating Scale, Nursing Child Assessment Feeding Scale (NCAFS)).

**E. Statistical techniques employed:** For the analyses for Aims 1 & 2, ANOVAs and chi-square were employed to compare groups on demographic and medical birth characteristics. Alpha levels were determined by Tukey corrections to control for Type I errors. To examine cognitive and language performance across time, each measurement was internally standardized creating z-scores at each visit using all available children. Standardization of scores at each time point allowed for the comparison of performance despite the fact that different age-appropriate tests were used. Analysis of the z-scores was accomplished using random coefficient models with restricted maximum likelihood estimation. The intercept and slope for child age were treated as random effects to capture the variability and
correlation in the data. The actual age of the child was used instead of visit age to better capture trends over time. These models were used to estimate and test relationships between birth groups at the follow-up visits ages (3, 8, 14 years). For **Aim 3**: Generalized estimating equations (GEE)\(^{107,108}\) was used for linear regression models to determine the association of birth group with parenting stress time, while also measuring the contribution of predictors. To determine whether covariates varied with age, a dataset was created which contained the regression slope for each outcome and subject with the independent factor as child age, creating parameter estimates for child age and each outcome. The regression slope was correlated with covariates to determine which might interact with age in the model (p < .20). Covariates were retained at p < 0.10, interactions at p < 0.05. Child IQ was evaluated as a potential mediator of the effects of HR-VLBW birth on parenting outcomes.

**IV. DETAILED FINDINGS**

**A. Aim 1:** To examine the differential stability of intelligence in cohorts of BPD, VLBW, and term children were examined three time points (3 years, 8 years and 14 years) of collected cognitive scores. Moderators of change were examined, including maternal IQ, gender, and SES. These analyses are complete, with manuscript in final revision stage and submission anticipated by June 1\(^{st}\).

1) All three groups of children evidenced quadratic trajectories in cognitive development, however there was a significant group by time interaction (p<.0001). Term children displayed increased cognitive performance between 3 and 8 years of age, with cognitive performance declining somewhat between 8 and 14 years. In contrast, BPD children evidenced a significant decline in cognitive performance between 3 and 8 years of age, with minor improvement noted between 8 and 14 years of age. Finally, VLBW children displayed minimal change between 3 and 14 years of age in cognitive performance.

2) Main effect of group (BPD vs. VLBW vs. Term) (p<.0001) were observed in cognitive performance, with all groups differing from each other (p’s<.05). Term children performed better than both VLBW groups and children with BPD performed more poorly than both the VLBW and Term controls.

3) Independent predictors of cognitive outcomes included child gender, maternal age at child’s birth, race, and maternal PPVT and WAIS (p’s <.0001).

4) BPD were on average .5 SD IQ points below TERM children at 3 years, .8 SD below at 8 years, and .7 SD below at 14 years. VLBW children were on average .3 SD below Term children at 3 years, .6 SD below at 8 years, and .4 SD below at 14 years of age. Finally, BPD children were on average .2 SD IQ points below VLBW at 3 years, 4 SD below at 8 years, and .4 SD below at 14 years. Thus, these findings suggest that VLBW children with and without BPD experience sustained effects of birth status on IQ across the school age period.

5) Among the BPD group, those who received steroids as part of their postnatal treatment were on average .7 SD IQ points below those that did not receive steroids (p<0.001, 95% CI: -1.01, -0.39). This effect was constant across all visits. Also it should be noted that our BPD group who had not been given steroids as part of their medical treatment looked comparable to our VLBW group in terms of mean IQ across the three time points. Thus, it is not BPD per se but rather severity of BPD in combination with steroid treatment that places children at risk for long term cognitive problems.

**B. Aim 2:** To examine the differential stability of linguistic skills (receptive and expressive language) and how factors such as chronic lung disease, very low birth weight, neurologic, and sociodemographic factors might differentially impact language skills. This manuscript is in preparation, but not yet submitted.

**Receptive Language:**

1) All three groups of children had similar trajectories in receptive language, however there was a main effect of group (BPD vs. VLBW vs. Term) (p<.0004) with all groups differing from each other (p’s<.05). Term children performed better than both VLBW groups and children with BPD performed more poorly than both the VLBW and Term controls.

2) Independent predictors of receptive language outcomes included neurologic risk and race (p’s <.0001)

3) When only neurologically intact children were considered in the analysis, both groups of VLBW children continued to perform more poorly than their Term peers (p’s <.007), and total days on oxygen was a significant predictor of outcome (p<.05).
4) When considering only children with BPD, neurologic risk was a significant predictor of outcome, and severity of BPD (defined in accordance with the NIH consensus definition) showed a non-significant trend (p<.098) for children with mild BPD to do better than those with moderate or severe BPD.

**Expressive Language:**

1) Although children with BPD did not differ significantly from their VLBW peers in expressive language, there was a significant (p<.5) time x group interaction, with both children with BPD and VLBW children without BPD achieved significantly reduced expressive language scores at age 8 (p's < .05) when compared to their Term peers.

2) Neurologic risk, maternal education and race were independent predictors of expressive language.

3) When considering only children with BPD, only neurologic risk was a significant predictor of expressive language outcome.

4) These findings suggest that VLBW with and without BPD have a different trajectory for expressive language than their Term peers.

**C. Aim 3:** To examine the impact that neonatal medical status and neurologic risk factors have on the trajectory of parenting stress, maternal mental health, and coping strategies. Analyses revealed that:

1) Although mothers of all children increased their level of education over time, mothers of Term children showed a faster increase than mothers of both groups of VLBW children (14.5 vs. 13.8, t=2.11, df = 239, p < .037).

