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Outcome of Extremely Low Birth Weight Infants with Congenital Heart Defects in the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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Abstract

Little is known about the outcomes of extremely low birth weight (ELBW) preterm infants with congenital heart defects (CHDs). The aim of this study was to assess the mortality, morbidity, and early childhood outcomes of ELBW infants with isolated CHD compared with infants with no congenital defects. Participants were 401–1,000 g infants cared for at National Institute of Child Health and Human Development Neonatal Research Network centers between January 1, 1998 and December 31, 2005. Neonatal morbidities and 18–22 months' corrected age outcomes were assessed. Neurodevelopmental impairment (NDI) was defined as moderate to severe cerebral palsy, Bayley II mental or psychomotor developmental index < 70, bilateral blindness, or hearing impairment requiring aids. Poisson regression models were used to estimate relative risks for outcomes while adjusting for gestational age, small for gestational-age status, and other variables. Of 14,457 ELBW infants, 110 (0.8 %) had isolated CHD, and 13,887 (96 %) had no major birth defect. The most common CHD were septal defects, tetralogy of Fallot, pulmonary valve stenosis, and coarctation of the aorta. Infants with CHD experienced increased mortality (48 % compared with 35 % for infants with no birth defect) and poorer growth. Surprisingly, the adjusted risks of other short-term neonatal morbidities associated with prematurity were not significantly different.

Fifty-seven (52 %) infants with CHD survived to 18–22 months' corrected age, and 49 (86 %) infants completed follow-up. A higher proportion of surviving infants with CHD were impaired compared with those without birth defects (57 vs. 38 %, $p = 0.004$). Risk of death or NDI was greater for ELBW infants with CHD, although 20% of infants survived without NDI.

Keywords

heart defects; congenital; follow-up studies

Introduction

Congenital cardiac anomalies are among the most commonly reported birth defects, with an incidence of 5–8/1000 live births [1]. As many as one in six infants born with cardiac anomalies are born preterm [2], yet little is known about the long-term outcome of these infants, especially extremely low birth weight (ELBW) preterm infants. It is unknown if ELBW infants with major structural cardiac anomalies survive beyond their initial hospitalization and what factors are associated with increased morbidity and mortality. Surgical advances now permit repair and/or palliation even in this high-risk group; yet concerns regarding the quality of life and anticipated long-term outcomes may influence surgical decision making and treatment options. The aims of this study were to assess mortality, morbidity and 18–22 months' corrected age neurodevelopmental outcomes in a cohort of preterm infants 401–1000 g at birth, with and without congenital heart defects treated at the clinical centers of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network. We hypothesized (1) that preterm ELBW infants with congenital cardiac defects and no co-occurring non-cardiac defect or syndrome would have higher morbidity and mortality as compared to ELBW infants without congenital defects or syndromes and (2) that infants with more severe lesions would have poorer outcomes.

Methods

Infants weighing 401–1000 grams born between January 1, 1998 and December 31, 2005 and admitted to one of the clinical centers of the Neonatal Research Network within 14 days of birth were studied. All centers were performing complex neonatal cardiac surgery during the study period. Infants with isolated CHD were compared with infants having no defects. Infants with other major birth defects, including those with chromosomal anomalies sometimes co-occurring with cardiac defects (e.g., trisomy 21, VACTERL association) were excluded. The study was approved by the institutional review committee at each center, and the parents provided informed consent for prospective follow-up as required.

Trained research nurses entered maternal, perinatal, and infant data collected from birth to discharge, death, or 120 days into a registry maintained by the Network. Infants hospitalized beyond 120 days were followed to one year [3]. Neonatal information recorded included birth weight (BW), gestational age (GA), gender, race, mode of delivery, survival, and coded cause of death. Diagnoses during the initial hospital stay were recorded for infants surviving >12 h and included presence of a patent ductus arteriosus (PDA), infections, necrotizing enterocolitis (NEC), intracranial hemorrhage (ICH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD). Major birth defects were recorded using codes from a predefined list. Defects not specified in the list were recorded using codes for “other” defects in each area (e.g., “other congenital heart defects”) with specific information entered in text fields. For all infants, pre-defined cause of death included “congenital malformation” and “other” for which specific information also was provided in a text field.

Growth charts developed by Alexander [4] were used to classify infants as small for GA at birth (SGA), defined by a birth weight <10th percentile. NEC was defined as modified Bell's Stage IIA or greater [5]. Early onset (within 72 hours of birth) sepsis (EOS) and late onset (after 72 hours) sepsis (LOS) were defined by a positive blood culture and antibiotic therapy for ≥ 5 days. Intracranial hemorrhage and cystic periventricular leukomalacia were defined by cranial sonogram, with ICH grade from sonogram showing the most severe hemorrhage. Retinopathy of prematurity was defined by ophthalmologic examination. Bronchopulmonary dysplasia was defined as chronic lung disease requiring supplemental oxygen at 36 weeks postmenstrual age (PMA). Growth parameters at 36 weeks' PMA included measures of weight, length, and head circumference taken between 35 and 37 weeks' PMA.

Surviving infants were eligible for a comprehensive follow-up visit at 18–22 months' corrected age which included a caregiver interview, medical and social history, and measurement of growth parameters, neurologic examination and a developmental evaluation (using the Bayley Scales of Infant Development –IIR [6]) administered by certified examiners trained to reliability. CP was defined as a non-progressive disorder characterized by abnormal tone in at least one extremity and abnormal control of movement and posture. Scores were reported for the Bayley Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI), with a score of <70 (>2 standard deviations below the mean) indicating significantly delayed performance. Infants who were profoundly delayed and untestable were assigned MDI and PDI scores of 49. The child's vision and hearing status were determined by caregiver report, and results of testing (when available). Neurodevelopmental impairment (NDI) was defined as one or more of the following: MDI < 70, PDI < 70, moderate to severe cerebral palsy, bilateral blindness or hearing loss requiring amplification.

