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Survival and Morbidity Outcomes of Very Low Birth Weight Infants with Down Syndrome

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Abstract

OBJECTIVE—Individuals with Down syndrome (DS) are at increased risk of several morbidities with lifelong health consequences. Little is known about mortality or morbidity risks in early infancy among very-low-birth-weight (VLBW) infants with DS. Our objective was to compare survival and neonatal morbidities between VLBW infants with DS and VLBW infants with other non-DS chromosomal anomalies, other non-chromosomal birth defects, and VLBW infants without major birth defects.

METHODS—Data were collected prospectively for infants weighing 401-1500 grams born and/or cared for at one of the study centers participating in the NICHD Neonatal Research Network from 1994 through 2008. Risk of death and morbidities including patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), late onset sepsis (LOS), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD), were compared between VLBW infants with DS and infants in the other groups.

RESULTS—Infants with DS were at increased risk of death (adjusted relative risk [RR] 2.47, 95% confidence interval [CI] 2.00-3.07), PDA, NEC, LOS, and BPD relative to infants with no birth defects. Decreased risk of death (RR 0.40, 95% CI 0.31-0.52) and increased risks of NEC and LOS were observed when comparing infants with DS to infants with other non-DS chromosomal anomalies. Relative to infants with non-chromosomal birth defects, infants with DS were at increased risk of PDA and NEC.

CONCLUSION—The increased risk of morbidities among VLBW infants with DS provides useful information for counseling parents and for caretakers in anticipating the need for enhanced surveillance for prevention of these morbidities.

Keywords

neonatal mortality; neonatal morbidity; preterm infants; Down syndrome; trisomy 21

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INTRODUCTION

Down syndrome (DS) is the most frequent chromosomal disorder in live-born infants, occurring in approximately 1 of 732 infants in the United States.[1] DS patients are at increased risk for several medical morbidities including cardiac and gastrointestinal abnormalities, gonadal deficiency, certain leukemias, immune and endocrine system defects, and early Alzheimer's disease.[2,3] Other morbidities including angiogenesis-dependent diseases such as solid tumors, diabetic retinopathy, atherosclerosis, and vascular anomalies, show a decreased incidence among DS patients compared to the general population.[4-11] Most available information is based on data from term or near-term infants with DS. Little information is available about morbidities occurring in early infancy among very-low-birth-weight (VLBW) infants with DS.

The increased gene dosage due to the additional copy of chromosome 21 might confer either protective or harmful effects on DS infants. Investigating the neonatal morbidities affecting VLBW DS infants might provide new insights into potential mechanisms of disease in DS and might ultimately lead to improved preventive or therapeutic interventions. In addition, this knowledge may help families and health-care providers anticipate the needs of DS infants for preventive and therapeutic health care.

We used data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) to examine survival and neonatal morbidities among VLBW DS infants compared to VLBW infants with other non-DS chromosomal anomalies, other non-chromosomal birth defects, and no major birth defects.

METHODS

Infants with birth weight 401-1500 grams born between January 1, 1994 and December 31, 2008 and cared for in NRN hospitals were studied. Twenty-two clinical centers participated during all (9) or some (13) of the years of enrollment. Trained research nurses entered maternal demographic, pregnancy and delivery information, and infant data collected from birth to hospital discharge, death, or 120 days into a registry of VLBW infants maintained by the Network. All VLBW infants born 1994-2007 who were admitted to a neonatal intensive care unit affiliated with the NRN before 14 days of age (inborn and outborn) were included in the registry. Eligibility criteria changed in January 2008 to inborn infants with birth weight 401-1000 grams or gestational age 22 to 28 weeks or infants enrolled in another NRN study. The registry was approved by the institutional review board at each center.

Neonatal information included birth weight (BW), gestational age (GA), sex, race, mode of delivery, survival or death, and cause of death. Small for gestational age (SGA) was defined as BW below the 10th centile.[12] Neonatal morbidities diagnosed during the hospital stay were recorded for all infants surviving >12 hours and included patent ductus arteriosus (PDA), Bell's stage ≥2 necrotizing enterocolitis (NEC),[13] bacterial or fungal sepsis, severe IVH (grade 3 or 4), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD). Late-onset sepsis (LOS) was defined by positive blood culture obtained after 72 hours of age and intent to treat with antibiotics for ≥5 days. ROP was defined by examination for infants still hospitalized at 28 days. BPD was defined as need for supplemental oxygen at 36 weeks postmenstrual age (PMA). Weight, length, and head circumference were measured at 36±1 weeks PMA.