2) Mothers of children with BPD endorsed feeling more negative financial and total impact than the other groups at all time points (p<.05), however a significant interaction of social support and total impact indicated that mothers of children with BPD above the 75th percentile in social support did not differ from mothers of VLBW or Term mothers.

3) By 14 years of age, mothers of children of VLBW without BPD showed a lower level of child-related stress, as measured by the Child Domain of the PSI, than either mothers of children with BPD or Term mothers ($\chi^2 = 5.1, df = 2,323, p < .02$).

4) While mothers of the three groups were not different in the type or extent of coping when their child was 3 years old, by 8 and 14 years of age, mothers of HR-VLBW children reduced their use of mental disengagement and denial, resulting in lower use compared to mothers of LR-VLBW and term children.

**V. DISCUSSION AND INTERPRETATION OF FINDINGS**

**A. Conclusions to be drawn from findings**

Results from the results of the analyses from Aim 1 indicate that development of children experiencing VLBW and BPD predisposes them to sustained cognitive problems through age 14. This is especially true for BPD children who experienced steroid treatment as part of their disease management. Impairment becomes more extensive with age and appears to stabilize between 8 and 14 years, with no improvement noted. Although school-based interventions may be helpful for addressing differences observed at 3 years, these cognitive differences become more pronounced at age 8 and persist at age 14.

Results from the analyses for Aim 2 above suggest that differences in receptive language appear to be rather stable over time, with children with BPD performing worse than their VLBW and Term peers. In addition, VLBW children with and without BPD did not catch up to their Term peers in receptive language skills by 14 years of age.

The findings from our analyses regarding maternal outcomes indicate that even mothers of VLBW children with BPD, despite their children’s high rate of disability and related parenting stress, demonstrate significant adaptation apparent in their satisfaction in parenting, and expressed feelings of mastery. This study indicates that their positive outcomes are related to a number of factors, including high levels of social support, higher educational attainment, lower use of avoidant coping strategies, and to their children’s better developmental outcomes.

**B. Explanation of study limitations**

The limitation of our study include: 1) our cohort of children with BPD were identified with criteria that differ slightly from current definition of BPD; 2) Fathers were not included in the study; 3) Maternal measures were restricted to self-report; and 4) There were lengthy intervals between follow up visits.

**C. Comparison with findings of other studies**

These studies confirm what previous, cross-sectional studies findings that VLBW, especially when combined with BPD puts children at risk for developmental delays. However, because of the size and design of the study
(longitudinal analysis, controlling for prenatal drug exposure, documentation of use of postnatal steroid use for treatment, documentation of neurologic risk, etc.), it delineates further the trajectory of development in children of VLBW with and without BPD when compared to their Term peers, and was able to examine other factors contributing to the differential outcomes in children.

In addition, it is the only study of its kind that examines the trajectory of maternal stress and coping throughout the child’s development. Our findings are consistent with studies of parents with children diagnosed with life threatening illnesses experienced post traumatic growth as well as stress and developed new perspectives and coping mechanisms in the face of traumatic life experiences. Post traumatic growth is a term that has been used to acknowledge the complexity of adjustment to traumatic stress which may lend to adaptive coping, in addition to the well-defined negative effects. Similarly, our findings support those of Saigal in which parents of 12-18 year old, extremely low birthweight children acknowledged negative effects and higher mental stress compared to parents of term children, but also felt greater self esteem and family satisfaction.

D. Possible application of findings to actual MCH health care delivery situations (including recommendations when appropriate)

These findings are important to clinicians and researchers as the lend further support to the need for asking about birth and neonatal events or illnesses specifically BPD, as these factors put children at higher risk for poor cognitive and language development.

Although, on the whole, mothers of VLBW children demonstrate significant resilience through their children’s early adolescence, mothers with low social supports, with avoidant coping styles, and those whose children have significant disabilities should continue to be monitored by health care and educational professionals. It will be important to educate providers about the role of coping mechanisms and social support in modifying stress.

E. Policy implications:

1) Children of VLBW, especially with BPD and high neurologic risk should be targeted early for early and sustained intervention, as they are at increased risk for developmental difficulties. Current reliance on school-based interventions (i.e., special education, speech therapy, occupational therapy and physical therapy) appears not to ameliorate the differences observed between high risk and typically achieving children. Wrap around services integrating school, home, and community services are necessary to address the problems encountered by medically fragile children. These services should begin early and remain in place throughout the school age period, with continual monitoring provided to ascertain where new services are need and old services can be eliminated.

2) Special attention needs to be given to receptive language deficits, as these often are not as apparent in young children and may be more severely affected in children with VLBW.

3) Funding toward research to prevent premature birth and complications associated with it such as BPD would lower societal, educational, and social burden.

F. Suggestions for further research

1) Research regarding the type, timing and intensity of therapies help to reduce the impact of VLBW and its complications such as BPD is important.

2) More research is needed into the best ways to support parents of VLBW children and help them develop adaptive coping mechanisms.

VI. LIST OF PRODUCTS

Peer reviewed articles


Presentations


Singer, L.T. Parenting Low Birthweight Children from Birth to Adolescence. Research and Policy lecture given at CWRU Shubert Center research lecture series, April 2009.


References:

35. Grunau RE, Whitfield MF, Fay TB. Psychosocial and academic characteristics of extremely low birth weight (< or =800 g) adolescents who are free of major impairment compared with term-born control subjects. *Pediatrics.* Dec 2004;114(6):e725-732.


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