Statistical Analysis

Statistical significance for unadjusted comparisons between groups was determined by Fisher's exact or chi-square tests for categorical variables and by Student *t* tests for continuous variables. Kaplan-Meier survival curves were used to estimate median length of hospital stay (time from birth to discharge with deaths treated as censored observations) and time to death distributions with statistical significance between groups determined by the log rank test.

Poisson regression models with robust variance estimators [7] were used to compare risk of death, in-hospital morbidities, and neurodevelopmental outcomes at 18–22 months' corrected age between children with CHD and with no major birth defect while adjusting for variables known to affect these outcomes. Models used data from the entire cohort and included a birth defect group indicator (CHD, other birth defect, no major birth defect) to allow for pairwise comparisons between infants with CHD and no major birth defects. Adjusted relative risks, 95% confidence intervals, and Wald chi-square tests are reported based on parameter estimates and variance estimators from these models. P-values were not adjusted for multiple comparisons.

Results

Study Population

14,457 ELBW infants were born between January 1, 1998 and December 31, 2005. 110 (0.76%) ELBW infants were born with an isolated CHD, 460 (3.2%) had other types of major birth defects, and 13,887 (96%) had no major birth defect. The proportion of infants with a CHD ranged from 0.3% to 1.75% across the 19 study centers (1–16 infants per center). Among those not included in the CHD group were 44 infants with other noncardiac

congenital anomalies or syndromes that included a CHD (14 with chromosomal abnormalities, one with Goldenhar syndrome, and 29 with multiple defects).

Of the 110 ELBW infants with a CHD, the most common defects were ventricular septal defects [VSDs (18%)] and Tetralogy of Fallot [TOF (14%)] (Table 1). Infants with CHD were of later GA, weighed more, and had larger average head circumference at birth than infants with no major birth defect (Table 2). A greater proportion of infants with CHD were SGA compared to those with no birth defect (27% vs. 15%, $p=0.001$). Although the proportion of infants with 1-minute Apgar score 3 was similar in both groups, the proportion at 5 minutes was smaller in the CHD group (7% vs. 20%, $p=0.001$). Maternal education and medical insurance at admission were collected beginning in 2002. Among the subgroup of infants born 2002–2005, no differences were found.

Mortality and Survival

Of the 110 infants with CHD, 62 (56%) survived to discharge compared to 66% of infants with no major birth defect (Table 3). Respiratory support was withheld or withdrawn within the first 24 hours of life for 9 (8%) infants with CHD and 1,745 (13% infants without a birth defect ($p=0.19$). The proportion of infants for whom support was limited decreased with increasing GA (CHD vs. no birth defect: <25 weeks = 33 vs. 30%; 25–28 weeks = 2.8 vs. 2.6%; and 29+ weeks = 4.8 vs. 1.3%). Infants with CHD had over one and a half times the risk of death before discharge (adjusted RR: 1.73, 95% CI: 1.36–2.20). However, deaths occurred later for infants with CHD. In the first 12 hours after birth, 5% of infants with CHD died compared to 13% of infants without a birth defect (adjusted RR 0.60, 95% CI 0.26–1.35, $p=0.22$). Among those who died, median time of death was day 16 for infants with CHD and day 3 for infants with no major birth defect.

Cause of death was coded as congenital malformation for 32 (67%) of the 48 infants with CHD who died during the initial hospitalization, including nine infants who died within 24h. Respiratory support was withheld or withdrawn for eight of these nine infants. For the remaining infants, death was attributed to sepsis/infection and/or NEC in seven infants (15%); respiratory distress syndrome with other complications in three infants (6%); BPD with or without complications in two infants (4%); severe ICH with or without complications in two infants (4%); and “other” in two infants (4%). In contrast, among the 4698 infants with no birth defects who died before discharge, death was most frequently attributed to immaturity (37%), followed by RDS (25%), and sepsis and/or NEC (16%).

After neonatal intensive care unit (NICU) discharge and before 18–22 months’ corrected age, five infants with CHD died (5% of 110) and 171 of those with no major birth defect died (1% of 13887) (Table 3). Among the five infants with CHD who died, cause of death was coded congenital malformation for one infant with transposition of the great vessels, as sepsis/infection for one infant, “other” for one infant (specified as “cardiac”), and “unknown” for two infants.

The proportion of infants with CHD who survived to 18–22 months’ corrected age varied by type of CHD (Table 4). All ten infants with pulmonary valve stenosis (PVS) survived to discharge with nine infants (90%) surviving to 18–22 months’ corrected age. Both infants with partial anomalous pulmonary venous return survived to 18–22 months’ corrected age. The proportion surviving with an atrial or ventricular septal defect was over 80%. In contrast, 5 of 15 infants (33%) with TOF and 4 of 9 infants (44%) with coarctation of the aorta (CoA) survived. None of the nine infants with hypoplastic left heart syndrome (HLHS) nor the two infants with hypoplastic right heart syndrome (HRHS) survived to hospital discharge.

Morbidities

Of the 110 ELBW infants with CHD, 105 (95%) survived >12 hours compared with 12,034 (87%) without major birth defects. A greater proportion of those with CHD had a PDA, which may have been secondary to prostaglandin therapy. No differences were found in the rates of NEC, seizures, late-onset sepsis, severe ICH, PVL or ROP (Table 5). Thirty-four infants with CHD died before 36 weeks PMA, 65 remained hospitalized, one was discharged, and five were transferred. Among the 71 infants with CHD assessed, 58% had BPD compared to 50% of infants without birth defects ($p=0.2$). Infants with CHD compared with those without CHD weighed less at 36 weeks PMA (1648 g vs. 1824 g, $p=0.02$) and had smaller head circumference (29 cm vs. 30 cm, $p<0.001$). Median hospital stay was 104 days for infants with CHD (25th–75th p: 77–141 days) compared with 93 days (25th–75th p: 73–117 days) for infants with no birth defects ($p=0.01$ by the log rank test).