Infants with a major birth defect were classified into one of the following groups: Down syndrome, non-DS chromosomal anomalies (CA), and other major birth defects (BD) but no chromosomal anomaly (defined in footnotes for Table 1).

Data Analysis

Infant characteristics and outcomes were compared between infants with DS and infants with non-DS CA, other BD, and no major birth defect. Statistical significance for unadjusted comparisons between groups was determined by Pearson chi-square or Student's t tests. Poisson regression models with robust variance estimators[14] were used to assess risk factors for DS, to examine the risk of death and morbidities for DS infants compared to infants in the other groups, and to assess risk factors for death among infants with DS, adjusting for baseline covariates associated with morbidity and mortality. Models examining outcomes of DS infants compared to others included a BD group indicator (DS, non-DS CA, other BD, no major BD) to allow for pairwise contrasts between DS infants and infants in each of the other groups. Covariates included are noted in table footnotes. Adjusted relative risks and 95% confidence intervals from these models were calculated. P-values were not adjusted for multiple comparisons. Analyses were conducted using SAS software.[15]

Primary morbidities examined were PDA, NEC, LOS, severe IVH and/or PVL, ROP of any stage, and ROP stage 3 or greater. Combined morbidity or death outcomes were also examined. Each composite outcome was recorded as "yes" if an infant had the morbidity or died before the outcome could be evaluated (for PDA and NEC, death within 12 hours; for LOS, death within 3 days; for IVH and PVL, death before sonogram; for ROP, death in first 28 days; for BPD, death before 36 weeks PMA) and "no" if an infant survived until evaluation and did not have the morbidity.

RESULTS

Study population

From 1994 through 2008, 50,332 VLBW infants were cared for at NRN centers. Of these, 133 were born with DS (0.26%); the percentage in individual centers ranged from 0 to 1.49% (adjusted for maternal age, p=0.3). The percentage of infants with DS by year ranged from 0.14% to 0.43% with no significant difference across the 15-year period (adjusted for maternal age and study center, p=0.7). Of the 133 infants with DS, a congenital heart defect (CHD) was reported for 39 (29%) and a gastrointestinal anomaly for 18 (13.5%); 8 infants (6%) had both. Complete atrioventricular septal defect with or without another defect (51.3%) was the most common CHD, followed by ventricular septal defect with or without atrial septal defect (20.5%), tetralogy of Fallot without other major lesion (12.8%), and others (15.4%). The study population also included 329 (0.65%) infants with non-DS CA and 2126 (4.2%) others with at least one major birth defect but no CA.

Infant characteristics

Mothers of infants with DS were older on average than mothers of infants with non-chromosomal BD or with no BD (Table 1). Birth weight was not significantly different between DS and other infants. Gestational age was lower for DS infants than for infants with non-DS CA but higher than for infants with no BD. Correspondingly, fewer DS infants were SGA compared to infants with non-DS CA and more were SGA compared to infants with no BD. Fewer DS infants were non-Hispanic black than were infants with no BD. The percentage of DS infants with Apgar scores ≤3 at 1 and 5 minutes was similar to infants with no BD and lower than infants with non-DS CA or other non-chromosomal BD.

Risk factors for DS

As expected, the risk of DS increased with maternal age (Table 2). The relative risk of having a DS infant was nearly twice as high for mothers 30-34 as for mothers <25, nearly three times as high for mothers 35-39, and highest for mothers ≥40 (adjusted RR 7.65). Infants from a multiple birth had one-half the risk for DS compared to singletons, and non-Hispanic black infants were less likely to have DS than were white infants. No difference in the risk for DS was found by sex.

Mortality

Overall, 40,231 (80%) infants survived and 10,101 (20%) died. In-hospital mortality was highest among infants with non-DS CA (71%), similar among infants with DS and infants with other BD (38%, 42% respectively), and lowest among infants with no BD (19%)(Table 3). The adjusted risk of death for infants with DS was more than twice that of infants with no BD (RR 2.47, 95% CI 2.00-3.07), lower than for infants with other CA, and not significantly different than for infants with other types of BD (Table 4).

Congenital malformation was coded most frequently as the cause of death for infants with non-DS CA (92%), and less frequently for infants with non-chromosomal BD (68%) and infants with DS (47%). Among the 8917 infants with no BD who died, death was most frequently attributed to immaturity (34%) (data not shown).

