Chapter 3. Results

We reviewed 1,693 full articles; 178 are used in this evidence report. The results of our research are presented in six major sections in this chapter. The first section reports the evidence on the association of VLBW with cerebral palsy (CP) and neurologic disabilities. The second section provides evidence that VLBW infants are at high risk for abnormal cognitive development and MR. The third section reports the evidence on the association of VLBW with disabilities of speech/language delay, hearing loss, behavioral disorders, and learning disabilities. The fourth section presents the evidence that VLBW (with or without other conditions) is associated with visual disability. The fifth section reports evidence on the association of VLBW (with or without other conditions) with pulmonary disability. The last section summarizes the evidence on the associations of VLBW with growth.

Evidence That VLBW With Or Without Other Conditions Is Associated With Cerebral Palsy (CP) And Neurologic Disability (Evidence Tables 1- 4)

This summary reports the evidence that VLBW infants, with or without other conditions or clinical risk factors, are at increased risk for disability due to CP and other neurologic/ neuromotor abnormalities. The evidence that VLBW is associated with MR is addressed in a separate section. The narrative regarding VLBW and CP/neurologic outcome is organized as follows:

1) Definition of CP, neurologic vulnerability of immature brain, and detection of brain injury

2) Evidence that VLBW infants have increased risk of CP/neurologic disability: estimates of prevalence and influence of degree of immaturity on risk of neurodevelopmental outcome

3) Evidence that VLBW plus other factors are associated with CP and neurologic abnormalities

    A. CNS injury (intracranial hemorrhage, cerebral white matter damage: periventricular leukomalacia, ventriculomegaly
    B. Antenatal risk factors
    C. Bronchopulmonary dysplasia (BPD) and postnatal systemic glucocorticoid therapy (Dexamethasone)
    D. Parenting/psychosocial factors
    E. Other postnatal factors

Definition of CP, Neurologic Vulnerability of Immature Brain, And Detection of Brain Injury.

CP is a neuromuscular disorder secondary to central nervous system injury, lesions or anomalies of the brain arising in the early stages of its development. The increased risk of VLBW infants for central nervous system injuries is due to increased vulnerability of the immature brain to cytotoxic, hypoxic-ischemic, and inflammatory injuries, impaired cerebrovascular autoregulation, and hemorrhage (Kuban and Leviton, 1994; Volpe, 2001).

CP manifests as a symptom complex of non-progressive, but often changing, neuromotor impairment syndromes (Kuban and Leviton, 1994; Mutch, Alberman, Hagberg, et al., 1992). The diagnosis of cerebral palsy is made in the presence of abnormal muscle tone, persistent or exaggerated primitive reflexes, and major delay in motor development. Classification of cerebral palsy is based on the extremities involved (monoplegia, hemiplegia, diplegia, and quadriplegia) and the characteristics of the neurologic dysfunction (spastic, hypotonic, dystonic, athetotic, or a combination (Kuban and Leviton, 1994; Mutch, Alberman, Hagberg, et al., 1992; Scrutton, 1992).

The availability of and refinement in neuroimaging technology, such as cranial ultrasound and magnetic resonance imaging (MRI), has improved our detection of brain injury of premature infants. The injuries detected via cranial ultrasound or magnetic resonance imaging include cerebral white matter damage (WMD) such as periventricular leukomalacia (PVL) and/or ventriculomegaly (VM), or intracranial hemorrhage (ICH). Detection of central nervous system injury, in turn has facilitated our understanding of risk factors associated with brain injury and has improved out ability to predict outcome of infants with evidence of brain injury.

Evidence That VLBW Infants have Increased Risk of CP And Neurologic Disability: Estimates of Prevalence And Influence of Degree of Immaturity on Risk of Neurodevelopmental Outcome

Prevalence of CP in Observational Studies

Thirty observational studies reported the prevalence of CP in VLBW and ELBW infant population (N= from 17 to 1187; BW= from 500 to1500g). Each patient's CP condition was defined from clinical signs and symptoms along with Bayley Scales. The percentage of CP reported from these studies varied from 6 to 97 (Table 1.1a).

Table 1.1a. Association of Cerebral Palsy with VLBW/Prematurity (Percentage of CP in observational studies)

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applicability	Quality
Hack, 2000 20358826	221	BW: <1000 GA: 26.4	Clinical	15%		A

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applicability	Quality
Hack, 1996 97066997	249	BW : 500-759 GA: 24	Clinical	1982-88: 10% 1990-92: 10%		A
Valkama, 2000 20233239	51	BW: 1153 GA: 29 (25-34)	According to Hasberg et al.	18%		A
	16	BW < 1000 g GA: ND		34%		
	14	ND		14%		
Vohr, 2000 20295211	1151	BW: 401-1000 g	ND	17%		A
	15	BW: 401-500 g		29%		
Victorian Infant Collaborative study Group, 1997	453	BW: 500-999 g GA: ND	Clinical and Bayley Scales	6.6% (1985-87) 9.3% (1991-92)		B
Victorian Infant Collaborative study Group, 1997	35	GA: 23-27 wk	Clinical and Bayley Scales	19.1% (1985-87) 12.5% (1991-92)		B
Victorian Infant Collaborative study Group, 1997 97466059	989	BW: 500-999 g GA: ND	Clinical and Bayley Scales	0% (1985-87) 12.5% (1991-92)		B
O'Shea, 1997 98049056	2076	BW: 681(501-800) GA: 25	Clinical	19% (1984-89) 7% (1989-94)		B
Piecuch, 1997 98012134	446	BW 500-999 GA: 24-25	Clinical and Bayley Scales	9%		B
Sethi, 1996 96334245	92	BW <1501 g GA: ND	Clinical	8.7%		B
Wood, 2001 20373840	283	GA ≤ 25 wks	Clinical and Bayley Scales	10%		B

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applicability	Quality
Palta, 2000 20096107	425	GA: 29 BW: 1003	Clinical (Physician dx at parent interview and confirmed by clinic record abstraction as well as blindness and use of corrective lenses)	13%	! !	B
Pierrat, 2001 27221167	39 39	GA: 29 BW: 1003	Criteria of Hagberg et al.	76% 97%	! !	B
Ambalavanan 2000 21031370	218	BW: 830G g GA: 26	Clinical Bayley Scales	28%	! !	B
Robertson, 1994 94181384	163	BW: 500-1500 GA: ND	Bax's definition	6.7%	! ! !	B
Salokorpi, 1999 99353226	143	GA: 26.7 BW: 820	Clinical	19%	! !	B
Shepherd, 1999 99165413	81	GA: 26-35 BW: 570-3200	Clinical	9%	! !	B
Sethi, 1996 96334245	66	BW <1501 g GA: ND	Clinical	20%	! ! !	B
Vohr, 1999 99332101	101	BW: 965 GA: 28	Presence of hypertonicity, hyperreflexia, and dystonic or spastic movement quality in the affected limbs	9%	! !	B
Cooke, 1999 99257637	1187	ND	Data from Regional Cerebral Palsy Register	11% (1986-89) 7.3% (1990-93)	! ! !	C
Emsley, 1998 98238139	64	BW: 753 GA: 23-25	Clinical	21% (1984-89) 18% (1990-94)	! !	C
Battin, 1998 99002694	44	GA: 23-25 BW: ND	Clinical	20%	!	C

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applicability	Quality
Blitz, 1997 97154301	100	BW: 776 GA: 27	Clinical BSID, MDI, PDI, CLAM	24%	! !	C
Chen, 1995 96009403 Cooke, 1999 993806719 Dammann, 2001 21221175	17 1187 324	BW: 1197 (625-1500)GA: 30 (27-36) ND BW: ND GA: ND	Spastic CP, diagnosed by "complete neuro exams" Data from Regional Cerebral Palsy Rgst ND	41% 10% 10%	! ! ! ! ! ! !	C C C
Spinillo, 1997 98021316 & 97277958 Spinillo, 1998 98237382	345	GA: 30 BW: 1371	Spastic diplegia, Hemiplegia, Tetraplegia, w/ moderate to severe interference with function or w mental retardation: MDI < 71	12%	!	C
Thompson, 1993 93234177	143	BW <1250 GA 32.0	Clinical (Neurological exam Greffther scale)	6%	!	C

The evidence of the literature by the methods of this review overwhelmingly supports that the risk of CP and major neurologic disability is increased among VLBW infants, especially extremely low birth weight (ELBW) infants, compared to full-term infants. Due to the improved survival of VLBW and ELBW infants, concerns remain that the incidence of neurodevelopmentally disabled children has increased and will increase. However, recent studies from developed nations that evaluated the change in prevalence of CP over time suggest that the incidence of CP is stable or modestly decreased compared to the 1980s, despite improved survival of extremely immature infants (Cooke, 1999; Emsley, Wardle, Sims, et al., 1998; Hack, Friedman, and Fanaroff, 1996; Piecuch, Leonard, Cooper, et al., 1997; The Victorian Infant Collaborative Study Group, 1997; The Victorian Infant Collaborative Study Group, 1997; The Victorian Infant Collaborative Study Group, 1997). This suggests that recent advances in neonatal care have had either no or modest effect on reducing the incidence of cerebral palsy. Differences among studies regarding incidence trends may be accounted for by the period of time under study, characteristics and risk factors of the patient population, neonatal care practices, as well as length and completeness of follow-up.

A study by Hack, Wilson-Costello, Friedman, et al. (2000) provides relatively recent information regarding the neurodevelopmental outcome at 20-months corrected age of 221 extremely immature infants born between 1992 to 1995. They found that 48% of the infants had

neurodevelopmental impairment (neurologic abnormality, subnormal MDI, blindness or deafness); 20% a major neurologic abnormality, and the incidence of CP was 15%.

Hack, Friedman, and Fanaroff (1996) prospectively studied at 20 months corrected age two cohorts of children who were born VLBW (birth weight <1500g) in a single U.S. center. The first cohort was born in 1982-1988 (N=166), which was an era prior to surfactant therapy and prior to widespread use of dexamethasone. The second cohort was born 1990-1992 (N=114) during an era when surfactant therapy and dexamethasone were used in the treatment of premature infants. The 20-month corrected age neurodevelopmental outcomes did not change appreciably between two cohorts (10% of infants had CP in both periods). In first period, 49% had major neurosensory abnormalities and/or MDI<80, compared to 35% in second period.

Vohr, Wright, Dusick, et al. (2000) evaluated the neurodevelopmental, neurosensory, and functional outcomes at 18-22 months corrected age of 1151 American, ELBW infants (401-1000 grams) born in 1993-1994. This recent study documented the increased incidence of abnormal neurologic outcome, including CP, in the cohort of ELBW infants. Overall, 25% had an abnormal neurologic examination, 37% had a Bayley II Mental Developmental Index <70, 29% had a Psychomotor Developmental Index <70, 17% of the cohort developed cerebral palsy (6.4% quadriplegia, 1.4% hemiplegia, 8.2% diplegia, 1.0% monoplegia), and 5% had seizure disorder. Within this narrow range and sample size of extremely premature infants, birth weight was not a significant predictor of neurologic outcome although there was a trend toward more CP among the lower birth weight categories (400-800 grams: CP range 29%-15% vs. 801-1000 grams: CP 15%). Factors significantly associated with increased neurodevelopmental morbidity included chronic lung disease, grades 3 to 4 intracranial hemorrhage, periventricular leukomalacia, glucocorticosteroid therapy for BPD, necrotizing enterocolitis, and male gender. This large, contemporary, prospective, multicenter US study emphasizes the high risk of neurologic and neurodevelopmental problems are noted in ELBW infants at 18-22 months age.

The Victorian Infant Collaborative Study Group published three studies in 1997 which evaluated the outcome of extremely premature infants. (The Victorian Infant Collaborative Study Group 1997a; The Victorian Infant Collaborative Study Group 1997b; The Victorian Infant Collaborative Study Group 1997c). One study compared survival and outcome of ELBW infants by birth weight (500-999 grams) with normal birth weight controls over the course of three eras (1979-1980, 1985-1987; 1991-1992). The second study compared survival and outcome of extremely premature infants by gestational age between 23-27 weeks with normal birth weight controls born during 1991-1992, and compared the change in survival and outcome with premature infants (23-27 weeks gestational age) born during 1986-1987. The third study evaluated the survival and outcome of outborn ELBW infants (BW 500-999 g) among 3 eras (1979-1980, 1985-1987; 1991-1992). In all three studies, the survival of extremely premature infants improved in 1991-1992 compared to the earlier eras of neonatal care by 'birth weight' criteria (500-999 g), by 'gestational age' criteria (23-27 weeks), or by 'outborn status and birth weight' criteria (500-999 grams).

In The Victorian Infant Collaborative Study Group (1997a) study that compared survival and outcome of extremely premature infants with birth weight 500-999 grams, survival improved in the 1991-1992 era to 56.2% compared to survival of 25.4% and 37.9% for 1979-1980, 1985-1987 respectively. The proportion of children with CP in the ELBW cohort was 13.5%, 6.6%, 9.3% for each of the three eras 1979-1980, 1985-1987, 1991-1992 respectively. The rate of CP was not significantly lower in 1991-1992 compared to the earlier eras. Severe sensorineural disability fell between the two earlier eras for infants with birth weight 500-749 grams (25% vs.

11.1% vs. 12.1%), but not for infants with birth weight 750-999 grams. The rate of severe sensorineural disability was higher across all three eras for the most immature infants (500-749 grams) compared to that of premature infants with birth weight 750-999 grams. ELBW children (500-999 grams) had significantly higher rates of sensorineural disability compared to normal birth weight children born ≥2499 grams in the latest era 1991-1992 (6.8% vs. 1.7%).

In The Victorian Infant Collaborative Study Group (1997b) study that compared survival and outcome of extremely premature infants by gestational age criteria (23-27 weeks) with normal controls born during 1991-1992, the rates of CP and deafness were not different compared to similar gestational age children born in 1985-1987, but the rate of blindness decreased. There was no significant difference in sensorineural disability between premature cohorts (23-27 weeks gestational age) born during 1986-1987 compared to 1991-1992.

In The Victorian Infant Collaborative Study Group (1997c) study of outborn ELBW infants (birth weight 500-999 grams) survival improved in the 1991-1992 era to 60.7% compared to the two earlier eras (34.6% and 36.7% for 1979-1980, 1985-1987 respectively). The proportion of CP was 11.1%, 0%, 12.5% for each of the three eras 1979-1980, 1985-1987; 1991-1992 respectively. Severe sensorineural disability fell between the two earlier eras for outborn ELBW infants. There was no comparison to normal birth weight controls in this study.

O'Shea, Klinepeter, Goldstein, et al. (1997)also demonstrated that the incidence of neurodevelopmental disability, assessed at 1 year of age, did not increase in extremely premature survivors (birth weight 501 to 800 grams) over the time period of 1979 through 1994, despite a significant improvement in survival of extremely premature infants. The proportion of children who developed cerebral palsy were 13%, 19%, and 7% for time periods 1979-1984, 1984-1989, 1989-1994, respectively. Similarly, the incidence of major neurosensory impairment did not increase across these same time periods (25%, 28%, and 21%). After adjusting for gestational age, which was inversely proportional to risk of major neurosensory impairment, major cranial ultrasound abnormalities were associated with an increased risk (OR 5.71, 95% CI 2.2, 14.84) and years of maternal education was associated with a decreased risk (OR 0.82, 95% CI 0.67, 1.0) of major neurosensory impairment.

Piecuch, Leonard, Cooper, et al. (1997) reviewed neurodevelopmental outcomes of a large (446) group of ELBW (500-999 gm) infants born between 1979-1991 at a mean age of 55±33 months of age (range 12 to >72 months). Within this narrow birth weight range of 500-999 g, they found that 15% of infants had abnormal neurologic/neurosensory outcome. Among the 442, 9% specifically had a diagnosis of CP or significant impairment in neuromotor function. There was no change in incidence of CP or neuromotor impairment over the time periods.