Characteristics and Outcomes of Children Followed-up

Survivors to 18–22 months' corrected age included 57 of 110 (52%) of infants with CHD and 9,018 of 13,887 (65%) of infants with no major birth defect. Among survivors, 86% in each group attended the follow-up assessment between September 1999 and December 2008. Of 49 infants with CHD evaluated, the most common heart defects were ventricular and atrial septal defects, PVS, and TOF --defects seen most frequently among all infants with CHD (Table 4). Together, infants with these defects comprised 71% of infants with CHD seen at follow-up and 51% of infants with CHD seen at birth.

CHD survivors were on average of later gestational age, and a higher proportion was SGA at birth compared to infants with no major birth defects who were assessed at follow-up (Table 6). Although the proportion of non-Hispanic black infants was similar in the two groups in the birth cohort, among those assessed at follow-up the proportion was higher among those with CHD than among those without birth defects (56% vs. 42%).

Risk of death before 18–22 months' corrected age or survival with NDI at 18–22 months' corrected age was greater for infants with CHD than those without CHD (80% vs. 63%; adjusted RR: 1.43, 95% CI: 1.29–1.58) (Table 7). Of those evaluated, 57% of survivors with CHD had NDI compared with 38% of infants with no defects ($p=0.004$). The percent of children with Bayley MDI score <70 was significantly higher among those with CHD (51% vs. 31%; adjusted RR: 1.61, 95% CI: 1.21–2.13, $p=0.001$) but not the percent with PDI <70 (33% vs. 21%, $p=0.1$). Moderate to severe CP was diagnosed in twelve percent of surviving infants with CHD compared with 7% having no birth defects ($p=0.1$). Risk of bilateral blindness was significantly higher for infants with CHD compared to infants without birth defects (6% vs. 0.8%; RR: 7.77, 95% CI: 2.52–23.93, $p=0.007$). None of the 48 survivors with CHD required hearing aids. Hypotonia was present in 6% of infants with CHD and in 5% of those without birth defects. Seven (14%) children with CHD were rehospitalized four or more times since the initial hospitalization compared with 7% of those without birth defects ($p=0.2$). Survivors with CHD showed poorer growth than those with no major birth defect.

Discussion

Of every 1000 infants in our ELBW series, 7.6 were diagnosed with CHD. Not surprisingly, these ELBW infants had a higher risk of death or neurodevelopmental impairment compared to infants with no structural anomaly or identifiable syndrome. For certain diagnoses such as Risk Adjustment in Congenital Heart Surgery-1 Category 1–2 lesions [8], both survival and 18–22 months' corrected age outcome were comparable to those of infants without birth defects. In contrast, the few infants with Category 4–6 lesions (infants who likely required

prostaglandin therapy and early palliative surgery) had 100% mortality or impairment. Although our series of ELBW infants is small, it provides more detailed follow-up data than any reported to date in this population. The finding that some ELBW infants with CHD survive without added morbidity is encouraging in view of the marked prematurity of this group. Even a low-risk lesion, such as a VSD, may present unique challenges for the management of an extremely preterm infant at risk for bronchopulmonary dysplasia, necrotizing enterocolitis, and intracranial hemorrhage or periventricular leukomalacia.

Limited information regarding the outcomes of VLBW and ELBW infants with CHD is available. Published studies focus primarily on select infants offered surgical intervention, with no information on excluded infants and no information on morbidities of concurrent control groups of ELBW infants with CHD. Using a prospectively collected population-based data base in Australia, Dimmick and colleagues reported on outcomes after surgery in infants with birth weight ≥ 2500 g [9]. A total of 121 LBW infants underwent cardiac surgeries; most (81%) underwent palliative procedures in the neonatal period. The two year mortality rate was 31%. Factors associated with mortality included BW <1500 g, low weight at surgery and low initial Apgar score. By two years-of-age, at least 33% of survivors were known to have neurodevelopmental delay and 41% were lost to follow-up. Kopf and Mello reported surgical outcomes for 32 low birth weight infants (1320–2500g) in Connecticut treated in a statewide cardiac surgery protocol [10]. Delay in surgery offered no survival benefit and increased costs. Other studies have reported a strong association between low birth weight, weight at time of surgical intervention and higher morbidity and mortality [11–12]. Sutton et al. reported on cardiac catheterization in infants weighing <1500 g in a 3:1 case-control study [13]. Many of their low birth weight infants were premature and had left-sided obstructive lesions. There were no significant differences in the rates of minor or major complications, blood transfusions or successful interventions between the LBW and control infants. There was a trend toward higher mortality in the LBW group. No data on longer term outcomes were reported.

Recently, Archer et al. reported on the distribution and mortality of VLBW infants with CHD *regardless* of surgical intervention [14]. They studied 99,786 infants with birth weights of 401–1500 g cared for in the NICUs of the Vermont Oxford Network. 893 neonates (GA 22–29 weeks) were found to have serious congenital heart disease (8.9 per 1000 as compared to 7.6 per 1000 in our $<1,000$ g cohort). The most common lesions were TOF, CoA and atrioventricular (AV) canal defects. Infants with septal defects were excluded. VSDs were the most common structural heart defect in our cohort and are the third most common indication for cardiothoracic surgery in VLBW infants [15]. Otherwise, the distribution of CHD was quite similar and interestingly, the percentage of premature infants with TOF again was higher than that reported among term infants [16]. Mortality rate before hospital discharge was 44%, identical to that in our birth cohort, and nearly double that reported among older preterm (<37 weeks) or low weight neonates [17–18]. No data on timing of deaths or longer term outcomes were provided.