Among the DS infants, there was no significant change in annual mortality rate across the study period. As with other VLBW infants, lower GA and smaller BW were associated with increased risk of death among DS infants. DS infants with CHD and/or gastrointestinal anomaly had nearly twice the risk of death as DS infants without these comorbidities (Table 5).

Morbidities

In-hospital morbidities were examined for the 46,480 infants who survived >12 hours. The percentage of infants with PDA was the same for infants with DS and with non-DS CA (both 58%) and lowest for infants with no BD (32%, Table 3). DS infants had twice the risk of PDA as infants with no BD (adjusted RR 2.22)(Table 4). NEC was diagnosed in 16% of infants with DS, 4% with non-DS CA, 9% with other BD, and 8% with no BD. The adjusted relative risks of NEC for DS infants compared with others overall ranged from 2.04 to 3.91, with the highest risks among those with CHD (Table 4). When early deaths were included in these outcomes, risk of PDA or death and NEC or death remained elevated for DS infants compared to infants without BD (Table 4). However, compared to infants with non-DS CA, many of whom died, DS infants without CHD were at lower risk of PDA or death and NEC or death (adjusted RR for PDA 0.76, for NEC 0.52). Among infants with CHD, differences were not found between infants with DS and non-DS CAs with respect to PDA or death and NEC or death.

Infants with DS were also at increased risk of LOS compared to infants with non-DS CA (adjusted RR 1.88) and infants with no BD (adjusted RR 1.49)(Table 4). Risk of LOS or death within 3 days was also increased for DS infants compared to infants with no BD (adjusted RR 1.29) but reduced compared to infants with non-DS CA and other BD (Table 4).

Among infants who were evaluated by cranial sonogram, the risk for severe IVH and for IVH or PVL was not significantly different for DS infants than for those in each of the other groups (Table 4). Risk of severe IVH/PVL or death in the first 28 days (before having a

cranial sonogram) was reduced for DS infants compared to infants with non-DS CA (adjusted RR 0.40) and infants with other BD (adjusted RR 0.64)(Table 4).

ROP examination was performed for 81% of the 38,506 infants still in the hospital at 28 days. Among those examined, the percent of DS infants diagnosed with ROP was similar to the percent of infants with non-DS CA (30% vs 33%) but less than among infants with other BD or no BD (48% for each). Similarly, the percent of DS infants diagnosed with ROP stage 3 or higher was smaller (1%) than among infants with other non-chromosomal BD and no BD (11% for each)(Table 3). However, after adjusting for study center, GA, BW, male sex, and number of days on supplemental oxygen (delivered by any method), there was no longer a significant difference in the risk of ROP between infants with DS and those with other BD (adjusted RR 0.74) or with no BD (adjusted RR 0.78)(Table 4). In contrast, risk of ROP or death before 28 days was significantly lower for DS infants compared to those with non-DS CA (adjusted RR 0.55) and those with other BD (adjusted RR 0.80)(Table 4).

BPD was diagnosed in a higher percentage of DS infants than in infants with no BD (38% vs 28%; adjusted RR 1.76). The risk of BPD or death before 36 weeks PMA was lower for DS infants compared to infants with non-DS CA (adjusted RR 0.63) and higher than for infants with no BD (adjusted RR 1.65). At 36 weeks PMA, DS infants, on average, had smaller weight, length, and head circumference than infants with no BD but larger weight and length than infants with non-DS CA (Table 3).

DISCUSSION

VLBW infants represent 1.5% of US births.[16] DS and VLBW both increase the risks of infant mortality and various morbidities; until now, little was known about the risks of these conditions in combination. Health care providers have been faced with the challenge of extrapolating their knowledge of the health risks for DS and VLBW to counsel the parents of infants who have both conditions.