Other studies within this review were not designed to compare change in incidence of specific neurodevelopmental outcomes over time, but they are valuable to note because they provide recent evidence of the increased prevalence of CP and neurosensory impairment in VLBW population. Similar to other reports, Sethi and Macfarlane (1996) found that 11% of VLBW children had a major impairment (9% cerebral palsy; 2% blind). Sethi and Macfarlane (1996) and Wood, Marlow, Costeloe, et al. (2000) evaluated all children born at 25 weeks or less in the United Kingdom and Ireland during 1995 and determined the neurologic and neurodevelopmental outcome at 30-months corrected age. The mean (±SD) scores on Bayley Mental (MDI) and Psychomotor Developmental Indexes (PDI) were 84±12 and 87±13, respectively (population mean 100). Ten percent had severe neuromotor disability. Among the children with neuromotor disability, 18 percent had CP, of which more than half (54%) was severe. Overall, 49% of the children had disability.

Cooke (1999) retrospectively studied a cohort of VLBW infants (birth weight not specified) born in the United Kingdom in 1982-1993 and followed until 3 years corrected age. Data were obtained from Regional CP Register. The authors found that prevalence of CP decreased significantly in early 1990s (p=0.046) compared to 2 periods in 1980s, despite the improved survival of VLBW infants. They found 10.9% (45/411) infants had CP in 1982-85, 10.9% (42/387) in 1986-1989 and 7.3% (29/398) in 1990-1993. The authors speculated that this improved survival and outcome was related to increased routine use of antenatal steroids in mothers at risk for preterm delivery.

Emsley, Wardle, Sims, et al. (1998) demonstrated that improved survival from 1984 through 1994 in premature infants at the limit of viability (23-25 weeks gestation) was associated with increase in disability. They examined prospectively 2 cohorts of premature infants born in 2 different periods 1984-1989 (N= 24) versus 1990-1994 (N=40) at 2 sites in US. Survival increased from 27% to 42% and the rate of disability increased from 38% to 68%. Although the proportions of survivors with cerebral palsy were similar between two time cohorts (1984-1989: 21% vs. 1990-1994: 18%), the increase in visual disabilities (blindness due to ROP, myopia, and squint) contributed to the overall increase in disability over time. A high illness severity score (as assessed by CRIB score) was strongly associated with disability. Within the second period (1990-1994), 38% of children had mild disability (myopia, language delay, mild hearing loss, hyperactivity or clumsiness), 13% had moderate disability (spastic diplegia, moderate learning disability), and 18% had severe disability (spastic quadriplegia, blindness, deafness, uncontrolled epilepsy or severe learning disabilities and multiple disabilities. Study sample numbers were small and there is no information on when the assessments of these infants were carried out or whether evaluators were blinded.

Battin, Ling, Whitfield, et al. (1998) compared the outcome of extremely low gestational age infants born between 23-25 weeks during 1991-1993 vs. similar gestational age infants born in 1983-1989. Major neurologic impairments were found in 36% of 44 infants born 1991-1993 and in 36% of infants born 1983-1989.

Prevalence of CP in Clinical Trials

Additional 5 studies (Table 1.1b), which were conducted to evaluate various interventions, confirmed similar increased incidences of CP in VLBW infants. Gerdes, Gerdes, Beaumont, et al. (1995) evaluated the 1-year outcome of infants with birth weight 700-1100 grams treated with either 1 or 3 doses of surfactant found no difference in outcomes between the two surfactant groups. Forty to 60% of these infants had some impairment (20-27% were severe impairments). CP was present in 12-16% (moderate to severe cerebral palsy in 6-9%).

Table 1.1b. Association of Cerebral Palsy with LBW / Prematurity (Percentage of CP in clinical trials)

Author, Year	Population	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applica-bility	Quality
Gerdes, 1995 95264241	BW 700-1100 g Treated with 2 surfactant	508	BW: 907 GA: 27	Clinical	12-16%	! ! !	A

Author, Year	Population	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applica-bility	Quality
	regimens						
Ment, 1996 97040638	BW 600-1250 g Indocin IVH prevention trial	431 ? 343 at 36 mos	BW 600-1250 g	Clinical	7% in both groups		A
Ment, 2000 20164956	Premature infants with IVH	343	BW: Sample 1: 988 Sample 2: 945 GA: 28	Clinical	1%		A
Tin, 2001 21143595	GA <28 wks	249	GA: 23-27	Clinical	15.4-16.9%		B
The Northern Nursing Initiative Trial Group 1996 96304894	GA <32 weeks	776	GA : 29 BW:1253	Clinical	11.2-14.1%		B
Roth, 2001 21262686	GA <33 wk	782	BW: Sample 1: 1350 Sample 2: 1324 GA: 29	Clinical	Impaired Neurodevelopment 28% and 36% Disabling 12-14%		C

Ment, Vohr, Oh, et al. (1996) found no difference in incidence of cerebral palsy between study groups of VLBW survivors (defined as 600-1250 grams) participating in the Multicenter Randomized Indomethacin IVH Prevention Trial (indocin 7% vs. 7% placebo) evaluated at 54 months' corrected age. In a study designed to evaluate whether differing oxygen saturation policies among nurseries in Northern England were associated with differences in incidence of retinopathy of prematurity (ROP) and cerebral palsy, Tin, Milligan, Pennefather, et al. (2001) found that the incidence of cerebral palsy (diagnosed at one year age) in premature infants born <28 weeks gestation during 1990-1994 ranged between 15.4% and 16.9% among the participating nurseries. There was no difference in incidence of CP in infants treated with oxygen saturation range 70-90% and 88-98% (15% vs. 17%, respectively).

The Northern Neonatal Nursing Initiative Trial Group (1996) conducted a trial in 1990-1992 to study the effect of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies born <32 weeks gestation on long-term outcome at 2 years age. They found no difference in sensorineural, neuromotor, or neurologic outcomes among the three groups (median or mean gestational ages not provided). Specifically, the incidence of severe disability was 11.3%, 11.2%, and 14.1% in the prophylactic early fresh-frozen plasma or gelatin-based plasma substitute or maintenance glucose infusion groups, respectively.

Roth, Amess, Kirkbride, et al. (2001) conducted a study designed to compare two methods of cranial ultrasound scanning (linear-array versus mechanical-sector) regarding accuracy of prediction of neurodevelopmental outcome. They enrolled all surviving premature infants born <33 weeks gestational age born between 1979 and 1988 (n=854). Of these, 92% were evaluated between ages 7 years and 2 months and 10 years and 6 months. In addition to showing there was no significant difference between the two methods, they found neurodevelopmental impairments in 28% and 36% of the two groups (linear-array versus mechanical-sector) and disabling

impairment was found in 12% and 14% of the two groups (linear-array versus mechanical-sector).

Evidence That Immaturity And The Degree of Immaturity (GA and/or BW) Influence The Risk of CP And Neurodevelopmental Disability In VLBW Infants

Five studies (Table 1.2a) support the increased risk of CP and neurologic disability in premature and extremely premature infants in the current era of neonatal care.

Table 1.2a. Association of Cerebral Palsy by Degree of Immaturity

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Definition of CP	% of CP	Applica-bility	Quality
Victorian Infant Collaborative study Group, 1997	453	BW: 500-999 g GA: ND	Clinical and Bayley Scale	BW 500-999g: 6.8% BW>2499: 1.7%	! !	B
Victorian Infant Collaborative study Group, 1997 97466059	989	BW: 500-999 g GA: ND	Clinical and Bayley Scale	0% (85-87) 12.5% (91-92)	! !	B
Murphy, 1997 97192793	293	BW: ND GA: 29 (24-32)	Clinical	32%	! ! !	B
Saigal, 2001 11483807	154	BW: 835, GA: 27	Clinical	ELBW group: 17% FT group: 0.8%	! !	B
Finnström, 1998 99041345	362	GA: = 23 BW: 798	Clinical	Entire cohort: 7% 23-24 wk: 14% 25-26 wk: 9% ≥27 wk: 3%	! ! !	**C**

The Victorian Infant Collaborative Study Group (1997) documented that ELBW children (500-999 grams) had significantly higher rates of sensorineural disability compared to normal birth weight children born ≥2499 g in the era 1991-1992 (6.8% vs. 1.7%), and that the rate of severe sensorineural disability was higher across all three eras for the most immature infants (500-749 grams) compared to that of premature infants with birth weight 750-999 g.

Another study by The Victorian Infant Collaborative Study Group (1997) compared survival and outcome of extremely premature infants by gestational age criteria (23-27 weeks) with normal birth weight controls born during 1991-1992. As expected, the investigators found the rate of sensorineural disability was higher in the premature cohort than the normal birth weight controls born in 1991-1992. None of the normal birth weight controls born had CP, blindness, or

deafness. In contrast, among the extremely premature infants followed through 2 years age, CP was diagnosed in 11% (half with quadriplegia, 20% hemiplegia, 20% with diplegia, and remainder mixed CP); 2.3% were blind; and 0.9% required hearing aids for sensorineural hearing deafness. The rates of cerebral palsy and deafness were not different compared to similar gestational age children born in 1985-1987, but the rate of blindness decreased. Compared with controls born in 1991-1992, the overall rate of sensorineural disability was higher in the premature cohort ($p<0.0001$).

Murphy, Hope, and Johnson (1997) conducted a case-control study to identified neonatal risk factors for cerebral palsy in very preterm babies (<32 weeks gestation) born between 1984 and 1990 independent of coexisting, previously identified antenatal and intrapartum factors. The incidence of CP among survivors increased with decreasing gestational age ($p<0.0001$).

Saigal, Stoskopf, Streiner, et al. (2001) compared the long-term outcome at 12 to 16 years of age between adolescents who were born ELBW vs. full-term controls, and evaluated changes over time. Their study confirmed that ELBW adolescents compared to full-term control adolescents had significantly higher proportion with neurosensory impairments (28% vs. 2%) including a greater prevalence of cerebral palsy (17% vs. 0.8%); greater current prevalence of seizures (7% v. 1%, $p=0.03$); higher proportion with multiple (≥ 3) health problems (35% vs. 7%, $p<0.001$); greater proportion with any functional limitation (81% vs. 42%, $p<0.0001$); greater utilization of health care resources in the proportion of adolescents who were seen by pediatricians, ophthalmologists, otolaryngologists, speech parthologists, occupational therapists; and greater proportion of parents with out-of-pocket expenses (10% vs. 1%, $p<0.001$).

Finnstrom, Otterblad Olausson, Sedin, et al. (1998) evaluated neurosensory outcome at 3 years age in extremely low birth weight infants (<1000 grams birth weight and ≥23 weeks gestation) born during 1990-1992 and enrolled in the national Swedish prospective study. Ninety-eight percent of surviving ELBW (mean birth weight 798±144 g) were assessed at median age of 3 years. The incidence of cerebral palsy for the entire cohort was 7%, which is 50 times higher than that reported in term infants in Sweden. The incidence of cerebral palsy for children born at 23-24, 25-26, ≥27 weeks gestation was 14%, 10%, and 3%, respectively. The overall incidence of major handicap in ELBW cohort was 7%. At least one handicap was noted in 14%, 9%, and 3% of each of the three gestational age groups, respectively. Severe intracranial hemorrhage (≥ grade 3), periventricular leukomalacia, and retinopathy of prematurity ≥ Stage 3 were significantly predictive of increased risk of handicap after adjusting for gestational age. This study illustrates that this cohort of ELBW children are at increased risk for adverse neurosensory outcome, and the risk increases with decreasing gestational age.

The evidence of the studies within this review clearly supports the increased risk of cerebral palsy and neurologic disability in premature infants in the current era of neonatal care, and that the risk for CP and adverse neurodevelopmental outcome is further increased in extremely premature infants.

Evidence That VLBW Plus Other Factors Are Associated With CP and Neurologic Abnormalities

CNS Injury (Intracranial Hemorrhage, Cerebral White Matter Damage: Periventricular Leukomalacia, Ventriculomegaly)

Numerous studies provide evidence that cerebral white matter damage (WMD), as manifested by periventricular leukomalacia (PVL) (such as echodensities and echolucencies), ventriculomegaly (VM), and posthemorrhagic infarct, as well as severe intracranial hemorrhage (ICH) are among the strongest predictors of cerebral palsy and other neurologic disabilities in VLBW infants (Ekert, Keenan, Whyte, et al., 1997; Holling and Leviton, 1999; Levene, 1990; Ment, Vohr, Allan, et al., 1999; Pasman, Rotteveel, Maassen, et al., 1998; Rademaker, Groenendaal, Jansen, et al., 1994). There are additional studies supporting this association that proceeded the time period of this literature review. Although the diagnosis of cerebral WMD is understandably made postnatally, WMD may originate antenatally and may also occur or continue to occur postnatally. The etiology of WMD appears to be related to the immature and incomplete development of the vascular supply to the cerebral white matter, the immaturity of cerebral blood flow regulation and increase risk for ischemic injury, and the vulnerability of the oligodendroglial precursor cell to cytotoxic injury (Volpe, 2001).

Fourteen studies (Table 1.3a) abstracted according the search criteria for this review are noted below:

Table 1.3a. Association of CP and neurologic abnormalities in VLBW with CNS injury

Author, Year	N	Mean BW, g; GA, wk Baseline	Risk Factors	Associations		Applicability	Quality
				Univariate	Multivariate		
Allan, 1997 97336492 Ment, 1996 97040638	**337**	Indomethacin grp: BW: 945 GA: 28 Placebo grp: BW: 988 GA: 28	PVL VM	↑* ↑*	↑* ↑*	! !	A
Piecuch, 1997 98012134	86	BW: Sample 1: 668 Sample 2: 790 Sample 3: 842 GA: 24-26	c-PVL and/or grade III or IV ICH	↑	↑	! ! !	A
Piecuch, 1997 97456215	445	BW: Sample 1: 668 Sample 2: 790 Sample 3: 842 Sample 4: 850 Sample 5: 942 GA:26-27	PVL ICH Gr 3 or 4	↑ ↑	↑ ↑	! ! !	A

Author, Year	N	Mean BW, g; GA, wk Baseline	Risk Factors	Associations		Applicability	Quality
				Univariate	Multivariate		
Hack, 2000 20358826	221	BW: 813 GA: 26	c-PVL and/or grade III or IV ICH	↑*	↑*	❗❗❗	A
Valkama, 2000 20233239	51	BW: 1153 GA: 29 (25-34)	Parenchymal lesions [a]	↑	↑	❗❗❗	A
Lefebvre, 1998 98387703	121	BW: 961 GA: 27	NBRS [c]	↑	↑	❗❗	A
Pierrat, 2001 27221167	60	BW: 1003 GA: 29	Grade II or III c-PVL	↑	↑	❗❗	B
Salokorpi, 1999 99353226	143	BW: 820 GA: 27	Grade III or IV ICH, PVL	↑*	↑	❗❗	B
Cioni, 2000 20150341	29	BW: ND GA: 31	WM damage; WM loss	↑*	↑	❗❗	B
Pennefather, 2000 20217908	558	BW: ND GA: < 32	Ocular abnormalities [b]	↑*	↑	❗❗❗	B
Wilkinson, 1996 97087405	10	BW: 1144 GA: 27	Severe c-PVL	↑	↑	❗	B
Rogers, 1998 98438124	41	BW: 1125 GA: 28	c-PVL	↑	↑	❗	B
Krageloh-Mann, 1999 99431017	29	BW: 1461 (690-2655) GA: 30 (27-34)	Abnormal brain MRI findings [x]	↑	↑	❗❗	C

[a] Parenchymal lesions was defined as hemorrhage, PVL, infarctions, and reduction in cerebral white matter on MRI findings
[b] Ocular abnormalities: cicatricial ROP, cortical visual impairment, and strabismus
[c] Neurobiologic Risk Score (NBRS) represents the summation of the occurrence or degree of the following variables: duration of ventilation, acidosis, seizures, presence and degree of ICH and PVL

A randomized, placebo-controlled clinical trial of indomethacin prophylaxis for intraventricular hemorrhage was conducted. Four hundred and thirty-one VLBW infants (BW 600-1250 g) were followed up at 36 months corrected age (Allan, Vohr, Makuch, et al., 1997). and 54 months corrected age (Ment et al, 1996; Ment et al, 2000, described in 3.B). They evaluated the determinants of CP and the relationships of these determinants to CP. Cerebral palsy was found in 9.5% of the VLBW infants at 36 months corrected age. The authors found that sonographic evidence of cerebral periventricular leukomalacia (PVL) and ventriculomegaly (VM) were associated with the highest detection rates for CP: 37% for PVL, 30% for VM, and 22% for grade 3 or 4 intracranial hemorrhage. Chorioamnionitis (Detection Rate = 28, 95% CI 16, 40, p=0.02) and surfactant therapy (p=0.005) were significantly associated with cerebral palsy in the univariate analyses, but were not independent predictors of cerebral palsy in the

multivariate analysis once indicators of cerebral WMD (PVL and VM), severe intracranial hemorrhage, and bronhopulmonary dysplasia (BPD) were included in the prediction model. Possible explanations for the difference in univariate and multivariate findings are the notable association of chorioamnionitis with parenchymal brain injury and sonographic evidence of WMD, and the fact that surfactant use is closely related to BPD. Cystic PVL had the strongest association with CP among the other cranial ultrasound findings (cystic PVL OR =16;. Grade III or IV IVH OR= 14; VM OR= 9). Cranial sonographic findings can be helpful in predicting CP as early as 3 days of age. The 40-week adjusted gestational age cranial ultrasound had the highest odds ratio for predicting CP at 3 years corrected age (OR 52%, 95% CI 26, 65). The three classic forms of CP (spastic diplegia, hemiplegia, and tetraplegia) were distributed equally among the children with CP (Allan, Vohr, Makuch, et al., 1997).