In our study, infants with CHD died later than infants without confirmed birth defects. It is possible that some non-CHD infants may have had undiagnosed anomalies. In addition, infants with CHD had poorer head and somatic growth and longer hospital stays, both of which are associated with poorer neurodevelopmental outcomes. Fifty-seven percent of children with CHD had NDI, and 12% had moderate-severe CP. Interestingly, 6% had hypotonia and only 31% had significant psychomotor delay (PDI <70), both of which are seen in term CHD patients. In term infants, the neurodevelopmental sequelae are diverse [19, 20]. In a recent cohort study with exclusion criteria similar to ours (i.e., excluding infants with expected developmental sequelae and syndromes), 42% of infants with CHD exhibited gross and fine motor delays (>1.5 SD below the mean), 25% exhibited global

delays and 41% exhibited abnormalities on neurological examination at 21 months' mean follow-up [21].

Limitations

Long-term follow-up may assist clinicians in planning interventions and support services and selecting treatment strategies that optimize disability-free survival. Despite carefully planned follow-up, our study has a number of limitations. First, our birth cohort is not population based. Secondly, we have no normal birth weight population for comparison, so we can only speculate on the contribution of preterm morbidities on the neurodevelopmental sequelae of our cohort. Third, congenital heart defects are rare; thus we had many fewer cases than controls. We elected to analyze all existing Neonatal Research Network (NRN) data while adjusting for all known and available confounders as opposed to performing a matched case control study. Fourth, we have no information on the intensive care and surgical management of the ELBW infants in our cohort because these data are not included in the NRN database (e.g., medications used; surgical procedures, including palliative or corrective approach; timing of interventions; and perioperative complications). Curzon et al. presented data on surgical outcomes of LBW infants compared to normal birth weight infants with CHD based on data from the Society of Thoracic Surgeons Congenital Heart Surgery Database, and they showed that outcomes varied by type of procedure [11]. The relative risk (RR) of mortality ranged from 2.7 to 5.4 for infants weighing 1–2.5 versus 2.5–4 kg at the time of surgical intervention. Surgical outcome data are important to the planning of care for preterm and LBW infants.

Preterm infants with CHD pose multiple diagnostic and therapeutic challenges in view of their small size and immaturity. Moreover, in view of the rarity of their condition and the heterogeneity of associated cardiac and noncardiac comorbidities, they present unique ethical and decision-management dilemmas (including deliberate therapeutic abstention in some cases). With the continued advancement of prenatal screening techniques and critical and surgical care management, the opportunity for focused cardiac interventions continues to expand. As these therapeutic techniques evolve (e.g., hybrid approaches [22–23], in utero valvuloplasty or atrial septostomy for HLHS or HRHS [24–30], larger numbers of premature neonates with CHD may survive. Beyond survival and short-term management options, comorbidities and long-term neurodevelopmental outcomes must be evaluated. This study sets the stage for detailed assessment of follow-up outcomes for these high-risk neonates.

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Appendix

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Ms. Nellie I. Hansen (DCC Statistician) had full access to all the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis.

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Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD; Bill Cashore, MD; Regina A. Gargus, MD FAAP; James R. Moore, MD; Bonnie E. Stephens, MD; Rachel V. Walden, MD Barbara Alksnis, PNP; Angelita M. Hensman, RN BSN; Dawn Andrews, RN MS; Kristin Angela, RN; Shabnam Lainwala, MD; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Lucy Noel; Victoria E. Watson, MS CAS.

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Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Kurt Schibler, MD; Edward F. Donovan, MD; Kate Bridges, MD; Jean J. Steichen, MD; Kimberly Yolton, PhD; Barbara Alexander, RN;

Teresa L. Gratton, PA; Cathy Grisby, BSN CCRC; Jody Hessling, RN; Holly L. Mincey, RN BSN; Marcia Worley Mersmann, RN CCRC.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; Ricki F. Goldstein, MD; Kathy J. Auten, MSHS; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, UL1 RR25008, M01 RR39) – Lucky Jain, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Ellen C. Hale, RN BS CCRC; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Linda L. Wright, MD; Elizabeth M. McClure, MEd.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Anna M. Dusick, MD FAAP; Diana D. Appel, RN BSN; Lon G. Bohnke, MS; Marilyn Bull, MD; Ann B. Cook, MS; Greg Eaken, PhD; Dianne E. Herron, RN; Darlene Kardatzke, MD; Carolyn Lytle, MD MPH; Lucy C. Miller, RN BSN CCRC; Heike M. Minnich, PsyD HSPP; Leslie Richard, RN; Leslie Dawn Wilson, BSN CCRC.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Betty K. Hastings; Elizabeth M. McClure, MEd; Jamie E. Newman, PhD MPH; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; Scott E. Schaefer, MS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University, California Pacific Medical Center, El Camino Hospital, and Lucile Packard Children's Hospital (U10 HD27880, M01 RR70) – David K. Stevenson, MD; Marian M. Adams, MD; Charles E. Ahlfors, MD; Barry E. Fleisher, MD; Susan R. Hintz, MD MS; M. Bethany Ball, BS CCRC; Joan M. Baran, PhD; Barbara Bentley, PhD; Lori E. Bond, PhD; Ginger K. Brudos, PhD; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN PNP; Jan T. Epcar, MA; Monica Hajdena-Dawson, MD; Jean G. Kohn, MD MPH; Carol G. Kuelper, PhD; Julie C. Lee-Ancas, PhD; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Robert D. Stebbins, MD.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Monica V. Collins, RN BSN MaEd; Stephanie A. Chopko, PhD; Shirley S. Cosby, RN BSN; Mary Beth Moses, PT MS PCS; Kathleen G. Nelson, MD; Myriam Peralta-Carcelen, MD MPH; Vivien A. Phillips, RN BSN; Julie Preskitt, MSOT MPH; Richard V. Rector, PhD; Sally Whitley, MA OTR-L FAOTA.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD; Paul R. Wozniak, MD; Maynard R. Rasmussen, MD; Yvonne E. Vaucher, MD MPH; Martha G. Fuller, RN MSN; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Chris Henderson, RCP CRTT; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Wade Rich, BSHS RRT; Cheryl Runyan; James Wilkes.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Charles R. Bauer, MD; Shahnaz Duara, MD; Maria Calejo, RN; Alexis N. Diaz, BA; Ruth Everett-

Thomas, RN MSN; Silvia M. Frade Eguaras, MA; Yamiley C. Gideon, BA; Sylvia Hiriart-Fajardo, MD; Amy Mur Worth, RN MS; Alexandra Stroerger.