The prevalence of DS among VLBW infants in our study, 0.26%, was twice the prevalence among all U.S. births, 0.13% (12.9 per 10,000 live births).[17] This higher rate is consistent with the general observation that infants with significant abnormalities are more likely to be born with low birth weight;[18,19] alternatively, it might reflect increased referral of DS infants to NRN centers. Among racial or ethnic groups, non-Hispanic black infants had the lowest risk of DS compared with non-Hispanic white infants, consistent with previous studies.[17,20] Although no differences in mean birth weight were observed among the different comparison groups of infants in this population, low weight for gestational age (SGA) was more common among DS infants (40%) than among infants with no birth defect (20%) but less common than among infants with non-DS CA (64%). At 36 weeks, DS infants showed impaired growth compared to infants with no BD, confirming the need for growth charts specific for DS infants.[21] The overall mortality among DS infants, 38%, was lower than for infants with non-DS chromosomal anomalies, 71%. The risk of death among DS infants was similar to infants with other BD. As expected, DS infants had approximately twofold increased risk of death compared to infants with no major BD. This increased risk can be explained partly by the congenital anomalies associated with trisomy 21, as DS infants with cardiac defects or gastrointestinal anomalies had approximately double the risk of death compared to DS infants without these anomalies. Others have reported that the risk of death increases with increasing number of BDs.[22]

DS infants were found to have increased risks of PDA, NEC, LOS, and BPD compared to infants with no major BD. It has been reported previously that congenital anomalies in preterm infants are strongly associated with neonatal morbidity.[23] Among our VLBW

infants with DS, the concurrent presence of CHD nearly doubled the risk of NEC. DS infants had increased risks of the composite outcomes of PDA or death, NEC or death, LOS or death, and BPD or death compared to infants with no BD.

When the morbidities of DS infants relative to infants with other non-chromosomal BD were examined, only PDA and NEC were more common among DS infants. Relative to infants with non-DS CA, the risks of NEC and LOS were increased among DS infants. The latter results probably reflect the higher mortality of the more disadvantaged infants with non-DS CA, as the risk estimates were reversed for the combined outcomes of NEC or death and LOS or death.

An intriguing finding of this study was that, despite the increased risk for other morbidities in DS infants compared to infants with no BD, the risk of ROP (any stage and stage ≥3) among survivors to 28 days was not increased. In fact, a smaller percentage of surviving infants with DS compared to no BD were diagnosed with ROP (30% vs 48%, $p<0.01$); however, after adjusting for baseline differences and days on supplemental oxygen, this difference was no longer statistically significant. One might have expected higher ROP risk with DS, given the growth impairment of DS infants, a factor that has been linked with ROP risk.[24,25] Given the higher mortality among DS infants compared to those with no BD, some of the DS infants might have been diagnosed with ROP had they survived. However, there was a trend toward lower risk of ROP for DS infants compared to infants with non-DS CA and infants with other BD, each of whom had higher mortality. Risk of ROP or death within 28 days was decreased significantly in DS infants compared to infants with non-DS CA and those with other BD.

ROP is characterized by retinal neovascularization as ischemia or hypoxia leads to upregulation of angiogenic factors, such as vascular endothelial growth factor (VEGF).[26] This process is a self-limiting phenomenon in the ROP mouse model, possibly due to the role of endostatin-like proteins.[26] Endostatin, encoded by the COL18A1 gene at 21q, has also been implicated in reducing the incidence of solid tumors among patients with DS due to its potent anti-angiogenic effects.[2,27] Two genes on chromosome 21, Down syndrome candidate region-1 gene (DSCR1) and DYRK1A, have also been implicated in decreasing the incidence of solid tumors among DS individuals. A single extra transgenic copy of DSCR1 significantly suppressed tumor growth in a mouse model of DS due to inhibition of VEGF signaling in endothelial cells.[28] In this model, DYRK1A was also found to inhibit VEGF-mediated endothelial proliferation.[28] DS individuals have significantly elevated serum levels of endostatin[2] and increased DSCR1 protein expression in comparison to normal controls.[28] These factors might play a role in the trend toward decreased ROP risk among DS infants. Copper-zinc superoxide dismutase (SOD) might also play a protective role. SOD, encoded on chromosome 21q22, is an essential enzyme in the metabolism of oxygen free radicals. A 50% increase in the activity of this enzyme has been found in tissues of individuals with DS.[29] Overexpression of SOD in an ROP model in transgenic mice has been shown to protect against oxygen-induced retinopathy.[30]

CONCLUSION

DS individuals face many challenges throughout life, including shortened lifespan and a number of other health risks. For DS infants who are born with VLBW, the risks of mortality and significant morbidity are magnified. Until now, there has been no information on the mortality and morbidity risks faced by this high-risk group. By recognizing the patterns of health problems expected with VLBW DS infants, health care providers can identify problems earlier and have better information to guide the medical care of these vulnerable infants and to inform their parents, in the hope of improving the quality of life for

this population. The observation of possible decreased risk of ROP is intriguing and could guide future research on the pathogenesis of ROP.