Piecuch, Leonard, Cooper, et al. (1997) reviewed neurodevelopmental outcomes of 446 ELBW (500-999 grams) infants born between 1979-1991. At a mean age of 55±33 months of age (range 12 to >72 months, they found that 15% of infants had abnormal neurologic/ neurosensory outcome. Among 442 infants, 9% specifically had a diagnosis of CP or significant impairment in neuromotor function. There was no change in incidence of CP or neuromotor impairment over the time period. Within this narrow range of extreme prematurity, there was a significant association between abnormal neurologic outcome and gestational age (i.e. the more immature the gestational age, the greater the risk of abnormal neurologic outcome). Approximately half the infants (46%) who had complicated ICH and or cystic PVL had abnormal neurologic outcome. The proportion of children with cerebral palsy or neuromotor impairment increased as the grade of intracranial hemorrhage increased as evidence by the strong association between abnormal outcome and cystic periventricular leukomalacia and/or grade III and IV intracranial hemorrhage. Mild to moderate neurologic delays were also associated with BPD.

Piecuch, Leonard, Cooper, et al. (1997) also evaluated outcome at a mean age of 32 ±17 months in extremely premature infants born at 24 to 26 weeks gestation between 1990-1994. The incidence of cerebral palsy was 11%, 20%, 11% across all three gestational ages (24,25,26 weeks) (p=ns). Abnormal neurologic outcome was documented in 33% of infants born at 24 weeks, 27% born at 25 weeks, and 11% born at 26 weeks gestation, but the difference was not statistically significant in this group of patients. Abnormal neurologic outcome was significantly associated with medical risk factors of cerebral injury (periventricular leukomalacia and severe intracranial hemorrhage (grade III or IV).

A study by Hack, Wilson-Costello, Friedman, et al. (2000) provides relatively recent information regarding the neurodevelopmental outcome at 20-months corrected age of 221 extremely immature infants born between 1992 to 1995. They found that 48% of the infants had neurodevelopmental impairment (neurologic abnormality, subnormal MDI, blindness or deafness); 20% a major neurologic abnormality, and the incidence of CP was 15%. Predictors of abnormal neurologic outcome included severe abnormal cranial ultrasound (OR, 8,09; 95% CI 3.69-17.71) and bronchopulmonary dysplasia. Rates of neurodevelopmental disability for children with Grade III or IV intracranial hemorrhage, periventricular leukomalacia, and ventriculomegaly were 69%, 75%, and 71% respectively. There was no difference in outcomes of ELBW infants who were AGA vs. SGA (birth weight <-2 SD).

With increased use of magnetic resonance imaging, it is becoming clear that cranial ultrasound under-diagnoses milder or diffuse lesions of cerebral white matter damage (de Vries, Eken, Groenendaal, et al., 1993; Levene, 1990). Valkama, Paakko, Vainionpaa, et al. (2000)

compared the value of neonatal brain magnetic resonance imaging (MRI) with cranial sonographic findings at full-term equivalent age for predicting neuromotor outcome in VLBW infants. Fifty-one infants (birth weight <1500 grams and gestational age <34 weeks at) had MRI and cranial ultrasound at 40 weeks equivalent gestational age, and were followed until 18 months corrected age. CP was diagnosed in 23%. All infants with cerebral palsy were <29 weeks gestation at birth. Parenchymal lesions (defined as hemorrhage, PVL, infarctions, and reduction in cerebral white matter) on MRI predicted cerebral palsy with 82% sensitivity and 97% specificity (OR 171, 95% CI 13.9, 2100). Parenchymal lesions on cranial ultrasound predicted cerebral palsy with 58% sensitivity and 100% specificity. Chen, Shen, Wang, et al. (1995) demonstrated that MRI at 1 year of age confirmed changes of PVL and that these findings correlated with cerebral palsy.

Lefebvre, Gregoire, Dubois, et al. (1998) demonstrated that the Neurobiologic Risk Score (NBRS) is useful in predicting 18-month outcome of very premature infants (mean birth weight 961±179 grams, gestation 27.0±1.2 weeks, born during 1987-1992). The NBRS represents the summation of the occurrence or degree of the following variables during the entire neonatal admission period: duration of ventilation, acidosis, seizures, presence and degree of intracranial hemorrhage and periventricular leukomalacia, infection, and hypoglycemia in premature infants. NBRS scores of low (0-4), moderate (5-7), or high (≥8) correlated with the prevalence of CP (4% vs. 19% vs. 41%), severe disability (0 vs. 24% vs. 50%), and of any disability (16% vs. 30% vs. 71%), respectively. The NBRS also correlated with mean developmental quotient and prevalence of developmental quotients <90.

Consistent evidence in 6 studies has showed strong association between severe abnormal cranial ultrasound findings (c-PVL and grade III or IV ICH) and CP or neurologic abnormalities. Evidence that cystic PVL is one of the strongest predictors of CP is noted in a study by Pierrat, Duquennoy, van Haastert, et al. (2001). These investigators compared the ultrasound evolution and neurodevelopmental outcome of infants with localized (grade II) and extensive (grade III) cystic periventricular leukomalacia (c-PVL). Between 1990 and 1998, all preterm infants ≤32 weeks gestational age admitted to the Level III neonatal units of Lille and Utrecht were enrolled in the prospective cranial ultrasound study. Cystic PVL was diagnosed in 96/3451 (2.8%). The mean gestational ages were the same (29±1.8 weeks) for both groups of c-PVL. CP was diagnosed in 22 of 29 survivors (74%) with grade II c-PVL and in 26 of 27 survivors (96%) with grade III c-PVL. In this cohort of infants with c-PVL, ventriculomegaly was another excellent predictor of CP as 29 of 30 infants with ventriculomegaly developed cerebral palsy. Also, the severity of CP was worse in grade III c-PVL than grade II c-PVL. All infants with grade III c-PVL had severe handicap. Nine of 39 (23%) infants with grade II c-PVL were free of motor sequelae through 24 months follow-up compared to only 1 of 39 (3%) with grade III c-PVL. Eighty-eight percent of grade III c-PVL/CP could not walk independently in contrast to 24% with grade II c-PVL/CP.

Salokorpi, Rajantie, Viitala, et al. (1999) also demonstrated a significant, positive association between abnormal cranial ultrasound (Grade III and IV hemorrhage, PVL) and subsequent diagnosis of cerebral palsy in children who were born ELBW (<1000 grams) between 1991 and 1994 (OR 7.94, 95% CI 2.75, 22.95). The overall prevalence of cerebral palsy was 17% in the survivors of this ELBW cohort.

Cioni, Bertuccelli, Boldrini, et al. (2000) evaluated infants at one year of age who were born preterm (mean 31 ± 2.8 weeks gestational age) during 1989-1991, had periventricular leukomalacia and abnormal neurological examination at full-term equivalent age. The purpose of

the study was to evaluate whether visual function abnormalities at one-year age were associated with neurodevelopmental outcome and findings on magnetic resonance imaging at the same time in this high-risk cohort. This study found a high incidence of CP (76%) and abnormal visual function in this cohort of infants. Seventy-nine percent had at least one abnormal visual function test and >50% had multiple abnormal visual function tests: 28% abnormal fixation; 66% strabismus; and 45% abnormal grating acuity, 31% reduced visual field, and 59% had abnormal horizontal optokinetic nystagmus. The degree of visual impairment correlated with MRI findings: size of later ventricles ($p<0.000$), white matter damage ($p=0.01$), white matter loss ($p=0.003$), abnormal corpus callosum ($p=0.03$), and abnormal optic radiation ($p<0.000$). The degree of visual impairment correlated with the degree of neurodevelopmental impairment ($p=0.000$). Visual impairment was the most important variable in determining the neurodevelopmental scores of infants with leukomalacia, and was more important than motor disability and the extent of lesions on MRI.

Visual and ocular abnormalities are often associated with neurodevelopmental abnormalities in VLBW infants with cerebral white matter damage. Pennefather and Tin (2000) investigated the incidence of ocular abnormalities associated with cerebral palsy after preterm birth. They found preterm children with CP had more ocular abnormalites than preterm children without cerebral palsy: cicatricial ROP (14.8% vs. 1.6%, $p<0.0001$); cortical visual impairment (11.1% vs. 0.2%, $p<0.0001$), and strabismus (51.9% vs. 8.4%, $p<0.0001$). This study emphasizes the importance of ocular assessment of children with cerebral palsy.

In studying the relationship between growth failure in preterm infants with cystic periventricular leukomalacia, Rogers, Andrus, Msall, et al. (1998) found that 39 of 41 preterm infants (all <33 weeks gestation, born 1988 to 1993, and followed through 59 months age) developed cerebral palsy. Growth failure in children with cystic PVL was attributed solely to oral feeding impairment.

Within this review, there is very strong evidence that central nervous system injuries, such as cerebral white matter damage (periventricular leukomalacia and ventriculomegaly) and severe intracranial hemorrhage, are highly predictive of subsequent CP and abnormal neurological outcome noted in VLBW infants.

Similarly, Krageloh-Mann, Toft, Lunding, et al. (1999) prospectively compared high-risk preterm infants with term-born children at 5.5-7.5 years of age during a case-control study in terms of neurological, neuropsychological, and magnetic resonance imaging (MRI) results. The proportion of preterm infants with history of maternal pre-eclampsia $p=0.03$), mechanical ventilation >7 days (0.03), and cerebral blood flow < 2ml O_2/100g/min ($p=0.03$) were significantly different between infants who had normal MRI versus abnormal MRI. The authors demonstrated specific morphological correlation of abnormal MRI results with major central nervous system disabilities, including CP (involvement of the motor tracts), mental retardation (bilateral extensive white matter reduction or cerebellar atrophy), and severe visual impairment (severe optic radiation involvement).

Antenatal Risk Factors

Increasing evidence indicates that antenatal events contribute to the etiology and sequence of events leading to neurologic impairment and CP in VLBW infants. Antenatal inflammation, chorioamnionitis, subclinical infection, and fetal hypoxia/acidosis may play an important role via stimulating a fetal inflammatory response that injures the immature cerebral white matter (Allan,

Vohr, Makuch, et al., 1997; Gaudet and Smith, 2001; Kato, Yamada, Matsumoto, et al., 1996; Murphy, Hope, and Johnson, 1997; O'Shea, Klinepeter, and Dillard, 1998; O'Shea, Klinepeter, Goldstein, et al., 1997; O'Shea, Preisser, Klinepeter, et al., 1998; Volpe, 2001). Other antenatal events such as premature rupture of membranes (which may be related to antenatal inflammation and infection) and abruption have been evaluated for their contribution to risk of cerebral palsy and/or neurodevelopmental disability in premature infants. (O'Shea, Klinepeter, and Dillard, 1998; O'Shea, Klinepeter, Goldstein, et al., 1997; O'Shea, Preisser, Klinepeter, et al., 1998). The degree of prematurity and central nervous system injury, as discussed above, plus other neonatal factors may influence the development of CP.

Ten studies identified by the criteria of this review report the association of CP and neurologic abnormalities with antenatal factors in VLBW infants (Table 1.3b).

Table 1.3 b. Association of CP and neurologic abnormalities with antenatal risk factors in VLBW infants

Author, Year	N	Mean BW, g; GA, wk Baseline	Risk Factors	Associations		Applica-bility	Quality
				Univariate	Multivariate		
Murphy, 1997 97192793	293	BW: ND GA: 29 (24-32)	Antenatal factors [a]	n.d.	↑*	❗❗❗	B
Redline, 1998 99086405	119	BW: 995 GA: 27	Fetal placental vascular lesions [b]	↑*	- ?	❗❗	B
O'Shea, 1998 98167528 98190123	723	BW 500-1500 GA: 25	Antenatal factors [c]	↑	-	❗❗❗	B
Spinillo, 1994 94257064	231	BW: 1750 GA: 33	Moderate to severe abruptio placenta	↑	- ?	❗❗	B
Kurkinen-Raty, 1998 98197235	156	BW: 1205 GA: PROM grp: 28.2 Vs Contorl grp: 28.3	Very early (17-30 wk) PROM	↔	. ↔	❗❗❗	B
Kurkinen-Raty, 2000 20284814	206	BW : 1294 GA: 24-33 wk	Delivery for maternal or fetal indications	↔	↔	❗❗	B
Ambalavanan 2000 21031370	218	BW: 829 GA: 26	IVH, PVL, BPD, lower mat edu	-	-	❗❗	B
Spinillo, 1997 98237382	345	BW: 1371 GA: 30	Increased risk of infection [d]	↑	↑	❗	C
Burguet, 1999 99126269	167	BW: 8%>2000 GA: 25-32	Antenatal factors [e]	n.d.	↑*	❗❗❗	C
Kato, 1996 97182916	228	BW: 1031 GA: 28	Antenatal factors [f]	↑*	. -	❗❗❗	C

[a] Including chorioamnionitis and neonatal sepsis, maternal infection, cerebral parenchymal damage, ventriculomegaly, patent ductus arteriosus, hypotension, blood transfusion, prolonged ventilation, pneumothorax, sepsis, hyponatremia, parenteral nutrition and seizure.
[b] Including chorionic plate thrombi, chorioamnionitis, and severe villous edema
[c] Including multiple gestation, chorioamnionitis, materanl antibiotics, and antepartum vaginal bleeding.
[d] Prolonged rupture of membranes and meconuim stained fluid

[e] Premature rupture of membranes (PROM) ≥ 48 hrs, monochorionic twin pacentation, and RDS
[f] Malpresentation, tocolytic agents (beta 2 stimulant plus magnesium sulfate)

A case-control study by Murphy, Hope, and Johnson (1997) demonstrated that antenatal, intrapartum, and postnatal factors are independently and interactively associated with development of cerebral palsy. Murphy et al identified new neonatal risk factors for cerebral palsy in very preterm babies (<32 weeks gestation, born between 1984 and 1990) independent of coexisting, previously identified antenatal and intrapartum factors. The factors were as follows (expressed as OR; 95% CI): chorioamnionitis and neonatal sepsis (7.1;1.2,40.6); any maternal infection and neonatal sepsis (4.2; 1.6,11.2); cerebral parenchymal damage on sonography (OR 32, 12.4, 84.4); ventriculomegaly (5.4; 3.0, 9.8); patent ductus arteriosus (2.3; 1.2, 4.5); hypotension (2.3, 1.3,4.7), blood transfusion (4.8; 2.5, 9.3); prolonged ventilation (4.8; 2.5,9.0), pneumothorax (3.5, 1.6, 7.6), sepsis (3.6;1.8,7.4); hyponatremia (7.9, 2.1, 29.6), and total parenteral nutrition (5.5; 2.8,10.5), and seizures (10.0; 4.1, 24.7). Cranial ultrasound abnormalities were more predictive of CP than cardiovascular disturbances. Murphy's study demonstrates that antenatal factors such as intrauterine inflammation, infection, and conditions that predispose to hypoxic-ischemic injury were significantly associated with development of CP. Both antenatal factors and postnatal factors were influenced by the degree of prematurity.