University of New Mexico Health Sciences Center (U10 HD27881, M01 RR997) – Lu-Ann Papile, MD; Conra Backstrom Lacy, RN; Ginny Laadt, PhD OTR; Debra V. Long, BSN; Jean Lowe, PhD; Rebecca Montman, RN.

University of Rochester, Golisano Children's Hospital at Strong (U10 HD40521, M01 RR44, UL1 RR24160) – Dale L. Phelps, MD; Gary J. Myers, MD; Linda J. Reubens, RN CCRC; Julie Babish Johnson, MSW; Erica Burnell, RN; Diane Hust, MS RN CS; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Mary Rowan, RN; Kelley Yost, PhD; Lauren Zwetsch, PNP.

University of Tennessee (U10 HD21415) – Sheldon B. Korones, MD; Henrietta S. Bada, MD; Tina Hudson, RN BSN; Marilyn Williams, LCSW; Kimberly Yolton, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; R. Sue Broyles, MD; Roy J. Heyne, MD; Sally S. Adams, MS RN CPNP; Cristin Dooley, PhD LSS; Alicia Guzman; Gaynelle Hensley, RN; Jackie F. Hickman, RN; Elizabeth Heyne, PsyD PA-C; Christine Lupino, MS; Linda A. Madden, RN CPNP; Susie Madison, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Catherine Twell Boatman, MS CIMI.

University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital, and Lyndon Baines Johnson General Hospital/Harris County Hospital District (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Patricia W. Evans, MD; Margarita Jiminez, MD MPH; Brenda H. Morris, MD; Saba Siddiki, MD; Esther G. Akpa, RN BSN; Nora I. Alaniz, BS; Susan Dieterich, PhD; Anna E. Lis, RN BSN; Georgia E. McDavid, RN; Margaret L. Poundstone, RN BSN; Maegan C. Simmons, RN; Patti Pierce Tate, RCP; Stacey Reddoch, BA; Sharon L. Wright, MT (ASCP).

Wake Forest University, Baptist Medical Center, Forsyth Medical Center, and Brenner Children's Hospital (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Cherrie D. Welch, MD MPH; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Barbara G. Jackson, RN BSN; Nancy J. Peters, RN CCRP; Carroll Peterson, MA; Ellen L. Waldrep, MS; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Virginia Delaney-Black, MD MPH; Yvette R. Johnson, MD MPH;; Geraldine Muran, RN BSN; Deborah Kennedy, RN BSN; Debra Driscoll, RN BSN; Laura A. Goldston, MA.

Yale University, Yale-New Haven Children's Hospital (U10 HD27871, UL1 RR24139, M01 RR125, M01 RR6022) – Richard A. Ehrenkranz, MD; Patricia Gettner, RN; Monica Konstantino, RN BSN; Linda Mayes, MD; JoAnn Poulsen, RN; Elaine Romano, MSN; Janet Taft, RN BSN; Joanne Williams, RN BSN.

Table 1

Type and frequency of congenital heart defects (CHD)

Type	No.	%
Ventricular septal defect	20	18.2
Tetralogy of Fallot +/- pulmonary atresia	15	13.6
Atrial septal defect	11	10.0
Pulmonary valve stenosis	10	9.1
Coarctation of aorta	9	8.2
Hypoplastic left heart syndrome	9	8.2
Pulmonary atresia	6	5.5
Transposition of great vessels	5	4.5
Double outlet right ventricle	5	4.5
Complete atrioventricular canal ^{1/}	3	2.7
Total anomalous pulmonary venous return	3	2.7
Partial anomalous pulmonary venous return	2	1.8
Hypoplastic right heart syndrome	2	1.8
Truncus arteriosus	1	0.9
Single ventricle	1	0.9
Tricuspid atresia	1	0.9
Interrupted aortic arch	0	0
Other cardiovascular anomalies ^{2/}	7	6.4
Total	110	100.00

^{1/} Includes 1 infant with complete AV canal and Tetralogy of Fallot.

^{2/} Includes large aortopulmonary collaterals ($n=1$), hypoplastic pulmonary arteries ($n=1$), right coronary artery originating from left cusp ($n=1$), anomalous left coronary artery ($n=1$), hypoplastic aortic arch ($n=1$), univentricular heart with common AV valve, total anomalous venous return and pulmonic stenosis ($n=1$), and multiple cardiac anomalies [partial anomalous pulmonary venous return to the superior vena cava, left pulmonary stenosis, secundum ASD, and anomalous coronary artery ($n=1$)].