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Appendix

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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ABBREVIATIONS

BD	birth defect
BPD	bronchopulmonary dysplasia
BW	birth weight
CA	chromosomal anomaly
CHD	congenital heart defect
CSF	cerebrospinal fluid
DS	Down syndrome
GA	gestational age
IVH	intraventricular hemorrhage
LOS	late-onset sepsis
NEC	necrotizing enterocolitis
NRN	NICHD Neonatal Research Network
PDA	patent ductus arteriosus
PMA	postmenstrual age
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity
VLBW	very-low-birth-weight

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TABLE 1

Characteristics of VLBW Infants with Down Syndrome (DS) Compared to Other VLBW Infants in the Neonatal Research Network Born 1994-2008

Characteristic, N (%) or Mean (SD)[1]	Group			
	DS N=133	Non-DS Chromosomal Anomaly[2] N=329	Other Birth Defect[3] N=2126	No Birth Defect N=47744
Maternal age (years)				
Mean (SD)	31 (8.0)	30 (7.8)	27 (6.8)***	27 (6.7)***
<25	33 (25)	101 (31)	905 (43)***	19321 (40)***
25-29	21 (16)	65 (20)	476 (22)	11219 (24)
30-34	31 (23)	64 (19)	396 (19)	9926 (21)
35-39	28 (21)	57 (17)	282 (13)	5754 (12)
40+	20 (15)	42 (13)	67 (3)	1493 (3)
Cesarean section delivery	72 (54)	220 (67)**	1297 (61)	27691 (58)
Multiple birth	21 (16)	39 (12)	418 (20)	12029 (25)*
Birth weight (grams)				
Mean (SD)	1036 (300)	1060 (293)	1042 (292)	1000 (304)
401-750	30 (23)	62 (19)	411 (19)	12519 (26)
751-1000	23 (17)	70 (21)	551 (26)	11202 (23)
1001-1250	42 (32)	92 (28)	530 (25)	11356 (24)
1251-1500	38 (29)	105 (32)	634 (30)	12667 (27)
Gestational age (weeks)				
Mean (SD)	29 (3.6)	31 (3.8)***	29 (3.3)	28 (3.0)***
<25	21 (16)	16 (5)*	225 (11)	8470 (18)***
25-28	33 (25)	89 (27)	789 (37)	20548 (43)
29+	79 (59)	224 (68)	1110 (52)	18707 (39)
Small for gestational age	53 (40)	209 (64)***	716 (34)	9349 (20)***
Male	59 (44)	143 (44)	1049 (49)	24353 (51)
Race/ethnicity				
Non-Hispanic black	37 (28)	91 (28)	686 (32)	19072 (40)*
Non-Hispanic white	67 (50)	144 (44)	950 (45)	18953 (40)
Hispanic	25 (19)	76 (23)	395 (19)	7619 (16)
Other	4 (3)	15 (5)	83 (4)	1958 (4)
Apgar at 1 minute ≤ 3	39 (30)	177 (54)***	901 (43)**	15100 (32)
Apgar at 5 minutes ≤ 3	15 (12)	81 (25)**	420 (20)*	5368 (11)

[1] SD= standard deviation. Information was missing for maternal age: 31 infants; cesarean section delivery: 60; multiple birth: 2; gestational age: 21; small for gestational age: 38; male: 4; race/ethnicity: 157; Apgar at 1 minute: 706; Apgar at 5 minutes: 693.

[2] Non-DS CA included trisomy 13, trisomy 18, Turner syndrome, triploidy, Klinefelter syndrome, DiGeorge syndrome, Wolf-Hirschhorn syndrome, and other chromosomal anomalies.

[3]Non-chromosomal birth defects included major birth defects of a single organ system (nervous, cardiovascular, gastrointestinal, genitourinary, bone and skeletal), inborn errors of metabolism, and multiple system anomalies.

[*] $p \leq 0.05$

[**] $p \leq 0.01$

[***] $p \leq 0.001$ for a test between infants with DS versus each of the other groups by the t-test (means for maternal age, birth weight, gestational age), Mantel-Haenszel chi-square test (categorical maternal age, birth weight, gestational age), or the general association chi-square test.