Redline, Wilson-Costello, Borawski, et al. (1998) examined the link between placenta pathology and neurologic outcome in VLBW infants. They analyzed placentas from mothers of children who were born VLBW and had subsequent neurologic impairments (CP and other neurologic abnormalities) vs. placentas from mothers of control children (matched for gestational age, birth weight, gender, race) to assess antenatal processes that might be associated with subsequent cerebral palsy and neurologic impairment in VLBW infants (born 1983-1991). They found that the presence of chorionic plate thrombi, seen only with chorioamnionitis, and severe villous edema were statistically associated with neurologic impairment, including CP, at 20 months corrected age. This study demonstrates an association between fetal placental vascular lesions associated with chorioamnionitis and subsequent neurologic impairment of VLBW infants.

O'Shea, Klinepeter, and Dillard (1998) conducted a case-control study to analyze associations between antenatal factors and CP in a geographically-based cohort of premature infants (birth weights 500-1500 grams) born between 1978 and 1989 and followed for 1 year. The prevalence of cerebral palsy was 9% among premature children returning for 1-year follow-up. As in other studies, gestational age was associated with risk of CP (OR per week increase in gestational age = 0.79 (95% CI 0.66, 0.93). Antenatal factors independently and strongly associated with cerebral palsy were multiple gestation, chorioamnionitis, maternal antibiotics, antepartum vaginal bleeding, and labor lasting less than 4 hours. Pre-eclampsia and delivery without labor were associated with decreased risk of CP. Although the focus of this study was on antenatal factors associated with CP, O'Shea et al also found that a majority of infants with CP had an antecedent major cranial ultrasound abnormality, most often intraparenchymal echodensity (70% of infants with diplegia; 52% with quadriplegia, 32% with diplegia vs. 2% of controls). Forty-seven percent of the cases had no major ultrasound abnormality.

Spinillo, Fazzi, Stronati, et al. (1994) compared early morbidity and neurodevelopmental outcome in low birth weight infants (<2500 grams) delivered after third trimester bleeding with consecutive controls of similar gestational age with no maternal history of third trimester bleeding. The period of study was between 1983-1989. This study demonstrated that moderate to

severe abruptio placenta is associated with increased risk of poor outcome (death or cerebral palsy) in low birth weight infants compared to controls (OR 3.9, 95% CI 1.2, 12.1).

Kurkinen-Raty, Koivisto, and Jouppila (1998) conducted two studies, which evaluated the long-term impact of very early preterm (17-30 weeks gestation) premature rupture of membranes (PROM) and of maternal or fetal indications for delivery. In the first study evaluating very early preterm PROM, the investigators demonstrated late, long-term pulmonary problems of preterm infants born to mothers with very early PROM, but the results of this study did not reveal any effect of very early PROM on neurologic outcome in this cohort. The infants followed in this study were compared to infants delivered from mothers with spontaneous preterm delivery without very early PROM during the same time period of 1990-1996. The mean gestational age at birth was similar between the PROM and Control groups (PROM 28.2 vs. Control 28.3 weeks). The incidence of cerebral palsy was high, but not different, in both preterm groups (18% vs. 16%, OR 1.2, 95% CI 0.4, 3.1) at one year of age.

In Kurkinen-Raty's second study, premature infants delivered between 24 and 33 weeks gestational age for either maternal or fetal indications were compared to premature infants of similar gestational age born to mothers who had spontaneous preterm delivery. There was no difference between the two groups with respect to neurologic outcome at one year of age. The mean gestational age at birth was similar between the two groups (Indicated Delivery 30.5 vs. Spontaneous Preterm Delivery 30.4 weeks). The incidence of cerebral palsy was similar to that reported by others and not different between the preterm groups (Indicated Delivery 6% vs. 11%, OR 0.6, 95% CI 0.2, 1.6) at one year of age. The incidence of delayed motor development was similar between groups (Indicated Delivery 10% vs. Spontaneous Preterm Delivery 9%, OR 1.2, 95% CI 0.5,3.0) (Kurkinen-Raty, Koivisto, and Jouppila, 2000).

Ambalavanan, Nelson, Alexander, et al. (2000) conducted a retrospective cohort study of a regional Level III NICU database to identify major determinants of adverse neurodevelopmental outcome in ELBW (<1000 grams birth weight) infants born 1990-1994. The determinants for major handicap included intraventricular hemorrhage, necrotizing enterocolitis ≥ Stage 2, black race, and no chorioamnionitis. Determinants of low psychomotor developmental index (PDI) included intraventricular hemorrhage, periventricular leukomalacia, BPD, lower maternal education, and no chorioamnionitis. These determinants accounted for <20% of the variance in neurodevelopmental outcomes. The study has limitations of being retrospective, small sample size, and short follow-up period. The determinants of neurodevelopmental outcome identified in this study are similar to other studies except one notable exception-'no chorioamnionitis'. Ambalavanan et al. found that infants with chorioamnionitis had higher MDI, and PDI and incidence of major handicap was similar between infants exposed to chorioamnionitis vs. no chorioamnionitis. Chorioamnionitis has been identified in numerous studies, as noted above, as an independent risk factor for cerebral white matter damage. The authors offered no clear explanation for these findings.

Spinillo, Capuzzo, Orcesi, et al. (1997) also evaluated effects of antenatal risks on neonatal death and CP in a cohort of preterm infants (24-33 weeks) delivered between 1987-1992. Among 310 infants assessed at 2 years, 12.5% had CP. Among children with cerebral palsy, 34% of CP was diagnosed in infants born between 23-33 weeks gestational age. Prolonged rupture of membranes (>48 hours) was associated with increased risk of CP in univariate analysis. Gestational age and meconium stained fluid were independent predictors of CP in the multivariate analysis. Both prolonged rupture of membranes and meconium stained fluid are associated with increased risk of infection. Thus, it is possible that these factors are co-variates

of subclinical antenatal infection that predisposes to brain injury and leads to cerebral palsy (Spinillo, Capuzzo, Orcesi, et al., 1997; Spinillo, Fazzi, Capuzzo, et al., 1997). Increasing gestational age was associated with decrease in odds of cerebral palsy.

Burguet, Monnet, Pauchard, et al. (1999) conducted a prospective, geographically-defined (France), collaborative study in 1990-1992 to identify antenatal risk factors of neurodevelopmental disabilities in very premature (GA<33 weeks), singleton or twin, non-malformed infants (n-203). The study was conducted prior to routine use of antenatal steroids. Among 171 survivors, 167 (98%) were evaluated at 2 years of age: 22 (13%) had CP; Significant risk factors for neurologic disabilities by a multivariate approach included premature rupture of membranes ≥48 h (OR 4.3, 95% CI 1.6-11.8); monochorionic twin placentation (OR 6.0, 95% CI 1.7-21.3), and respiratory distress syndrome (OR 2.8, 95% CI 1.1-7.1). Incidence of CP was 7% in infants without PROM, 20% in infants with PROM <48 hrs, 30% in PROM 48 hrs to 7 days, 11% in PROM >7 days, chi-square trend: p=0.004.

Kato, Yamada, Matsumoto, et al. (1996) noted additional antenatal factors are significantly related to increased risk of CP and neurologic impairment. These factors include malpresentation, tocolytic agents (beta 2 stimulant plus magnesium sulfate).

Bronchopulmonary Dysplasia (BPD) And Postnatal Systemic Glucocorticoid Therapy (Dexamethasone)

Numerous studies have documented that mechanical ventilation (especially prolonged mechanical ventilation), and bronchopulmonary dysplasia (BPD), or neonatal chronic lung disease, are associated with adverse neurodevelopmental outcome in premature infants (Cheung, Barrington, Finer, et al., 1999; Kim, Namgung, Chang, et al., 1999; Murphy, Hope, and Johnson, 1997; Palta, Sadek-Badawi, Evans, et al., 2000; Pasman, Rotteveel, Maassen, et al., 1998; Salokorpi, Rajantie, Viitala, et al., 1999; Thompson, Buccimazza, Webster, et al., 1993). In addition, there is increasing evidence that the use of postnatal systemic glucocorticoid therapy, specifically dexamethasone, for the prevention or treatment of neonatal chronic lung disease may have an adverse effect on long-term neurologic development and increase the risk of CP (Barrington, 2001; Shinwell, Karplus, Reich, et al., 2000).

Eight studies (Table 1.3c) identified in this review provide evidence that BPD and systemic dexamethasone may be factors influencing the risk of CP and neurologic impairment in VLBW infants.

Table 1.3 c. Association of CP and neurologic abnormalities in VLBW with BPD and BPD and postnatal systemic glucocorticoid therapy

Author, Year	N	Mean BW, g; GA, wk Baseline	Risk Factors	Associations Univariate	Associations Multivariate	Applica-bility	Quality
Allan, 1997 97336492	**337**	BW: 600-1250 GA: 28	BPD	↑	**ND**	❗❗	A
O'Shea, 1999 99318938	95	Dexamethasone grp: BW: 747 (420-1362) GA: 25 (23-29) Placebo grp: GA: 26 (23-31) BW: 775 (495-1324)	BPD and Dexametha-sone	↑	-	❗❗❗	A
Hack, 2000 20358826	221	BW: 813 GA: 26	BPD and postnatal steroid	↑	-	❗❗❗	A
DeReginer, 1997 98041177	**174**	GA: 27 BW: 1014	BPD	↑*	-	❗❗❗	B
Gregoire, 1998 98232532	217	BW: 1039 GA: 24-28	BPD oxygen dependency [a]	↔	«	❗❗	B
Palta, 2000 20096107	425	GA: 29 BW: 1003	BPD; IVH	↑*	-	❗❗	B
Victorian Infant Collaborative study Group, 2000 20307288	346	Corticosteroids & No corticosteroids: BW: <1000 GA: <28	Postnatal steroid Rx	↑*	↑*	❗❗	B
Cheung, 1999 99146391	164	BW: 961 GA: 27	Predischarge apnea [b] duration of ventilation and IVH	↑*	↑*	❗❗	B

[a] Oxygen dependency: requiring oxygen at 28 days but not at 36 weeks CGA, requiring oxygen at 36 weeks CGA; and, not oxygen dependent
[b] Frequency and degree of oximetry desaturation: duration of ventilation and IVH

In Allan's study of the determinants of cerebral palsy in a cohort of VLBW (600-1250 g) infants enrolled in a randomized, placebo-controlled clinical trial of indomethacin prophylaxis for intraventricular hemorrhage, 15% of 177 infants with BPD and 4% of 203 infants without BPD had CP at 36 months corrected age ($p<0.001$) (Allan, Vohr, Makuch, et al., 1997).

O'Shea, Kothadia, Klinepeter, et al. (1999) demonstrated that a 42-day tapering course of dexamethasone in VLBW infants, with severe, evolving neonatal chronic lung disease, was associated with an increased risk of cerebral palsy (25% dex vs. 7% placebo, OR 5.3, 95% CI 1.3, 21.4) and abnormal neurologic examination (45% dex vs. 16% placebo, OR 3.6, 95% CI 1.2, 11.0). More dexamethasone recipients had major intracranial sonographic abnormalities compared to placebo controls (21% vs. 11%). This study was not able to determine if the increased risk was due to an adverse effect of dexamethasone per se or to improved survival of infants who were already at increased risk for neurologic disability.

Hack, Wilson-Costello, Friedman, et al. (2000) found in a former-ELBW group at 20 months' corrected age that chronic lung disease, or bronchopulmonary dysplasia, and postnatal

steroids were predictive of subnormal MDI and abnormal neurologic outcome. The effects of systemic postnatal steroids independent of chronic lung disease was not evaluated.

deRegnier, Roberts, Ramsey, et al. (1997) evaluated whether there was an association between severity of BPD in VLBW infants and 5-year neurodevelopmental, sensory, and growth outcome. In order to isolate the effect of BPD on outcome, infants were excluded if they had conditions known to adversely affect neurosensory status (e.g. intraparenchymal cranial ultrasound abnormalities or ventriculomegaly). They demonstrated that the risk of adverse neurodevelopmental and sensory outcome increased with decreasing gestational age and with increasing severity of BPD in VLBW infants: no BPD (3.6% adverse neurodevelopmental); mild BPD (21.4% adverse neurodevelopmental); severe BDP (31.6% adverse neurodevelopmental) ($p<0.001$). The odds of cerebral palsy was significantly increased in the BPD group (vs. no BPD group) (unadjusted odds 6.4, 95% CI 1.05, 139.8).

Gregoire, Lefebvre, and Glorieux (1998) prospectively compared health and developmental outcomes at 18 months of three cohorts of premature infants (GA 24-28 weeks): infants requiring oxygen at 28 days but not at 36 weeks CGA, infants requiring oxygen at 36 weeks CGA, and infant who were not oxygen dependent at 28 days. No significant difference in incidence of CP was found between the 3 groups, but a significantly lower mean developmental quotient was found in infants requiring oxygen at 36 weeks CGA.

Palta, Sadek-Badawi, Evans, et al. (2000) found that and bronchopulmonary dysplasia (odds ratio, 2.3; 95% confidence interval, 1.2-4.6) and intraventricular hemorrhage (odds ratio, 2.3 per grade; 95% confidence interval, 1.8-2.8) were independently predictive of cerebral palsy and of functional outcome in their study of 425 VLBW (<=1500 g) infants born 1988-1991 in one of 6 NICUs who were followed to an average age of 5 years. The study was designed to compare outcomes before and after introduction of surfactant. Cerebral palsy was present in 12.6% of the children, and the incidence did not change after the introduction of surfactant.

Investigators of The Victorian Infant Collaborative Study Group (2000) studied the association between postnatal systemic glucocorticosteroid therapy and sensorineural outcome at 5 years of age among children who were born extremely premature (<1000 gram or gestational age <28 weeks) during 1991-1992. Survivors treated with systemic glucocorticoid therapy compared to those without corticosteroid therapy had significantly higher rates of cerebral palsy (23% vs. 4%), blindness (4% vs. 1%), and intelligence quotient greater than 1 SD below the mean (54% vs. 32%), respectively. The association between adverse sensorineural outcome and postnatal glucocorticoid therapy remained significant after adjustments for potentially confounding factors.

Cheung, Barrington, Finer, et al. (1999) prospectively evaluated the relationship between prehospital discharge apnea with subsequent neurodevelopment at 24 months adjusted age in premature infants (<1250 grams birth weight and ≤32 weeks gestational age) during 1990-1993 (mean 961±185 grams; mean gestational age 27±2 weeks). The frequency and degree of oximetry desaturation during predischarge apnea correlated with mental and motor developmental scores, especially those with grade 3 or 4 intraventricular hemorrhage. Duration of ventilation and grade of intraventricular hemorrhage remained the most powerful predictors of mental and motor development in the total premature population.