Table 2

Maternal and neonatal characteristics

Characteristic ^{1/}	Group		P-value ^{3/}
	CHD ^{2/} N=110	No Birth Defect N=13887	
Maternal age (years)			
Mean (SD)	27 (6.5)	27 (6.7)	0.7
< 25	46 (42)	5694 (41)	
25–29	30 (27)	3269 (24)	
30–34	16 (15)	2869 (21)	
35–39	14 (13)	1641 (12)	
40+	4 (4)	403 (3)	
Mother married, n (%)	41 (38)	6302 (46)	0.1
Antenatal steroids, n (%)	80 (74)	9908 (72)	0.7
Cesarean section delivery, n (%)	76 (69)	7833 (56)	0.01
Multiple birth, n (%)	29 (26)	3281 (24)	0.5
Outborn, n (%)	17 (15)	1629 (12)	0.2
Birth weight (grams)			
Mean (SD)	768 (160)	733 (159)	0.02
401–750	48 (44)	7403 (53)	
751–1000	62 (56)	6484 (47)	
Gestational age (weeks)			
Mean (SD)	27 (2.5)	25 (2.2)	<0.001
< 25	18 (16)	5020 (36)	
25–28	71 (65)	7658 (55)	
29+	21 (19)	1206 (9)	
SGA, n (%)	30 (27)	2125 (15)	0.001
Head circumference (cm), mean (SD)	24 (2.0)	23 (1.8)	0.004
Length (cm), mean (SD)	33 (2.8)	33 (2.8)	0.5
Male, n (%)	55 (50)	7027 (51)	0.9
Race/ethnicity, n (%)			
Non-Hispanic black	47 (44)	5834 (42)	0.6
Non-Hispanic white	35 (32)	5209 (38)	
Hispanic	20 (19)	2275 (16)	
Other	6 (6)	535 (4)	
Apgar at 1 minute ³	43 (40)	6283 (46)	0.2

Characteristic ^{1/}	Group		P-value ^{3/}
	CHD ^{2/} N=110	No Birth Defect N=13887	
Apgar at 5 minutes ³	8 (7)	2681 (20)	0.001
Infants born 2002–2005	N=64	N=7279	
Mother had high school degree at admission, n (%) ^{4/}	32/47 (68)	3608/5238 (69)	0.9
Mother's medical insurance at admission, n (%) ^{4/}			
Medicaid/public	35/63 (56)	3490/7043 (50)	0.7
Private	23/63 (37)	2741/7043 (39)	
Both private and public	0/63 (0)	72/7043 (1)	
Self-pay/uninsured	5/63 (8)	740/7043 (11)	

^{1/} Information was missing for maternal age: 11 infants; mother's marital status: 191; antenatal steroids: 50; c-section delivery: 21; multiple birth: 1; gestational age: 3; SGA: 11; head circumference: 1548; length: 1363; race/ethnicity: 36; Apgar at 1 minute: 264; Apgar at 5 minutes: 266; mother's education at admission: 2058 of 7343 infants born 2002–2005; mother's medical insurance: 237 of 7343 infants. The majority of infants with missing information were in the No Birth Defect group.

^{2/} Infants included in this group had CHD without non-cardiac anomalies.

^{3/} P-value for a difference between groups by the t-test (for continuous variables), Fisher's exact test, or the chi-square test of general association.

^{4/} Maternal education and medical insurance at admission were not collected until 2002.

Table 3

Mortality for ELBW infants with congenital heart defects (CHD) compared to infants with no major birth defect

	Group	
	CHD N=13887	No Birth Defect N=110
Birth hospitalization		
Survived to discharge, n (%)	62 (56)	9189 (66)
Died before discharge, n (%)	48 (44)	4698 (34)
Adjusted relative risk for death, CHD vs. No Birth defect (95% CI) ^{1/}	1.73 (1.36–2.20)	1.0
Died before discharge by time of death, n (%) ^{2/}		
<=12 hrs	5 (5)	1853 (13)
>12–24 hrs	4 (4)	204 (1)
>1–3 days	3 (3)	576 (4)
4–7 days	7 (6)	359 (3)
8–14 days	4 (4)	420 (3)
15–28 days	9 (8)	500 (4)
29+ days	16 (15)	785 (6)
Died after discharge and before 18–22 mo. corrected age, n (%) ^{2/}	5 (5)	171 (1)
Total deaths between birth and 18–22 mo. corrected age, n (%) ^{2/}	53 (48)	4869 (35)
Adjusted relative risk for death, CHD vs. No Birth defect (95% CI) ^{1/}	1.81 (1.46–2.24)	1.0

^{1/} CI = confidence interval. Relative risk, CI, and p-value by the Wald chi-square test from a modified Poisson regression model that included study center, gestational age (<23, 23–24, 25–28, 29–32, 33+), SGA, male sex, race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), and birth defect group (CHD, other birth defect, no birth defect).

^{2/} Percents are among all infants including survivors. Timing of death was missing for 1 infant with no major birth defect. Among survivors to discharge, the percent who died after initial discharge were CHD: 8%, no birth defect: 2%.

Table 4

Type of congenital heart defect (CHD) and survival among infants with isolated CHD

Type (RACHS-1 Category) ^{1/}	Total N	N died 12 h	N (%) survivors > 12 h ^{2/}	Total died before initial discharge	N (%) survivors to discharge ^{2/}	Died after initial discharge	N (%) survivors to 18–22 mo ^{2/}	N (%) 18–22 mo survivors with follow-up
Tetralogy of Fallot +/- pulmonary atresia (2–3)	15	0	15 (100)	8	7 (47)	2	5 (33)	5/5 (100)
Transposition of great vessels (3–4)	5	1	4 (80)	2	3 (60)	2	1 (20)	1/1 (100)
Pulmonary atresia (3–4)	6	0	6 (100)	4	2 (33)	0	2 (33)	2/2 (100)
Truncus arteriosus (4)	1	0	1 (100)	1	0 (0)	-	0 (0)	-
Total anomalous pulmonary venous return (4)	3	0	3 (100)	2	1 (33)	0	1 (33)	0/1 (0)
Partial anomalous pulmonary venous return (1)	2	0	2 (100)	0	2 (100)	0	2 (100)	2/2 (100)
Hypoplastic left heart syndrome (6)	9	2	7 (78)	9	0 (0)	-	0 (0)	-
Hypoplastic right heart syndrome (3–6)	2	0	2 (100)	2	0 (0)	-	0 (0)	-
Coarctation of aorta (2)	9	0	9 (100)	5	4 (44)	0	4 (44)	2/4 (50)
Complete atrioventricular canal ^{3/} (3)	3	0	3 (100)	2	1 (33)	0	1 (33)	1/1 (100)
Single ventricle (3–6)	1	1	0 (0)	1	0 (0)	-	0 (0)	-
Double outlet right ventricle (3)	5	0	5 (100)	3	2 (40)	0	2 (40)	2/2 (100)
Tricuspid atresia (4)	1	0	1 (100)	1	0 (0)	-	0 (0)	-
Atrial septal defect (1–2)	11	0	11 (100)	2	9 (82)	0	9 (82)	9/9 (100)
Ventricular septal defect (2)	20	0	20 (100)	3	17 (85)	0	17 (85)	14/17 (82)
Pulmonary valve stenosis (2)	10	0	10 (100)	0	10 (100)	1	9 (90)	7/9 (78)
Other cardiovascular anomalies ^{4/}	7	1	6 (86)	3	4 (57)	0	4 (57)	4/4 (100)
Total	110	5	105 (95)	48	62 (56)	5	57 (52)	49/57 (86)