TABLE 2

Risk of Down Syndrome (DS) among VLBW Infants in the Neonatal Research Network Born 1994-2008

Characteristic[1]	Total N	Infants with DS N (%)	Adjusted Relative Risk for DS (95% CI)[2]	P-value[2]
Maternal age (years)				
40+	1622	20 (1.23)	7.65 (4.41-13.27)	<0.001
35-39	6121	28 (0.46)	2.86 (1.73-4.73)	
30-34	10417	31 (0.30)	1.87 (1.15-3.05)	
25-29	11781	21 (0.18)	1.12 (0.65-1.93)	
<25	20360	33 (0.16)	1.0	
Race/ethnicity[3]				
Non-Hispanic Black	19886	37 (0.19)	0.58 (0.39-0.87)	0.03
Hispanic	8115	25 (0.31)	0.91 (0.58-1.44)	
Other	2060	4 (0.19)	0.48 (0.18-1.32)	
Non-Hispanic White	20114	67 (0.33)	1.0	
Multiple birth				
Yes	12507	21 (0.17)	0.47 (0.29-0.76)	<0.001
No	37823	112 (0.30)	1.0	
Infant sex				
Male	25604	59 (0.23)	0.78 (0.55-1.09)	0.15
Female	24724	74 (0.30)	1.0	

[1] Information was missing for maternal age: 31 infants; race/ethnicity: 157; multiple birth: 2; infant sex: 4.

[2] CI = confidence interval. Relative risks, CIs and p-values by the Score test from a modified Poisson regression model which included maternal age, infant race/ethnicity, multiple birth, and infant sex. Study center could not be included due to sample size limitations.

[3] Race/ethnicity was collected for the infant, but not the mother.

TABLE 3

In-Hospital Mortality and Morbidities in VLBW Infants with Down Syndrome (DS) Compared to Other VLBW Infants in the Neonatal Research Network Born 1994-2008

Outcome, N (%) or Mean (SD)[1]	Group			
	DS N=133	Non-DS Chromosomal Anomaly N=329	Other Birth Defect N=2126	No Birth Defect N=47744
Survived	82 (62)	96 (29)	1226 (58)	38827 (81)
Died	51 (38)	233 (71)***	900 (42)	8917 (19)***
Died within 12 h	12 (9)	77 (23)***	349 (16)*	3414 (7)
Infants who survived > 12 h	N=121	N=252	N=1777	N=44330
PDA	70 (58)	146 (58)	878 (50)	14154 (32)***
NEC	19 (16)	10 (4)***	159 (9)*	3409 (8)***
Infants who survived > 12 h with CHD	N=38	N=77	N=799	--
PDA	22 (58)	53 (69)	457 (57)	--
NEC	9 (24)	3 (4)**	83 (10)*	--
Infants who survived > 12 h without CHD	N=83	N=175	N=978	N=44330
PDA	48 (58)	93 (53)	421 (43)**	14154 (32)***
NEC	10 (12)	7 (4)*	76 (8)	3409 (8)
Infants who survived > 3 d	N=120	N=209	N=1639	N=42942
Late-onset sepsis	32 (27)	29 (14)**	488 (30)	10237 (24)
Infants who had a cranial sonogram within 28 days[2]	N=107	N=207	N=1603	N=41324
Severe IVH	14 (13)	15 (7)	210 (13)	4878 (12)
Infants who had a late cranial sonogram[3]	N=99	N=178	N=1444	N=38450
PVL	4 (4)	6 (3)	87 (6)	1618 (4)
Infants with sufficient information to include in analysis [4]	N=96	N=180	N=1440	N=38449
Severe IVH or PVL	14 (15)	20 (11)	255 (18)	5630 (15)
Infants still in the hospital at 28 days who had an ROP examination	N=74	N=82	N=1112	N=30019
ROP[5]	22 (30)	27 (33)	535 (48)**	14358 (48)**
ROP stage 3 or higher[5]	1 (1)	5 (6)	119 (11)**	3400 (11)**
Infants alive at 36 weeks PMA	N=94	N=109	N=1273	N=37816
BPD[6]	36 (38)	55 (50)	562 (44)	10482 (28)*

Outcome, N (%) or Mean (SD)[1]	Group			
	DS N=133	Non-DS Chromosomal Anomaly N=329	Other Birth Defect N=2126	No Birth Defect N=47744
Infants with growth measurements at 36 w PMA, Mean (SD)[7]	N=84	N=123	N=1139	N=30620
Weight (g)	1783 (482)	1497 (389)***	1784 (431)	1937 (390)***
Length (cm)	41.1 (2.9)	39.7 (3.3)**	41.3 (3.2)	42.4 (2.9)***
Head circumference (cm)	29.5 (1.8)	29.3 (2.3)	30.2 (2.1)***	30.9 (1.7)***