Parenting/ Psychosocial Factors

One study (Table 1.3d) was identified in this review that evaluated the association of CP and neurologic abnormalities to parenting / psychosocial factors in VLBW infants.

Table 1.3d. Association of CP and neurologic abnormalities in VLBW infants parenting / psychosocial risk factors

Author, Year	Pop	N	Mean BW, g; GA, wk Baseline	Risk Factors	Associations Univariate	Multivariate	Applica-bility	Quality
Leonard,1990 90204169	BW <1250 g	129	BW: 1003 GA: 29	Poor parenting	↔	ND	⁇	B

Leonard, Clyman, Piecuch, et al. (1990) (Table 1.3 D) followed a cohort of 129 premature infants (BW <1250 g) for more than 4.5 years to determine the independent effects of medical risk factors (intracranial hemorrhage and bronchopulmonary dysplasia) and a social-parenting risk factor (abuse or neglect) on neurodevelopmental outcome. Neurologic disability (including neuromotor and cerebral palsy) increased with severity of intracranial hemorrhage (ICH Grade I or II = 0% vs. ICH Grade III or IV = 21%). Neurologic abnormalities were higher in infants with a positive parenting risk factor (17% vs. 6%) but the difference was not statistically significant in contrast to the significant influence of parenting risk factor on cognitive outcome. Low socioeconomic status per se could not account for adverse effects of poor parenting (abuse or neglect). This and other studies illustrate the vulnerability of high-medical risk VLBW infants to parenting, social, and environmental risk factors. It underscores the importance of having constructive parenting, social, and environmental milieu for children at increased risk for neurodevelopmental problems related to their biomedical risk of being VLBW.

The relationship between biological/medical risk factors and parenting/ psychosocial risk factors on subsequent neurodevelopmental outcome is complex. The interaction of these factors may have additive or synergistic positive or negative effects on an infant's outcome. Full expression of disabilities is influenced in part by parenting, social, and environmental factors.

Other Postnatal Factors

Table 1.3e. Association of CP and neurologic abnormalities in VLBW plus other factors (Gender. Size for GA)

Author, Year	N	Mean BW, g; GA, wk Baseline	Risk Factors	Associations Univariate	Multivariate	Applica-bility	Quality
Allan, 1997 97336492	**337**	BW: 600-1250 GA: 28	Gender, AGA / SGA	↔	↑	❗❗	A

				Associations			
Dezoete, 1997 97359687+	105	BW: 835 GA: 27	AGA / SGA	↔	ND	! ! !	B
Spinillo, 1994 94257064	231	BW: 1750 GA: 33	Male sex	↑	↑	! ! !	C
Spinillo, 1997 98237382	345	BW: 1371 GA: 30	Male sex	↑	↑	!	C
Dammann, 2001 21334215	324	BW: < 1500 GA: ND	AGA / SGA	↔	ND	! !	C

The association between gender and CP varies among studies. Two of Spnillo et al. studies indicate that male sex was significantly associated with CP among premature infants (Spinillo, Capuzzo, Orcesi, et al., 1997; Spinillo, Fazzi, Stronati, et al., 1994). However, Allan, Vohr, Makuch, et al. (1997) found gender not to be a significant antecedent of CP.

With respect to size for gestational age, Allan, Vohr, Makuch, et al. (1997), Dezo ete, MacArthur, and Aftimos (1997), and Dammann, Dammann, Allred, et al. (2001) found no association between growth restriction (when matched for gestational age) and CP.

Evidence That VLBW With Or Without Other Conditions Is Associated With Abnormal Cognitive Development And MR (Evidence Tables 1- 4)

This portion of the VLBW Project examines the evidence linking clinical factors that alone, in combination, or in addition to birth weight predict significant cognitive disability in former very low birth weight infants. The narrative in this section is organized as follows:

1. Definitions and Assessment of Cognitive Development
2. Evidence that VLBW Infants Are At Increased Risk of MR and Estimates of Prevalence
    - A. VLBW
    - B. ELBW
    - C. Changes in incidence of MR with time
3. Evidence that Specific Risk Factors are Independently Associated with MR in VLBW Infants
    - A. Birth weight
    - B. Gestational age
    - D. Acquired intracranial lesions
        - i. ICH
        - ii. PVL
        - iii. IVH, Indomethacin, and MR
    - E. Bronchopulmonary dysplasia (BPD)
    - F. Surfactant therapy
    - G. Social Risk, Race, and Maternal Education

    i. Social risk
    ii. Race
    iii. Maternal Education
H. Gender
I. Illness Severity
J. Ante-partum and intrapartum factors
    i. Antenatal corticosteroid therapy
    ii. Intrauterine growth retardation (IUGR) / Small for gestational age (SGA)
K. NEC
L. Sepsis and Meningitis
M. Postnatal Corticosteroid Therapy
N. Other

Definitions and Assessment Of Cognitive Development

The American Association on Mental Retardation defines *mental retardation* (MR) as sub-average general intellectual functioning that originates in the developmental period, manifests before 18 years of age, and is associated with impairment in adaptive behavior (American Association on Mental Retardation, 1992). MR can result from a wide variety of insults that may affect the developing brain, including chromosomal disorders, single gene defects, syndromes including primary brain malformations, toxic exposures, infections, and environmental problems. In addition, many acquired conditions complicating the hospital course of VLBW infants may increase risk for cognitive delay and MR. Moreover, epidemiological factors leading to premature birth may contribute to sub-optimal cognitive development subsequently.

Table 2.1. Representative ability test scores defining significantly delayed or deficient cognitive development/mental retardation

	Score		
	Bayley MDI	Stanford-Binet IQ	WISC-R
Significantly delayed/deficient	< 70	<68	<70

Representative ability test scores defining significantly delayed or deficient cognitive development/mental retardation. (Task Force for the Handbook of Psychiatric Measures, 2000; Wodrich, 1984)

In general, cognitive development in childhood is assessed with standardized tests that examine a broad range of abilities and yield a score. The child's test score is related to chronological age-appropriate standards or percentile ranks in order to assess relative progress and identify those developing abnormally. In the case of premature infants, chronological age is usually corrected for degree of prematurity when the performance of children less than three years of age is compared to age-appropriate standards. Several well-validated standardized developmental scales are available for assessing cognitive development in early childhood (Task Force for the Handbook of Psychiatric Measures, 2000; Wodrich, 1984). Such tests naturally overlap each other with respect to areas of cognitive development examined, but differ in many

aspects including specific purpose and methods, calibration, appropriate age of use, level of training required for administering personnel, and degree of correlation with eventual adult function. They differ, as well in their usefulness for making specific diagnoses; the interested reader should consult specific references for further information on this robust subject. The Bayley Scales of Infant Development Mental Development Index (Bayley MDI), Stanford-Binet Intelligence Scale (Stanford-Binet IQ) and Wechsler Intelligence Scale for Children-Revised (WISC-R) are representative tests of cognitive development that are widely used as clinical and research tools for assessing premature infants

Evidence that VLBW Infants Are at Increased Risk of MR and Estimates of Prevalence

Eleven studies (Table 2.2) were reviewed in this section. Studies were categorized into three subsections: A. VLBW infants (BW< <1500 g), B. ELBW infants (BW < 1000 g); C. Changes in incidence of MR with time. Table 2.2 summarized Part A and Part B results. Part C results are in Table 2.3.

Table 2.2. Incidence of Mental Retardation in VLBW / ELBW Infants

Author, Year	N	Mean BW, g; GA, week Baseline	Measures	Association (% of MR)	Applic-ability	Quality
Hack, 1996 97060805	249	BW: 1177 GA: 30	Major neurosensory abnormality	↑ (VLBW 10% vs. nl BW 0%)	! ! !	A
Corbet, 1995 95264244	597	BW: 933 GA: 27	MDI < 69	17%	! ! !	A
Gerdes,1995 95264241	508	BW: Sample 1: 907 Sample 2: 911 GA: 27	Bayley MDI <70	1 dose 22% 3 dose 18%	! ! !	A
Vohr, 2000 20295211	1056	BW: 401-1000	Bayley MDI <70	37%	! ! !	A
Ambalavanan 2000 21031370	218	BW: 829 GA: 26	Bayley MDI <68	12%	! ! !	A
Hack, 2000 20358826	221	BW: 813 GA: 26	MDI < 70	42%	! ! !	A
Piecuch, 1997 (in Pediatrics) 97456215	446	BW: 500-999 GA: 24-25	Cognitive abnormality and/or other neurological deficits	35%	! !	B
Saigal, 2001 11483807	154	ELBW grp: BW: 835 GA: 27	Neurosensory impairment	↑ (28% vs. 2%)	! !	B

Author, Year	N	Mean BW, g; GA, week Baseline	Measures	Association (% of MR)	Applic-ability	Quality
			Learning disability	↑ (34% vs. 10%)		
			DQ –3 to –2 SD	6%		
Doyle, 2001 11433066 Victorian Infant Collaborative study Group, 1997 97290716	225	BW: ND GA: 23-27	IQ < -2 SD	↑ (15.4% vs. 4.1%)		B
Casiro, 1995 95264245	89	Exosurf: BW: 652 GA: 26 Placebo: BW: 661 GA: 25	Bayley MDI < 69	23-31%		B
Agustines, 2000 20279724	36	BW: 674 (500-750) GA: 25 (24-29)	MDI < -2 SD	28%		B
Battin, 1998 99002694	44	BW: < 800 GA: 23-25	MDI < -2 SD	18%		C

↑ increased the risk of MR, compared to NBW controls
↑* significantly increased the risk of MR, compared to NBW controls

VLBW

The evidence identified by our search methods demonstrates clearly that VLBW infants have high rates of cognitive abnormality in early childhood compared with normal birth weight controls. Hack, Weissman, and Borawski-Clark (1996) found that among 249 VLBW infants from a 1977-1979 cohort the incidence of major neurosensory impairment at 8 years of age was 10% versus 0% of normal birth weight controls. When the same cohort was evaluated at 20 years of age, the prevalence of IQ <70 was 6.7%, a 4-fold increase in risk compared with term controls (Hack, Flannery, Schluchter, et al., 2002). Others have found comparable rates of MR in VLBW infants (Corbet, Long, Schumacher, et al., 1995; Gerdes, Gerdes, Beaumont, et al., 1995). Given current rates of birth and VLBW in the United States (Guyer, Hoyert, Martin, et al., 1999), these results suggest that there may be more than 3500 new cases of MR in the United States each year in former VLBW infants.

ELBW

Among ELBW infants the prevalence of MR appears to be still higher. Vohr, Wright, Dusick, et al. (2000) reported for the 12-center National Institute of Child Health and Human Development Neonatal Research Network reported developmental outcomes of ELBW survivors from a cohort born 1993-1994. Of 1,056 infants assessed at 18 to 22 months-corrected age, 37% had Bayley MDI <70. Ambalavanan, Nelson, Alexander, et al. (2000) retrospectively studied 218 ELBW infants and found Bayley MDI <68 in 12% at 18 months of age

Hack, Wilson-Costello, Friedman, et al. (2000) and colleagues studied determinants of neurodevelopmental outcome among ELBW infants born between 1992 and 1995. This study was noteworthy for a high rate of follow-up: Of 333 ELBW infants admitted during the study period, 241 survived to 20 months corrected age and 221 were studied. Among the studied cohort, 14% had intraventricular hemorrhage ≥ grade 3, 7% had periventricular leukomalacia, and 40% were dependent upon supplemental oxygen at 36 weeks-corrected age. At the time of 20 month evaluation, 42% had Bayley MDI <70 and 26% had borderline scores (70 to 84). Forty eight percent had at least one significant neurodevelopmental impairment defined as subnormal MDI score, neurological abnormality, blindness, or deafness, while 20% had two or more impairments.

Piecuch, Leonard, Cooper, et al. (1997) studied cognitive development in 446 ELBW infants. All infants in this study were born between 1979-1991, and were followed to 55 ± 33 months of age. The authors found entirely normal neurological development in 61% of infants, without cognitive, neurosensory, or neurological deficit. Cognitive abnormality occurred alone or in combination with other deficits in 35%.

Saigal, Stoskopf, Streiner, et al. (2001) examined outcomes at 12-16 years of age among 154 infants 500-1,000 g at birth compared with 125 full-term controls. The ELBW infants compared to full-term controls were significantly more likely to have neurosensory impairment (28% versus 2%) or learning disability (34% versus 10%).

Others found similarly high rates of cognitive delay among extremely premature infants in studies based on gestational age. In a series of population-based cohort studies, Australia's Victorian Infant Collaborative Study Group found that among infants 23-27 weeks gestation (equivalent to ELBW AGA infants) born 1991-92 and examined at two and five years of age, incidence of IQ > 2 SD below the mean was 15.4%, compared with 4.1% among full-term controls (Doyle, Casalaz, and The Victorian Infant Collaborative Study Group, 2001; The Victorian Infant Collaborative Study Group, 1997).

Others have found similar rates of MR in ELBW infants or subgroups. In a study of infants 500-749 grams, Casiro, Bingham, MacMurray, et al. (1995) found an overall incidence of Bayley MDI <69 of 23-31%. Agustines, Lin, Rumney, et al. (2000) examined infants 500-750 grams at 30 months corrected age. Battin, Ling, Whitfield, et al. (1998) found that 18% (8 of 44) of ELBW infants 23-26 weeks gestation had Bayley MDI >2 standard deviations below the mean when examined at 18 months. Overall, 36% of this cohort had significant impairment, and 14% had multiple handicaps. Bayley MDI was normal in 32% of infants, and was >2 SD below the mean in 28%. Unfortunately, only 57% of patients were studied at follow-up, and small numbers (total n=36) precluded subgroup analysis.

Changes in incidence of MR with time

Evidence identified by our search of 4 studies suggests that the incidence of MR in ELBW infants may not be changing with time, despite recent increases in survival rates in this birth weight category. (Table 2.3).

Table 2.3. Changes in incidence of MR with time in LBW infants

Author, Year	N	Year of Birth	Mean BW, g; GA, week Baseline	Measures	Association (% of MR)	Applic-ability	Quality
Hack, 1996 97066007	166	1982-1988	BW: 687 (560-740) GA: 26 (22-31)	MDI < 70	26%	! ! !	A
	114	1990-1992	BW: 671 (502-742) GA: 26 (22-31)	MDI < 70	20%		
Victorian Infant Collaborative study Group, 1997 97290716	212	1985-1987	BW: 500-999 GA: ND	DQ < -3 SD	6%	! !	B
				DQ –3 to –2 SD	4%		
Doyle and Victorian Infant Collaborative Study Group, 2001 11433066	241	1991-1992	BW: 500-999 GA: ND	DQ < -3 SD	6%		
				DQ –3 to –2 SD	5%		
Battin, 1998 99002694	44	1991-1993	BW: < 800 GA: 23-25	Sig. impairment	36%	! !	C
				Multi. Handicaps	14%		

Hack, Friedman, and Fanaroff (1996) compared neurodevelopmental outcome for a cohort of infants birth weight 500-750 g born 1982-1988 to those of a similar cohort born 1990-1992. They found no significant difference in neurodevelopmental outcomes at 20 months-corrected age between the two eras. Overall, 26% of infants in the 1982-1988 cohort had subnormal cognitive function with Bayley MDI <70 compared with 20% in the 1990-1992 cohort.

The Victorian Infant Collaborative Study Group found no difference in outcomes among 1991-92 infants when compared with a 1985-87 control cohort (Doyle, Casalaz, and The Victorian Infant Collaborative Study Group, 2001; The Victorian Infant Collaborative Study Group, 1997).

Battin, Ling, Whitfield, et al. (1998) found that among ELBW infants 23-26 weeks gestation born in 1991-1993, the rates of significant impairment (36%) and multiple handicaps (14%) were

not significantly changed compared with a 1983-1989 cohort born prior to routine use of surfactant or antenatal steroids.