^{1/} Risk Adjustment in Congenital Heart Surgery (RACHS)-1 Category [8]

^{2/} Percents are among total number of infants with each CHD. Number of survivors to 18–22 months includes children lost to follow-up but presumed alive.

^{3/} Includes 1 infant with complete AV canal and Tetralogy of Fallot.

^{4/} Includes large aortopulmonary collaterals ($n=1$), hypoplastic pulmonary arteries ($n=1$), right coronary artery originating from left cusp ($n=1$), anomalous left coronary artery ($n=1$), hypoplastic aortic arch ($n=1$), univentricular heart with common AV valve, total anomalous venous return and pulmonic stenosis ($n=1$), and multiple cardiac anomalies [partial anomalous pulmonary venous return to the superior vena cava, left pulmonary stenosis, secundum ASD, anomalous coronary artery ($n=1$)]

Table 5

In-hospital diagnoses and morbidities

Outcome ^{1/}	Group		Adjusted Relative Risk CHD vs. No Birth Defect (95% CI) ^{2/}	Adjusted P-value ^{2/}
	CHD	No Birth Defect		
Infants who survived > 12 h	N=105	N=12034		
PDA, n (%)	65 (62)	5481 (46)	1.52 (1.30–1.78)	<0.001
NEC, n (%)	13 (12)	1271 (11)	1.23 (0.73–2.04)	0.4
Seizures, n (%)	9 (9)	1183 (10)	0.99 (0.54–1.81)	0.9
Infants who survived > 3 days	N=98	N=11253		
Late-onset sepsis, n (%)	42 (43)	4422 (39)	1.18 (0.95–1.46)	0.1
Infants who had a cranial sonogram w/in 28 days	N=99	N=11594		
Severe ICH, n (%) ^{3/}	14 (14)	2087 (18)	0.96 (0.60–1.56)	0.9
Infants who had a cranial sonogram w/in 28 days or after 28 days ^{4/}	N=99	N=11628		
PVL, n (%)	5 (5)	612 (5)	1.02 (0.43–2.41)	0.9
Severe ICH or PVL, n (%)	18 (18)	2331 (20)	1.07 (0.71–1.62)	0.7
Infants still in the hospital at 28 days who had a ROP exam	N=69	N=9206		
ROP, n (%)	47 (68)	6395 (69)	1.08 (0.94–1.24)	0.3
ROP stage 3 or higher, n (%)	14 (20)	1969 (21)	1.11 (0.72–1.69)	0.6
Infants alive at 36 w PMA	N=71	N=9503		
BPD, n (%) ^{5/}	41 (58)	4716 (50)	1.15 (0.94–1.41)	0.2
Infants with growth measurements at 36 w PMA,				
Mean (SD) ^{6/}	N=68	N=8794		
Weight (g)	1648 (479)	1824 (389)	NA	0.02
Length (cm)	40 (3.9)	41 (2.9)	NA	0.3
Head circumference (cm)	29 (2.4)	30 (1.8)	NA	<0.001

^{1/} PDA=patent ductus arteriosus; NEC=necrotizing enterocolitis; ICH=intracranial hemorrhage; PVL=periventricular leukomalacia; ROP=retinopathy of prematurity; BPD=bronchopulmonary dysplasia; SD= standard deviation; NA=not applicable.

Information was missing for infants in the groups shown for PDA: 10 infants; NEC: 2; seizures: 2; Late-onset sepsis: 7; ICH: 7; PVL: 5; ICH/PVL: 40; ROP: 1; ROP stage 3+: 9; BPD: 6 infants. The majority of infants with missing information were in the No Birth Defect group.

^{2/} CI = confidence interval. Relative risks, CIs, and p-values for categorical outcomes from a modified Poisson regression model fit to each outcome that utilized data from the entire cohort and included study center, gestational age (<23, 23–24, 25–28, 29–32, 33+), SGA, male sex, and birth defect group (CHD, other birth defect, no birth defect). P-values are by the Wald chi-square test and indicate whether risk differs between the groups (relative risk different from 1.0). Adjusted p-value for continuous outcomes (weight, length, head circumference at 36 w PMA) were by the t-test from a linear regression model that included study center, gestational age, SGA, male sex, and birth defect group.

^{3/} Severe ICH was defined as grade 3 or 4.

^{4/} PVL was determined based on a sonogram taken within 28 days of birth and/or a sonogram taken after 28 days and closest to 36 weeks PMA. Severe ICH/PVL outcome percents were based on infants with non-missing ICH and PVL outcomes, except that a diagnosis of either condition was sufficient to set the outcome to yes.

^{5/} BPD was defined as supplemental oxygen use at 36 weeks PMA. 85% of surviving infants were still in the hospital at 36 w PMA. BPD was defined based on oxygen use at discharge or transfer for the remainder, unless status at 36 w was known.

^{6/}Ns shown are infants who have at least one 36 w measurement. In this group of infants, information was missing for weight: 12 infants; length: 970, head circumference: 366.