[1] SD= standard deviation; PDA=patent ductus arteriosus; NEC=necrotizing enterocolitis; CHD=congenital heart defect; IVH=intraventricular hemorrhage; PVL=periventricular leukomalacia; ROP=retinopathy of prematurity; BPD=bronchopulmonary dysplasia. Information was missing for PDA: 29 infants; NEC: 19; late-onset sepsis: 44.

[2] Severe IVH was defined as grade 3 or 4. Excludes 37 infants with missing results.

[3] PVL based, for infants born before August 1998, on sonogram findings at 2 weeks or greater and, for infants born after August 1998, on sonogram findings within 28 days or closest to 36 weeks PMA and after 28 days. Excludes 26 infants with missing results.

[4] Percents were based on infants with non-missing IVH and PVL outcomes, except that a diagnosis of either condition was sufficient to set the outcome to yes. Excludes 3403 infants with missing results.

[5] Information was missing for ROP: 6 infants; ROP stage 3 or higher: 27 infants.

[6] BPD was defined as supplemental oxygen use at 36 weeks PMA. Excludes 1548 infants with missing information and 239 infants born at 36 weeks GA or later.

[7] Numbers (Ns) shown are infants who have at least one 36-week measurement. In this group of infants, information was missing for weight: 38 infants; length: 3550, head circumference: 1505.

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$ for a test between infants with DS versus each of the other groups by the t-test (means for weight, length, head circumference) or the chi-square test.

TABLE 4

Relative Risks of Death and/or Morbidities for VLBW Infants with Down Syndrome (DS) Compared to Other VLBW Infants in the Neonatal Research Network Born 1994-2008

Outcome	Adjusted Relative Risk (95% CI)[1]		
	DS vs Non-DS chromosomal anomalies	DS vs Other birth defect	DS vs No birth defect
Death	0.40 (0.31-0.52)***	0.83 (0.66-1.04)	2.47 (2.00-3.07) ***
PDA	0.97 (0.78-1.19)	1.25 (1.04-1.49)*	2.22 (1.87-2.64)***
NEC	3.91 (1.88-8.10)***	2.04 (1.31-3.17)**	2.51 (1.65-3.81)***
PDA with CHD[2]	0.96 (0.67-1.37)	1.27 (0.94-1.73)	2.60 (1.93-3.51)***
NEC with CHD[2]	5.39 (1.57-18.50)**	2.70 (1.44-5.07)**	3.77 (2.07-6.86)***
PDA without CHD	0.98 (0.76-1.27)	1.33 (1.06-1.66)*	2.08 (1.69-2.57)***
NEC without CHD	3.11 (1.24-7.82)*	1.77 (0.95-3.27)	1.93 (1.08-3.44)*
Late-onset sepsis	1.88 (1.22-2.92)**	1.09 (0.81-1.47)	1.49 (1.12-1.99)**
Severe IVH	1.63 (0.83-3.20)	1.17 (0.72-1.87)	1.54 (0.98-2.44)
Severe IVH or PVL	1.23 (0.66-2.28)	0.94 (0.59-1.51)	1.32 (0.83-2.08)
ROP	0.96 (0.63-1.46)	0.78 (0.57-1.07)	0.89 (0.65-1.22)
Adjusted for days on O_2	0.93 (0.62-1.40)	0.74 (0.54-1.02)	0.78 (0.57-1.07)
ROP stage 3 or higher	0.29 (0.04-2.08)	0.22 (0.04-1.31)	0.27 (0.05-1.63)
Adjusted for days on O_2	0.26 (0.04-1.83)	0.18 (0.03-1.05)	0.19 (0.03-1.09)
BPD	0.76 (0.55-1.04)	1.06 (0.83-1.35)	1.76 (1.39-2.24)***
Composite outcomes of morbidity or death			
PDA or death within 12 h	0.79 (0.66-0.94)**	1.04 (0.88-1.22)	1.91 (1.63-2.23)***
NEC or death within 12 h	0.67 (0.48-0.95)*	0.92 (0.68-1.24)	1.88 (1.41-2.51)***
PDA or death within 12 h with CHD[2]	0.86 (0.62-1.21)	1.22 (0.91-1.64)	2.36 (1.77-3.15)***
NEC or death within 12 h with CHD[2]	1.96 (0.86-4.46)	2.08 (1.16-3.76)*	3.00 (1.70-5.30)***
PDA or death within 12 h without CHD	0.76 (0.62-0.94)**	1.0 (0.83-1.20)	1.77 (1.48-2.12)***
NEC or death within 12 h without CHD	0.52 (0.36-0.76)***	0.66 (0.47-0.94)*	1.60 (1.15-2.23)**
Late-onset sepsis or death within 3 d	0.63 (0.50-0.81)***	0.76 (0.61-0.94)*	1.29 (1.05-1.59)*
Severe IVH/PVL or death within 28 days and no cranial sonogram	0.40 (0.30-0.55)***	0.64 (0.49-0.83)***	1.25 (0.96-1.61)
ROP or death within 28 days	0.56 (0.47-0.67)***	0.78 (0.67-0.92)**	1.09 (0.93-1.28)
Adjusted for days on O_2	0.55 (0.45-0.66)***	0.80 (0.67-0.96)*	1.11 (0.94-1.32)
ROP ≥ stage 3 or death within 28 days	0.31 (0.24-0.41)***	0.65 (0.51-0.82)***	1.38 (1.10-1.73)**
Adjusted for days on O_2	0.33 (0.25-0.45)***	0.67 (0.51-0.87)**	1.42 (1.10-1.83)**
BPD or death before 36 w PMA	0.63 (0.52-0.76)***	0.92 (0.78-1.08)	1.65 (1.41-1.94)***