Evidence that Specific Risk Factors Are Independently Associated With MR in VLBW Infants

Forty-four studies were reviewed in this section. Table 2.4 summarizes results of each individual study in methodological quality order.

Table 2.4. Association of Mental Retardation / Disability to Independent Risk Factors in LBW infants

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	MR / Disability measures	Association (% of MR / Disability in overall sample)	Applic-ability	Quality
Anderson, 1996 96314587 Smith, 1996 9708185 Wildin, 1995 95385294 Wildin, 1997 97422739	112	BW: 1944 GA: 29	SES status	Bayley's MDI & PDI	↔ m	❗❗❗	A
Corbet, 1995 95264244	597	Surfactant: BW: 934 GA: 27 Placebo: BW: 931 GA: 27	Synthetic surfactant Rx	MDI < 69, PDI<69, CP, Sensorineural hearing deafness, Blindness, ROP	↔	❗❗❗	A
Hack, 2000 20358826	221	BW: 813 GA: 26	BW 500-749 g vs. 750-999 g	MDI < 70	↔	❗❗❗	A
			GA, IVH ≥ grade III, PVL, gender		↔ m		
			CLD/BPD		↑* m		
			High social risk		↑* m		
			Black race		↑		
Kraybil, 1995 95264242	258	Surfactant BW: 1022 GA: 28 Placebo: BW: 1028 GA: 28	Surfactant Rx	MDI < 69, PDI<69, CP, Sensorineural hearing deafness, Blindness, ROP	↔	❗	A
Lefebvre, 1998 98387703	50	GA: 27 BW: 961 (585-	Low risk	DQ < 80	12%	❗❗	A
	37		Moderate risk		24%		

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	MR / Disability measures	Association (% of MR / Disability in overall sample)	Applic-ability	Quality
	34	1450)	High risk		71%		
Ment, 1996 97040638 Ment, 2000 20164956	431 ? 343 at 36 mos ? 337 at 54 mos	<u>Indomethacin:</u> BW: 945 GA: 28 <u>Placebo:</u> BW: 988 GA: 28	Low dose indomethacin decreased both incidence and severity of IVH	IQ < 70	↓	! !	A
Schmidt, 2001 21298249	1202	<u>Indomethacin:</u> BW: 782 GA: 26 <u>Placebo:</u> BW: 783 GA: 26	Indomethacin decreased the frequency of IVH and PVL	Survived w/o neurosensory impairment	↑	! ! !	A
Wood, 2000 20373840	283	BW: ND GA: 22-25	GA	Disability [i]	↑ (23%)	! ! !	A
				MDI < -2 SD	(19%)		
Singer, 1997 98049057 Singer, 2001 21163669	206	GA: 28 BW: 1077	IVH, BPD	MDI < 70	↔ [m] (15%)	! ! !	A
			Minority race		↑		
Whitaker, 1996 97040639	597	BW: 1481 GA: 32	GA, gender	IQ < 68 (Stanford-Binet) Borderline intelligence	↔ [m]	! ! !	A
			IVH, parenchymal lesions enlargement		↑* [m]		
			Maternal social risk		↑* [m]		
Ambalavanan 2000 21031370	218	BW: 829 GA: 26	IVH ≥ grade III, BPD	MDI < 68	↑* [m] (12%)	! !	B
Buhrer, 2000 20280896	352	GA: 29 (23-37) BW: 1149 (430-1495)	CRIB	IQ (Griffiths) < -2 SD	↔ [m] (22%)	! ! !	B
Cheung, 1998 99059896	164	BW: 955 GA: 27 (22-32)	IVH ≥ grade III	MDI < -3 SD	↑ (10%)	!	B
deReginer, 1997 98041177	174	BW: 1014 GA: 27	Mild / Severe CLD [a]	MDI < -2 SD	5%	! ! !	B
Dezoete, 1997 97359687	105	BW: 835 GA: 27	IVH ≥ grade III	Moderate /Severe disability [b]	↑*	! ! !	B

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	MR / Disability measures	Association (% of MR / Disability in overall sample)	Applic-ability	Quality
Doyle, 2001 11433066 Victorian Infant Collaborative study Group, 1997 97290716	225	BW: Sample 1: 797 Sample 2: 932 GA: Sample 1: 26 Sample 2: 27	GA	Major disability [c]	↑* (19%)		B
Ekert,1997 97251211	104	BW: 962 GA: 27	Visual evoked potentials	Abnormal neurodevelopmental outcome	↔		B
Finer, 1999 99436635	10	BW: : 663 (440-968) GA: 25 (24-28)	ELBW requiring CPR	Abnormal neuromotor function	↔ [m]		B
Futagi, 1999 99450356	276	<u>Surfactant cohort:</u> BW: 786 GA: 27 <u>Presurfactant cohort:</u> BW: 834 GA: 27	Surfactant Rx	Neurodevelopmental outcomes	↔		B
Katz-Salamon, 2000 20332284	86	GW: 907 GA: 26	BPD	Lower Griffith developmental scores	↑*		B
Koller, 1997 97193708	203	BW: 1170 GA: 31	BW, GA, health index, neurological status @ 1 yr, male gender; maternal educ.	Worse cognitive development pattern (Bayley scales)	↑*		B
Pierrat, 2001 27221167	60	BW: 1003 GA: 29	Grade II or III c-PVL	Motor delay [f]	↑		B
Piecuch, 1997 98012134	18	GA = 24 BW: 668	GA, male gender	Deficient Bayley scores	↑		B
Vohr, 1999 99332101	278	BW: 965 GA: 28	Early IVH [h] vs. Late IVH	Binet IQ < 70	↑* (38% vs. 19%)		B
Gerner, 1997 97329414	171	BW: 1047 GA: 28	PVL	Worse Griffith mental development, performance subscales	↑* [m]		B
Gregoire, 1998 98232532	48	BW: 997 GA: 27	Mild BPD [a]	Total disability [d]	↑		B
	93	BW: 930 GA: 27	Severe BPD [a]		↑*		

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	MR / Disability measures	Association (% of MR / Disability in overall sample)	Applic-ability	Quality
Leonard,1990 90204169	129	BW: 1003 GA: 29	BPD	IQ < -2 SD (Stanford-Binet)	↔	! ! !	B
			IVH ≥ grade III, at risk parenting [e]	IQ < -2 SD (Stanford-Binet)	↑*		
				Neurologic abnormalities	↑*		
Piecuch, 1997 (in Pediatrics) 97456215	446	BW: 500-999 GA: 24-25	100g subgroups of BW<1000 g	Cognitive abnormality and/or other neurological deficits	↔ (35%)	! !	B
			GA		↔		
Piecuch, 1997 98012134	18	GA = 25 BW: 790	GA,male,gender	Deficient Bayley scores	↑	! !	B
	30	GA = 25 BW: 790					
	38	GA = 26 BW: 842					
Schendel, 1997 98033417	920	VLBW grp: BW: 1088 GA: 28 LBW: grp: BW: 2184 GA: 36	VLBW	Greater DELAY [g] (DDST-II)	↑*	! ! !	B
Stathis, 1999 99325758	23	GA: 28 (27-28) BW: 860 (837-833)	HC < 3%tile	McCarthy general cognitive index < 70	61%	! !	B
	13		HC 3-10 %tile		77%		
	40		HC > 10 %tile		30%		
Van Wassenaer, 1997 98103082	158	BW: < 1500 g GA: 25-30	Thyroxine Rx	Worse Bayley MDI	↓	! !	B
			BW		↑		
Vohr, 2000 20295211	1151	BW: 501-1000 g GA: ND	100g subgroups of BW<1000 g	MDI < 70	↔ [m] (37%)	! ! !	B
			IVH ≥ grade III, severe BPD [a]		↑* [m]		
			Surfactant replacement Rx		↔ [m]		
			White race		↓ [m]		

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	MR / Disability measures	Association (% of MR / Disability in overall sample)	Applic-ability	Quality
Cooke RW, 1999 99380719	87	BW: 1103 (630-1500) GA: 29 (24-35)	White matter disorder, PVL, Ventriculo-megaly, MRI abnormality	IQ	↔		C
Goetz, 1995 96119489	14	BW: 550-1100 GA: ND	IVH, c-PVL	Mild / severe cognitive delay	↑		C
Blitz, 1997 97154301	100	BW: 776 GA: 27	IVH ≥ grade III, BPD	MDI < 70	↑* [m] (9%)		C
Thompson, 1997 972683338	55	BW: 1100 (700-1500) GA: 28 (24-33)	Higher neurobiologic risk score (NBRS)	Worse cognitive performance (McCarthy Scales)	↑		C
Gaillard, 2001 21221175	84	BW: 816 (520-2710) GA: 26 (23-34)	Antenatal steroids and postnatal surfactant Rx	Neurodevelop-mental outcomes	↑		C
Kato, 1996 97182916	228	BW: 1031 GA: 28	Antenatal factors [j]	MR	↑* [m]		C

[a] "Mild CLD/BPD" – requiring supplemental oxygen at 28 days but not at 36 weeks PMA; "Severe CLD/BPD" – requiring oxygen at 28 days and 36 weeks PMA
[b] Moderate/Severe Disability: "Severe disability" / Category I – =1 of the following: (1) Sensorineural deafness (requiring hearing aids). (2) Bilateral blindness. (3) Severe cerebral palsy. (4) Developmental delay (adjusted Bayley mental scores 2 or more SD below mean). "Moderate disability" / Category II - – =1 of the following: (1) Adjusted Bayley mental scores between 1 and 2 SD below mean. (2) Mild-moderate CP w/o developmental cognitive delay. (3) Impaired vision requiring spectacles.
[c] Major disability was defined as blindness, deafness, CP or IQ > 2 SD below the mean for NBW controls
[d] Total disability
[e] At risk parenting was defined as referral by a health professional for neglect or mild abuse
[f] Motor delay - 12, 18, 24 month outcome as the protocol of Amiel-Tison and Stewart, and Touwen
[g] "DELAY" defined by 9 measures of performance on Denver Developmental Screening Test II at age 15 months corrected.
[h] Early IVH: IVH occurring within the first 6 postnatal hours
[i] Disability was defined as need for physical assistance to perform daily activities
[j] Malpresentation, tocolytic agents (beta 2 stimulant plus magnesium sulfate)

[m] Multivariate association

DQ = Griffiths Development Quotient

All association is univariate, unless noted.
↑ Significantly increased the risk of MR/Disability associated with VLBW or GA; and, presence of other factors
↑* Significantly increased the risk of MR/Disability associated with VLBW or GA; and, presence of other factors
↔ No association
↓ Significantly decreased the risk of MR/Disability associated with VLBW or GA; and, presence of other factors

Birth Weight

Our search methods identified significant evidence that birth weight is a useful factor in identifying VLBW infants at especially high risk for MR. For example, Koller, Lawson, Rose, et al. (1997) found that birth weight was useful in differentiating longitudinal pattern of cognitive development. Using the Bayley MDI, Stanford-Binet IQ, and WISC-R, the investigators followed 203 VLBW infants until 6 years of age, obtaining four cognitive scores at yearly intervals. They identified five developmental patterns: average-stable (13% of the sample); average-declining to low average (24%); average-declining to below average (43%); very low-increasing to low average (8%); and very low-stable (12%). Biological factors known during the neonatal hospitalization that allowed differentiation of these patterns included birth weight, as well as gestational age, level of maternal education, and a simple neonatal health index that incorporated length of stay adjusted for birth weight. Assessments of neurological status and head circumference at 1 year added significant prognostic information, with abnormal neurological status at 1 year showing an association with a pattern of very low, stable scores.

There is evidence that risk for developmental delay may be significantly elevated even among apparently normal VLBW infants. Schendel, Stockbauer, Hoffman, et al. 1997 studied the relationship between VLBW and developmental delay in a 1989-1991 population-based cohort. All study subjects were asymptomatic for disabling conditions and were free of obvious developmental delay when examined at median 15 months corrected age. The investigators compared VLBW infants to LBW infants weighing 1,500-2,499 grams and to singleton controls with birth weight ≥2,500 grams, using the Denver Developmental Screening Test II. They found that apparently well VLBW children were at greater risk for both moderate and severe delay than were either of the larger birth weight comparison groups.

Based on the evidence identified by our search methods, birth weight appears less useful in identifying ELBW infants at highest risk for MR. The NICHD Neonatal Research Network found no association between cognitive outcome and birth weight (within the birth weight range of 500-1000) in 1,151 ELBW infants at 18 to 22 months corrected age (Vohr, Wright, Dusick, et al., 2000). The proportion of infants with Bayley MDI <70 showed no statistically significant trend over 100-gram subgroups of birth weight <1000 g, and birth weight (within the birth weight range of 500-1000) was not significantly associated with cognitive outcome in multivariate logistic regression after adjusting for other factors.

Hack, Wilson-Costello, Friedman, et al. (2000) 1992-1995 ELBW cohort also showed no significant differences in performance on the Bayley MDI between infants born 500-749 g (38% with Bayley MDI <70) versus those who weighed 750-999 at birth (50%). Among 12 infants weighing 500-599 grams at birth, 67% had Bayley MDI <70. This rate varied from 35%-45% for 100 gram subgroups between 600-999 grams birth weight. These differences were not statistically significant but the subgroups were small. The high rate of subnormal Bayley MDI among infants 750 to 999 grams birth weight, and the even higher rate of subnormal Bayley MDI among infants 500 to 599 grams birth weight, is noteworthy.

Piecuch, Leonard, Cooper, et al. (1997) studied cognitive development at 55 ± 33 months of age in ELBW infants born between 1979-1991. They found no association between outcome and birth weight in univariate analysis examining birth weight in 100-gram subgroups within the narrow weight range for ELBW.

Gestational Age

Among the studies identified by our search methods, the evidence that gestational age is useful in identifying VLBW infants at high risk for MR was mixed. Koller, Lawson, Rose, et al. (1997) found that gestational age was associated with subsequent pattern of cognitive development after accounting for other factors in VLBW infants followed through 6 years of age. However, in their study of cranial ultrasound abnormalities and cognitive outcomes at 6 years of age in infants <2000 grams birth weight, Whitaker, Feldman, Van Rossem, et al. (1996) found that gestational age was not significantly associated with MR after adjusting for ultrasound findings, duration of mechanical ventilation, and other factors.

Evidence supporting gestational age as a predictor of MR was also mixed for ELBW infants. The Victorian Infant Collaborative Study Group evaluated performance at 5 years for 225 infants born between 1991-1992 at 23-27 weeks gestation controls (Doyle, Casalaz, and The Victorian Infant Collaborative Study Group, 2001; The Victorian Infant Collaborative Study Group, 1997). This study found that, among infants surviving to discharge, survival with major disability at 5 years decreased significantly from 40% at 23 weeks to 6% at 27 weeks, a near-linear decrease with advancing gestational age for infants <28 weeks gestation. Major disability (defined as blindness, deafness, cerebral palsy, or IQ score greater than two standard deviations below the mean for normal birth weight controls) was present in 19% of the cohort as a whole.

Wood, Marlow, Costeloe, et al. (2000) examined developmental outcomes among 283 infants born less than 25 weeks gestation and examined at 28-40 months. Twenty-three percent had severe disability (defined as need for physical assistance to perform daily activities), and 19% had Bayley indices greater than three standard deviations below the mean. Forty-nine percent had no disability. In this study, survival without disability increased from 0.7% at 22 weeks' gestation to 23% at 25 weeks.

Piecuch, Leonard, Cooper, et al. (1997) studied the cognitive development of infants born between 1990-1994 at 24-26 weeks gestation. Measured with the Bayley MDI at 18 months mean corrected age, infants born at 24 weeks gestation were less likely to be normal then infants born at 26 weeks (28% versus 71%), and more likely to show deficient cognitive development (39% versus 11%).