Table 6

Maternal and neonatal characteristics for children evaluated at 18–22 months' corrected age

Characteristic ^{1/}	Group		P-value ^{2/}
	CHD N=49	No Birth Defect N=7778	
Maternal age at delivery (years)			
Mean (SD)	28 (7.2)	27 (6.7)	0.7
< 25	21 (43)	3003 (39)	
25–29	10 (20)	1866 (24)	
30–34	8 (16)	1695 (22)	
35–39	7 (14)	965 (12)	
40+	3 (6)	248 (3)	
Antenatal steroids, n (%)	38 (79)	6342 (82)	0.6
Cesarean section delivery, n (%)	34 (69)	5037 (65)	0.6
Multiple birth, n (%)	9 (18)	1772 (23)	0.6
Birth weight (grams)			
Mean (SD)	797 (162)	789 (136)	0.7
401–750	16 (33)	3028 (39)	
751–1000	33 (67)	4750 (61)	
Gestational age (weeks)			
Mean (SD)	27 (2.5)	26 (2.0)	0.001
< 25	6 (12)	1572 (20)	
25–28	31 (63)	5310 (68)	
29+	12 (24)	894 (11)	
SGA, n (%)	16 (33)	1291 (17)	0.006
Male, n (%)	23 (47)	3645 (47)	1.0
Race/ethnicity, n (%)			
Non-Hispanic black	27 (56)	3263 (42)	0.007
Non-Hispanic white	10 (21)	2952 (38)	
Hispanic	6 (13)	1266 (16)	
Other	5 (10)	292 (4)	
Apgar at 1 minute ≤ 3	16 (33)	2641 (34)	0.9
Apgar at 5 minutes ≤ 3	1 (2)	573 (7)	0.3
Mother was primary caretaker at follow-up, n (%)	40 (82)	7124 (92)	0.02
Primary caretaker was married, n (%)	22 (46)	4291 (56)	0.2
Primary caretaker had high school degree at follow-up, n (%)	38 (79)	5901 (77)	0.9

Characteristic ^{1/}	Group		P-value ^{2/}
	CHD N=49	No Birth Defect N=7778	
Child's medical insurance at follow-up, n (%)			
Medicaid/public	35 (71)	4668 (60)	0.3
Private	13 (27)	2405 (31)	
Both private and public	1 (2)	480 (6)	
Self-pay/uninsured	0 (0)	170 (2)	

^{1/} Information was missing for maternal age: 1 infant; antenatal steroids: 24; c-section delivery: 9; gestational age: 2; SGA: 2; race/ethnicity: 6; Apgar at 1 minute: 84; Apgar at 5 minutes: 83; primary caregiver at follow-up: 34; primary caregiver marital status: 56; mother's education at follow-up: 371; primary caregiver's education at follow-up: 101; child's insurance: 55. The majority of infants with missing information were in the No Birth Defect group.

^{2/} P-value for a difference between groups by the t-test (for continuous variables), Fisher's exact test, or the chi-square test of general association.

Table 7

Outcomes at 18–22 months' corrected age

Outcome ^{1/}	Group		Adjusted Relative Risk CHD vs. No Birth Defect (95% CI) ^{2/}	Adjusted P-value ^{2/}
	CHD	No Birth Defect		
Infants who died before follow-up or survived and were evaluated at follow-up	N=102	N=12647		
Death or NDI, n (%)	79/99 (80)	7583/12024 (63)	1.43 (1.29–1.58)	<0.001
Infants who survived to follow-up	N=49	N=7778		
NDI, n (%)	26/46 (57)	2714/7155 (38)	1.45 (1.13–1.87)	0.004
MDI score < 70, n (%)	23/45 (51)	2253/7181 (31)	1.61 (1.21–2.13)	0.001
PDI score < 70, n (%)	15/45 (33)	1520/7119 (21)	1.44 (0.93–2.21)	0.1
Moderate to severe CP, n (%)	6/49 (12)	515/7745 (7)	1.86 (0.89–3.87)	0.1
Bilateral blindness (< 20/200), n (%)	3/49 (6)	61/7744 (<1)	7.77 (2.52–23.93)	0.007
Hearing loss requiring amplification bilaterally, n (%)	0/48 (0)	150/7713 (2)	NA	1.0
4 re-hospitalizations since initial discharge, n (%)	7/49 (14)	532/7740 (7)	1.64 (0.83–3.25)	0.2
Mean (SD) growth measurements				
Weight (kg)	9.83 (1.25)	10.46 (1.60)	NA	0.3
Recumbent length (cm)	79 (4.4)	81 (4.3)	NA	0.04
Head circumference (cm)	46 (2.2)	47 (1.9)	NA	<0.001

^{1/} NDI=neurodevelopmental impairment; MDI=Bayley Scales of Infant Development (BSID-II) Mental Development Index; PDI=BSID-II Psychomotor Development Index; CP=cerebral palsy. NDI could not be determined for 626 children who survived and attended the follow-up visit. Information was missing for infants in the groups shown for MDI: 601 infants; PDI: 663; cerebral palsy: 33; blindness: 34; hearing loss: 66; re-hospitalizations: 38. The majority of infants with missing information were in the No Birth Defect group.

^{2/} CI = confidence interval. Relative risk for blindness and p-values for blindness and hearing loss were unadjusted due to small sample sizes. For the other outcomes, adjusted relative risks, CIs, and p-values were from a modified Poisson regression model that utilized data from the entire cohort. The model fit to the death or NDI composite outcome included study center, gestational age (<23, 23–24, 25–28, 29–32, 33+), SGA, male sex, and birth defect group (CHD, other birth defect, no birth defect). Models fit to NDI, MDI, PDI, and CP included these variables as well as severe ICH, PVL, BPD, mother's education at follow-up (high school degree or more, < high school degree, unknown), and child's medical insurance at follow-up (public, private, public and private, self-pay/uninsured). Adjusted p-values for growth measures were determined by Student *t* test from a linear regression model that included the covariates listed.