PDA=patent ductus arteriosus; NEC=necrotizing enterocolitis; CHD=congenital heart defect; IVH=intraventricular hemorrhage; PVL=periventricular leukomalacia; ROP=retinopathy of prematurity; BPD=bronchopulmonary dysplasia.

[1] CI = confidence interval. Relative risks and CIs from a modified Poisson regression model fit to each outcome which included study center, gestational age (<25, 25-28, 29+ w), birth weight (401-750, 751-1000, 1001-1250, 1251-1500 g) and male sex in addition to the birth defect group indicator. In a secondary analysis, number of days on supplemental oxygen was also included in the model assessing ROP. Supplemental oxygen was defined as oxygen received by any method including high-frequency ventilation, conventional ventilation, nasal synchronized intermittent mandatory ventilation (SIMV), continuous positive airway pressure (CPAP), nasal cannula, hood, or incubator.

[2] CHD diagnosed among DS infants, infants with non-DS chromosomal anomalies and infants with other birth defect.

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$ for a test of whether the relative risk was significantly different from 1.0 by the Wald chi-square test based on estimates from the Poisson regression model fit to the outcome.

TABLE 5

Factors Influencing Risk of Death Among 133 VLBW Infants with Down Syndrome in the Neonatal Research Network Born 1994-2008

Characteristic	Total N	Died N (%)	Adjusted Relative Risk of death (95% CI)[1]	P-value[1]
Gestational age (weeks)				
<25	21	20 (95)	2.66 (1.30-5.44)	0.01
25-28	33	14 (42)	1.78 (1.01-3.13)	
29+	79	17 (22)	1.0	
Birth weight (grams)				
401-750	30	24 (80)	2.47 (1.29-4.74)	0.09
751-1000	23	9 (39)	1.65 (0.81-3.36)	
1001-1500	80	18 (23)	1.0	
Sex				
Male	59	27 (46)	1.46 (0.99-2.16)	0.06
Female	74	24 (32)	1.0	
Race/ethnicity				
Non-Hispanic black	37	15 (41)	0.99 (0.62-1.58)	0.8
Hispanic	25	10 (40)	1.05 (0.63-1.74)	
Other	4	3 (75)	1.18 (0.81-1.73)	
Non-Hispanic white	67	23 (34)	1.0	
Congenital heart defect				
Yes	39	17 (44)	1.83 (1.10-3.03)	0.02
No	94	34 (36)	1.0	
Gastrointestinal defect				
Yes	18	10 (56)	1.73 (1.06-2.83)	0.03
No	115	41 (36)	1.0	

[1] CI = confidence interval. Relative risks, CIs and p-values by Score or Wald chi-square tests from a modified Poisson regression model which included the variables shown. Study center could not be included due to sample size limitations.