Two methodologically strong studies found that gestational age (within the range of 23-27 weeks) was not useful in identifying ELBW infants at risk for MR. Hack, Wilson-Costello, Friedman, et al. (2000) noted no decrease in rate of subnormal Bayley MDI with advancing gestational age among 221 infants born at 23-27 weeks gestation. Bayley MDI <70 occurred in 38-53% of these infants at 20 months corrected age, and decreased to 17% of infants born at 28 weeks gestation. Similarly, Piecuch, Leonard, Cooper, et al. (1997) studied determinants of cognitive delay in ELBW infants born between 1979-1991, and found that gestational age (within the range for ELBW infants) was not an independent predictor related to cognitive outcome.

Acquired Intracranial Lesions

Intraventricular Hemorrhage (IVH). Intraventricular hemorrhage (IVH) is one of the strongest independent predictors of MR for both VLBW and ELBW infants. Our search methods

identified many methodologically sound studies in which IVH, particularly severe grade III or IV IVH, was a significant predictor in both univariate analysis and multivariate modeling.

Whitaker, Feldman, Van Rossem, et al. (1996) performed a prospective cohort study to examine neonatal cranial ultrasound abnormalities and cognitive outcomes at 6 years of age in infants <2000 g birth weight. Study subjects were a large regional cohort born in central New Jersey between 1984 and 1987, who received screening cranial ultrasounds according to a standard protocol. The investigators found MR in 6% of children with a history of isolated germinal matrix and/or intraventricular hemorrhage, 41.3% of infants with cerebral parenchymal lesions and/or ventricular enlargement, and 1.3% of infants with no ultrasound abnormality. After adjusting for maternal social risk and other perinatal and neonatal risk factors, isolated germinal matrix/intraventricular hemorrhage was associated with MR (adjusted OR for the combined risk factor, 4.6; 95% CI 1.2 to 18.6). The authors estimated that 5% of cases were attributable to germinal matrix/intraventricular hemorrhage. They did not differentiate outcome by grade of IVH in their analysis. The effect they estimated for parenchymal lesions and/or ventricular enlargement was much larger than for isolated germinal matrix/intraventricular hemorrhage.

Using data from Ment, Oh, Ehrenkranz, et al. (1994), a trial of early postnatal indomethacin for prevention of IVH, Vohr, Allan, Scott, et al. (1999) found that VLBW infants who experience the early onset of IVH may be at especially high risk for cognitive handicaps at 3 years corrected age. In this study, children with IVH occurring within the first 6 postnatal hours were significantly more likely to have Stanford-Binet IQ scores <70 than children without early IVH (38% vs 19%).

The NICHD Neonatal Research Network found a significant association between cognitive outcome and cerebral ultrasound abnormalities in ELBW infants at 18 to 22 months corrected age (Vohr, Wright, Dusick, et al., 2000). In their analysis, infants with a combined outcome IVH ≥ stage III or PVL were more than twice as likely to have Bayley MDI <70 as those without these findings, after adjusting for the effect of other clinical factors.

Ambalavanan, Nelson, Alexander, et al. (2000) found Bayley MDI <70 in 7% of ELBW subjects without IVH, 29% of those with grade III IVH, and 44% of those with grade IV IVH. In this study, the presence of IVH ≥ grade III was the strongest determinant of subnormal MDI after adjusting for the presence of NEC ≥ stage 2, bronchopulmonary dysplasia, absence of chorioamnionitis, low maternal education level, and multiple gestations. However, the regression model's overall predictive performance was poor.

Other investigators have described increased adjusted or unadjusted risk of impaired cognitive development in VLBW or ELBW infants with grade III or IV IVH seen at 1 to 5 years of age (Blitz, Wachtel, Blackmon, et al., 1997; Cheung, Barrington, Finer, et al., 1999; Dezoete, MacArthur, and Aftimos, 1997; Leonard, Clyman, Piecuch, et al., 1990).

Our search methods did identify some methodologically sound studies in which IVH was not predictive of MR. Hack, Wilson-Costello, Friedman, et al. (2000) examined cognitive development prospectively among ELBW infants born 1992-1995. Among infants with IVH ≥ grade III, 53% had MDI <70. In stepwise multivariate regression analysis male sex, social risk, and chronic lung disease were significant predictors of Bayley MDI <70 at 20 months corrected age. After adjusting for these factors and birth weight, the presence of a grade III or grade IV IVH was not a risk factor for abnormally low MDI, although it was associated with an eight-fold increase in odds of any neurodevelopmental abnormality (MDI<70, neurologic abnormality, or unilateral or bilateral blindness or deafness). Similarly, Singer, Yamashita, Lilien, et al. (1997)

found that IVH was not associated with performance on the Bayley MDI in VLBW infants at 36 months corrected age after adjusting for the effects of birth weight, race, and a neurologic risk score.

Periventricular leukomalacia (PVL). Periventricular leukomalacia (PVL) was found to be another of the strongest independent predictors of cognitive impairment in several of the studies identified by our search methods. Whitaker, Feldman, Van Rossem, et al. (1996) found a strong association between cerebral parenchymal lesions and cognitive development in their study of neonatal cranial ultrasound abnormalities and cognitive outcomes at 6 years of age in infants <2000 grams birth weight. Parenchymal lesions/ventricular enlargement were strongly associated with MR in multivariate regression analysis (adjusted OR for the combined risk factor parenchymal lesions/ventricular enlargement versus normal intelligence, 65.8; 95% CI, 19.1 to 227.4). The authors estimated that half of the cases of MR were attributable to parenchymal lesions/ventricular enlargement independent of other factors. Gerner, Katz-Salamon, Hesser, et al. (1997), a study of development in VLBW infants at 10 months corrected age, found that presence of PVL showed independent adverse association with total Griffiths' Mental Developmental Scale and with the Performance subscale after adjusting for duration of mechanical ventilation. Among a selected cohort of 10 Australian infants <35 weeks gestation or <1500 grams birth weight with severe bilateral cystic PVL, all had severe neurodevelopmental abnormalities when evaluated at mean chronological age of 27.3 months (Wilkinson, Bear, Smith, et al., 1996).

Among the studies identified by our search, not all found an independent relationship between PVL and cognitive development. Hack, Wilson-Costello, Friedman, et al. (2000) found Bayley MDI <70 at 20 months corrected age among 63% of ELBW infants with PVL. However, as was the case in this study with IVH, in multivariate regression analysis PVL was not significantly associated with cognitive development after adjusting for the effects of gender, birth weight, and social risk.

Using cranial magnetic resonance scans at 15-17 years of age, Cooke and Abernethy (1999) examined the relationship between intracranial structural anomalies and neurodevelopment in 87 VLBW infants with learning disorders but without cerebral palsy. Thirty-seven VLBW subjects had abnormalities on MRI, including 28 with PVL. The study found no significant differences in intelligence quotient between subjects with MRI lesions and those with normal scans.

It is likely that not all cases of PVL are identified. Among 14 VLBW infants with periventricular leukomalacia, Goetz, Gretebeck, Oh, et al. (1995) found that 8 had normal studies in the first week of life, four had intraventricular hemorrhage, and two had periventricular echodensities. Cystic PVL developed between 17 and 104 days of age and occurred later in those infants whose initial study was normal. Tone abnormalities were found in 11 of the 12 infants who received developmental follow-up, and severe cognitive delays were common in the older infants. Similarly, Pierrat, Duquennoy, van Haastert, et al. (2001), a study of PVL in infants <32 weeks gestation, found that localized PVL developed after the first month of life in 53% of cases, and disappeared by 40 weeks PMA in 34%. Mild ventriculomegaly at 40 weeks PMA followed localized PVL in 23.7% of cases.

IVH, indomethacin, and MR. The identified evidence is equivocal regarding the effect of early indomethacin on subsequent cognitive development. Ment and colleagues demonstrated that early indomethacin therapy is associated with a decrease in both the incidence and severity

of IVH in VLBW infants, and described cognitive outcomes to 4.5 years (Ment, Vohr, Allan, et al., 2000; Ment, Vohr, Oh, et al., 1996). They performed a randomized placebo-controlled trial of 431 neonates 600-1250 g birth weight with no evidence of IVH at 6 to 11 hours of age and found that within the first 5 days, significantly fewer infants developed IVH in the indomethacin-treated group (12% vs 18%). One indomethacin-treated infant developed grade IV IVH versus 10 placebo-treated infants. Eighty-nine percent of survivors were examined at 36 months of age and 88% at 54 months of age. Of note, the mean gestational age was significantly younger for the children seen at follow-up who received indomethacin than for those who received placebo. At 36 months, Stanford-Binet IQ scores for children who received indomethacin were not significantly different from those who received placebo. However, at 54 months, the investigators observed significantly less mental retardation among children randomized to early low-dose indomethacin. For the indomethacin group, 9% had an IQ <70, 12% had an IQ of 70-80, and 79% had an IQ >80, while for the placebo group, 17% had an IQ <70, 18% had an IQ of 70-80, and 65% had an IQ >80.

Schmidt, Davis, Moddemann, et al. (2001) studied 1775 ELBW infants randomized to receive prophylactic indomethacin or placebo. Despite a reduction in frequency of severe IVH and PVL, the study found that prophylaxis with indomethacin does not improve the rate of survival without neurosensory impairment at 18 months.

It appears clear that early indomethacin reduces the incidence of severe IVH. While it is reasonable to hope that this promising finding will result in improved cognitive outcomes, the identified studies do not demonstrate this consistently. Prophylactic treatment of VLBW infants with early indomethacin remains the subject of further study.

Bronchopulmonary Dysplasia (BPD)

Our methods located many studies documenting a significant independent relationship between neonatal chronic lung disease, also known as bronchopulmonary dysplasia (BPD), and abnormal cognitive development in both VLBW and ELBW infants. deRegnier, Roberts, Ramsey, et al. (1997) studied the effect of BPD upon neurodevelopment in VLBW infants who survived until discharge. When compared with infants who had no supplemental oxygen requirement after 28 days of life, those requiring oxygen at both 28 days chronological age and at 36 weeks postmenstrual age were significantly more likely to have Bayley MDI >2 standard deviations below the mean. Gregoire, Lefebvre, and Glorieux (1998) found similar results BPD may have a deleterious effect on cognitive development even in the absence of IVH or PVL. Katz-Salamon, Gerner, Jonsson, et al. (2000) compared 43 VLBW infants with BPD, but without IVH or PVL, and 43 VLBW without BPD, IVH, or PVL at 10 months of corrected age using the Griffiths developmental test. BPD was associated with significantly lower performance scores on each Griffiths subscale.

Not all identified studies found an independent association between BPD and cognitive development in VLBW infants. Leonard, Clyman, Piecuch, et al. (1990) examined the independent effects of intracranial hemorrhage and severe BPD, together with a parenting risk factor (referral by a health professional for neglect or mild abuse) on neurodevelopmental outcome at mean 60 months in 129 infants ≤ 1250 g birth weight. The study found that for subjects without any intracranial hemorrhage or parenting risk factors, the presence of severe BPD was not related to cognitive outcome. Singer compared VLBW infants with and without

BPD (defined as typical radiographic changes with supplemental oxygen requirement >28 days) to healthy term controls. At 36 months corrected age, 21% of VLBW infants with BPD had Bayley MDI <70 compared to 11% of VLBW infants without BPD and 4% of full term controls. Abnormal MDI was evident by 8 months of age in the majority of cases in both VLBW groups. In hierarchical multivariate regression analysis, however, BPD was not associated with performance on the Bayley MDI after adjusting for the effects of birth weight, race, and a neurologic risk score (Singer, Yamashita, Lilien, et al., 1997; Singer, Siegel, Lewis, et al., 2001).

Among ELBW infants, our search methods located strong studies supporting the relationship between BPD and MR. After controlling for male sex, social risk, and birth weight, Hack, Wilson-Costello, Friedman, et al. (2000) found that oxygen dependence at 36 weeks postconceptional age was predictive of Bayley MDI <70 among 221 ELBW infants born 1992-1995. Supplemental oxygen requirement at 36 weeks post conceptual age more than doubled the adjusted risk of subnormal Bayley MDI in this cohort. Of 89 infants with BPD in this study, 55% had MDI <70 at 20 months corrected age. The NICHD Neonatal Research Network found that persistent supplemental oxygen requirement at 36 weeks post-conception increased risk of Bayley MDI <70 at 18-22 months in ELBW infants by more than 50% after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). Ambalavanan, Nelson, Alexander, et al. (2000) found increased risk of MDI <70 at 18 months corrected age among ELBW infants who developed BPD. BPD was associated with subnormal MDI after adjusting for severe IVH, NEC ≥ stage 2, and absence of chorioamnionitis, presence of BPD, low maternal education level, and multiple gestation. Blitz, Wachtel, Blackmon, et al. (1997) found that BPD was associated with Bayley MDI <70 in ELBW infants at 1 year of age after adjusting for other clinical risk factors.

Surfactant Replacement Therapy

The evidence identified by our search methods strongly suggests that, while surfactant therapy improves survival among VLBW infants, its use is not an independent predictor of cognitive development. The NICHD Neonatal Research Network found that surfactant replacement therapy was not associated with cognitive outcome at 18-22 months in ELBW infants after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). In separate studies Corbet, Long, Schumacher, et al. (1995) and Kraybill, Bose, Corbet, et al. (1995) found no differences in neurodevelopmental status at 1 year among infants treated with a single dose of surfactant compared with placebo, despite lower mortality. Futagi, Suzuki, Goto, et al. (1999) found similar results at 6-7.5 year follow-up. Gaillard's suggestion that neurodevelopmental outcome at 3 years of age for VLBW infants who require prolonged mechanical ventilation may be improved by treatment with antenatal steroids and postnatal surfactant requires further study (Gaillard, Cooke, and Shaw, 2001).

Race, Social Risk, and Maternal Education

Our search methods identified many strong studies documenting a significant independent association between social risk factors and cognitive development in VLBW infants. Methods used to measure social risk are numerous, however, and the identified evidence is not always sufficient to distinguish the independent effects of various commonly examined elements of social risk, such as race, economic status, or level of maternal education.

Social Risk Measured With Scoring Systems. Hack, Wilson-Costello, Friedman, et al. (2000) examined the relationship of cognitive development to social risk among ELBW infants born 1992-1995, using a simple social risk score. The score assigned 1 point each for single parenthood, black race, and maternal education less than high school. High social risk, as assessed with this score, was significantly associated with cognitive outcome at 20-months corrected age, after adjusting for gender and BPD. Social risk factors increased odds of Bayley MDI <70 by 50%. However, using a similar risk scale, Whitaker, Feldman, Van Rossem, et al. (1996) did not find this association in a cohort with larger birth weights examined at a later chronological age. In their study of infants <2000 g birth weight seen at 6 years, maternal social risk was assessed with a composite risk assessment score that incorporated maternal education, race, public assistance income, marital status, and age. After adjusting for cerebral ultrasound findings, maternal social risk was associated with risk for borderline intelligence but not with true MR at 6 years of age.

Not all studies found an independent relationship between social risk and cognitive development. Wildin found that Hollingshead social status (Hollingshead, 1975) did not contribute to assessment of risk for cognitive delay when information from 6 and 12 month examinations was considered (Wildin, Anderson, Woodside, et al., 1995; Wildin, Smith, Anderson, et al., 1997). Data was from the longitudinal study of University of Texas Health Sciences Center in Houston and the University of Texas Medical Branch in Galveston. The quality of parent-infant interactions may play an important role in cognitive development of VLBW infants. Smith, Landry, Swank, et al. (1996) used home observations to assess the impact of maternal behaviors on infant development in VLBW infants with severe neonatal complications and those with milder complications compared to term controls at 6 and 12 months. Severe complications included the presence of bronchopulmonary dysplasia, IVH ≥ grade III, and/or PVL. The investigators found that active maternal maintenance of infant interest was positively related to infant development for all groups. During toy play and daily activities, maternal attention-maintaining was most strongly related to cognitive and language skills for both preterm groups than for the FT infants. The impact upon cognitive development of this aspect of parenting deserves further investigation.

Leonard, Clyman, Piecuch, et al. (1990) examined the relationship of at-risk parenting (defined as referral by a health professional for neglect or mild abuse) to cognitive development at mean 60 months in 129 infants ≤ 1250 g birth weight. This study found that the parenting risk factor was strongly associated with cognitive outcome after accounting for the effects of intraventricular hemorrhage and chronic lung disease. The authors concluded "that infants with medical risk factors may have additional social risk factors, and that both of these influences must be considered in an examination of the long-term sequelae of neonatal complications."

The variably among studies with respect to association of social risk/parenting risk and cognitive outcome may be accounted for by differences among studies with respect to population characteristics, sample size, age of assessment, ascertainment of other potential confounding factors, accuracy of methods/measures used to determine social risk, parenting risk, and other socioeconomic markers.

Race. The identified evidence suggests that race may be an independent predictor of cognitive development in VLBW infants. After adjusting for the effects of birth weight and a simple neurological risk score, Singer, Yamashita, Lilien, et al. (1997) found that minority race

was more strongly associated with poor performance on Bayley MDI than chronic lung disease or IVH in VLBW infants at 36 months corrected age. The NICHD Neonatal Research Network found that among ELBW infants at 18-22 months, whites were at about 40% lower risk for Bayley MDI <70 after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). In Hack's cohort of 1992-1995 ELBW infants examined at 20 months corrected age, black race was among the social risk factors associated with an approximately 50% increased risk of subnormal Bayley MDI (Hack, Wilson-Costello, Friedman, et al., 2000).

Level of Maternal Education. Our search methods located strong studies in which level of maternal education was identified as a significant independent predictor of abnormal cognitive development. After adjusting for biological risk with the Neurobiologic Risk Score, Thompson Jr., Gustafson, Oehler, et al. (1997) demonstrated that maternal education level was a significant determinant of VLBW infant cognitive performance at 4 years of age. Koller, Lawson, Rose, et al. (1997) found that level of maternal education was associated with subsequent pattern of cognitive development after accounting for other factors. In this study, maternal education appeared to be especially important among children born at the upper end of the VLBW range, who had fewer risk factors than those with lower birth weights.

The relationship between level of maternal education and subsequent infant cognitive development appears to be important in the ELBW subgroup as well. In univariate analysis Piecuch, Leonard, Cooper, et al. (1997) found a strong relationship between social risk and cognitive development in ELBW infants born between 1979-1991. The NICHD Neonatal Research Network found that level of maternal education was a significant determinant of cognitive development in ELBW infants at 18-22 months (Vohr, Wright, Dusick, et al., 2000). In their multivariate regression analysis, maternal education less than high school graduate level increased risk of Bayley MDI <70 almost two-fold. Maternal education level was also a determinant of neurodevelopmental outcome in Ambalavanan's study of ELBW infants (Ambalavanan, Nelson, Alexander, et al., 2000), which found that low maternal education level was associated with increased risk of Bayley MDI <70 after adjusting for severe IVH, NEC ≥stage 2, absence of chorioamnionitis, presence of bronchopulmonary dysplasia, and multiple gestation.

Gender

Our search methods identified few strong studies examining the independent relationship of gender and MR in VLBW infants. The identified evidence suggests that gender may be a significant independent predictor of MR among ELBW infants, but this relationship may be less significant in larger birth weight categories. Among infants <2000 g birth weight, Whitaker, Feldman, Van Rossem, et al. (1996) found that gender was not significantly associated with MR after adjusting for ultrasound findings and duration of mechanical ventilation. However, in the NICHD Neonatal Research Network's study of ELBW infants at 18-22 months, males were twice as likely as females to have Bayley MDI <70, after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). Hack found similar odds of MR in ELBW males compared to females after adjusting for social risk and the presence of chronic lung disease, and suggested that this may reflect higher illness severity among males(Hack, Wilson-Costello, Friedman, et al., 2000). Others found that ELBW males were at higher risk of cognitive impairment than

females in unadjusted analyses (Piecuch, Leonard, Cooper, et al., 1997; Wood, Marlow, Costeloe, et al., 2000).

Illness Severity

Some clinical risk factors for MR (e.g. severe IVH or PVL) offer obvious mechanisms by which they increase risk of cognitive impairment, i.e. cerebral parenchymal damage. Other identified risk factors may act as proxies for the physiological disarray that accompanies severe illness in general. Transient but recurrent physiological disturbances such as metabolic acidosis, hypotension, etc., may have a cumulative effect and may increase risk for MR (Goldstein, Thompson, Jr., Oehler, et al., 1995). Neonatal illness severity scoring systems may capture this risk effectively. Our search methods identified several studies providing evidence that such scoring systems may be useful in identifying infants at risk for MR.

Lefebvre, Gregoire, Dubois, et al. (1998) examined the nursery Neurobiologic Risk Score as a predictor of cognitive development in VLBW infants. The original NBRS incorporated intracranial ultrasound abnormalities, need for and duration of mechanical ventilation, and the presence of acidosis, infection, hypoglycemia, or seizures at any time during the initial hospitalization (Brazy, Eckerman, Oehler, et al., 1991). Lefebvre found that infants less than 28 weeks gestation who were at high risk as assessed with the NBRS at the time of nursery discharge had significantly higher rates of severe delay or any delay at 18 months corrected age as measured with the Griffiths Mental Development Scale. Thompson Jr., Gustafson, Oehler, et al. (1997) found similar results in VLBW infants at 4 years of age. Brazy, Eckerman, Oehler, et al. (1991) found that the NBRS measured at 2 weeks of age and at discharge was significantly correlated with Bayley MDI at 6, 15, and 24 months.

After adjusting for the effects of birth weight and race, Singer, Yamashita, Lilien, et al. (1997) found that a simple neurological risk score was more strongly associated with performance on Bayley MDI than chronic lung disease or IVH in VLBW infants at 36 months corrected age. In this study infants were assigned a score of 1 if any of the following were present: minor neurological malformation, seizures, echodense craniosonographic lesions, porencephaly, hydrocephalus, ventriculoperitoneal shunt, meningitis, or periventricular leukomalacia; infants without such findings received a score of 0.

Buhrer, Grimmer, Metze, et al. (2000) examined the ability of the Clinical Risk Index for Babies (CRIB) to predict long-term neurodevelopmental impairment in 352 VLBW infants born 1992-1997. The CRIB score incorporates birth weight, gestational age, the presence of congenital malformations, worst base excess, and maximum and minimum appropriate fraction of inspired oxygen (FIO2) during the first 12 hours of life. Griffiths scales of mental development general quotient was > 2 standard deviations below average in 22% of the studied infants. CRIB scores were independently associated with neurodevelopmental impairment, but did not significantly contribute to identification of affected infants when compared with birth weight alone.

Durations of various therapies such as mechanical ventilation, intravenous nutrition, etc., are markers of illness severity and may be tested as independent predictors of outcome; our search methods identified several such studies examining cognitive development. Whitaker, Feldman, Van Rossem, et al. (1996) found that after adjusting for ultrasound findings, the number of days on mechanical ventilation was strongly associated with risk for MR at 6 years of age in infants <2000 g birth weight. In univariate analysis, Piecuch, Leonard, Cooper, et al. (1997) found a

significant association between duration of oxygen requirement and cognitive delay in ELBW infants.

Antepartum And Intrapartum Factors

The evidence identified by our search methods was equivocal regarding the utility of antepartum and intrapartum factors as independent predictors of MR. Kato, Yamada, Matsumoto, et al., (1996) performed a retrospective study of perinatal factors and outcome at 12 months in 228 singleton VLBW infants without major anomaly. Regression analysis found that malpresentation, use of tocolytic agents and cord arterial pH <7.20 were associated with combined outcome of cerebral palsy (CP) and mental retardation (MR). The authors suggested that delivery method was not an independent risk factor for CP/MR, but that malpresentation was a significant risk factor regardless of route of delivery. Multiple gestation was a determinant of neurodevelopmental outcome at 18 months in Ambalavanan, Nelson, Alexander, et al. (2000), a study of ELBW infants. In this study multiple gestation was associated with increased risk of Bayley MDI <70 after adjusting for severe IVH, NEC ≥stage 2, absence of chorioamnionitis, presence of bronchopulmonary dysplasia, and low maternal education level.

However, our search methods identified strong studies suggesting that antepartum factors do not provide a useful contribution to prediction of MR in ELBW infants after accounting for other clinical factors. For example, after adjusting for other clinical factors in multivariate regression analysis, the NICHD Neonatal Research Network found no association between cognitive outcome and use of antenatal steroids, maternal hypertension, route of delivery, or inborn versus outborn birth in 1151 ELBW infants at 18 to 22 months corrected age (Vohr, Wright, Dusick, et al., 2000). Similarly, after controlling for male sex, social risk, and birth weight, Hack, Wilson-Costello, Friedman, et al. (2000) found no association between subnormal Bayley MDI and multiple birth, cesarean section delivery, antenatal steroid therapy, or history of chorioamnionitis. Interestingly, Ambalavanan, Nelson, Alexander, et al. (2000) found that the presence of chorioamnionitis was associated with a lower adjusted risk of MR in ELBW infants at 12-18 months corrected age.

Antenatal Corticosteroid Therapy. The NICHD Neonatal Research Network found that antenatal steroid therapy was not associated with cognitive outcome at 18-22 months in ELBW infants after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). Gaillard, Cooke, and Shaw, (2001) suggest that neurodevelopmental outcome at 3 years of age for VLBW infants who require prolonged mechanical ventilation may be improved by treatment with antenatal steroids and postnatal surfactant; this warrants further study.

Intrauterine Growth Retardation (IUGR)/Small for Gestational Age (SGA). The identified evidence regarding IUGR/SGA as an independent risk factor for MR was equivocal. Korkman, Liikanen, and Fellman (1996) documented worse cognitive development at 5-9 years among VLBW infants who were SGA compared with VLBW infants who were AGA. However, the NICHHD Neonatal Research Network found that SGA ELBW infants were not at increased risk for cognitive delay compared with their AGA peers after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). Others observed no difference between AGA and SGA

ELBW infants in univariate or multivariate analyses (Hack, Wilson-Costello, Friedman, et al., 2000; Piecuch, Leonard, Cooper, et al., 1997).

NEC

Our methods located no studies examining the relationship between NEC and subsequent cognitive development in VLBW infants. Among ELBW infants, the identified evidence was equivocal. Ambalavanan, Nelson, Alexander, et al. (2000) found increased risk of MDI <70 among ELBW infants who developed NEC ≥ stage 2. In this study NEC was associated with subnormal MDI after adjusting for severe IVH, absence of chorioamnionitis, presence of bronchopulmonary dysplasia, low maternal education level, and multiple gestation. However, other strong studies do not support an independent association of NEC and MR in ELBW infants. Hack, Wilson-Costello, Friedman, et al. (2000) found Bayley MDI <70 at 20 months corrected age among 64% of ELBW infants with NEC. However, in multivariate regression analysis, NEC was not significantly associated with cognitive development after adjusting for the effects of gender, birth weight, and social risk. Similarly, The NICHD Neonatal Research Network found no association between cognitive outcome and NEC ≥ stage 2 in ELBW infants at 18 to 22 months corrected age (Vohr, Wright, Dusick, et al., 2000) after adjusting for the effect of other clinical factors in multivariate regression analysis.

Sepsis and Meningitis

Our search methods did not identify studies that examined the relationship between sepsis or meningitis and subsequent cognitive development in VLBW infants. Among ELBW infants, The evidence suggests that the occurrence of sepsis or meningitis is not a useful independent predictor of abnormal cognitive development. The NICHD Neonatal Research Network found that neither early-onset nor late-onset sepsis was associated with cognitive outcome at 18-22 months in ELBW infants after adjusting for other clinical factors (Vohr, Wright, Dusick, et al., 2000). Similarly, Hack, Wilson-Costello, Friedman, et al. (2000) found that sepsis and meningitis were not significantly associated with cognitive development after adjusting for the effects of gender, birth weight, and social risk in ELBW infants seen at 20 months corrected age.

Postnatal Corticosteroid Therapy

There is much concern presently regarding the effect of postnatal systemic corticosteroid exposure (specifically, dexamethasone) on neurodevelopment in VLBW infants. Our search methods identified studies that justify such concern for the ELBW the subgroup. Postnatal systemic steroid therapy (dexamethasone) was a significant determinant of cognitive development in ELBW infants at 18-22 months in the NICHD Neonatal Research Network study (Vohr, Wright, Dusick, et al., 2000). After adjusting for clinical factors including need for oxygen at 36 weeks PCA and several clinical markers of severe illness, the study found that treatment with postnatal steroids increased risk of Bayley MDI <70 almost two-fold. The Victorian Infant Collaborative Study Group (1997) found that among infants 23-27 weeks

gestation born 1991-92 and followed until five years of age, infants treated with postnatal dexamethasone had worse IQ scores than those not receiving steroids. This nonrandomized study was likely to be significantly confounded, however; since the steroid group had lower mean gestational age, and no mention is made of illness severity or other potential confounders. In a case control subanalysis using the same cohort, the investigators found that the IQ scores were significantly lower in the corticosteroid group, and the difference was much smaller.

Other

Seven studies examined factors that may be useful in identifying VLBW infants at highest risk for abnormal cognitive development. The identified evidence suggests that some of these factors are not independently associated with cognitive outcome, while others require further study.

Table 2.5. Association of Mental Retardation / Disability with other Risk Factors in LBW infants

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	MR / Disability measures	Association (% of MR / Disability in overall sample)	Applicability	Quality
Wildin, 1995 95385294 Wildin, 1997 97422739	112	BW: 1944 GA: 29	SES status	Bayley's MDI & PDI	↔ *m*		A
Stathis, 1999 99325758	23	GA: 28 (27-28) BW: 860 (837-833)	HC < 3%tile	McCarthy general cognitive index < 70	↑*		B
	13		HC-3-10%tile		↑*		
	40		HC> 10 % tile		↑*		
Koller, 1997 97193708	203	BW: 1170 GA: 31	BW, GA, health index, neurological status @ 1 yr, male gender; maternal educ.	Worse cognitive development pattern (Bayley's scales)	↑*		B
Ekert,1997 97251211	104	BW: 962 GA: 27	Visual evoked potentials	Abnormal neurodevelop-mental outcome	↔		B
Finer, 1999 99436635	10	BW: : 663 (440-968) GA: 25 (24-28)	ELBW requiring CPR	Abnormal neuromotor function	↔ *m*		B
Van Wassenaer 1997 98103082	158	BW: < 1500 g GA: 25-30	Thyroxine Rx	Worse Bayley MDI	↓		B
			BW		↑*		

We identified evidence that examinations in the first 6 – 12 months of life may substantially refine estimates of risk of subsequent cognitive impairment.

Wildin's follow-up of this cohort at 40 months suggests that examinations at 6 and 12 months add significant prognostic information to data from the newborn period when predicting long-term outcome (Wildin, Anderson, Woodside, et al., 1995; Wildin, Smith, Anderson, et al., 1997).

Stathis, O'Callaghan, Harvey, et al. (1999) examined the relationship of head circumference and head-circumference growth velocity during the first year of life with cognitive development in 87 VLBW infants born between 1977 and 1986. Subjects were assessed using the McCarthy Scale at 6 years of age. The investigators found that head circumference <3% at 4 months, 8 months, and 12 months, as well as head growth velocity between birth and 4 months were significantly associated with cognitive ability at 6 years.

Assessments of neurological status and head circumference at 1 year added significant prognostic information in Koller, Lawson, Rose, et al. (1997), with abnormal neurological status at 1 year showing an association with a pattern of very low, stable scores.

Visual evoked potentials were not predictive of abnormal neurodevelopmental outcome in infants <32 weeks gestation (Ekert, Keenan, Whyte, et al., 1997).

In a small study by Finer, Tarin, Vaucher, et al. (1999), infants <750 g at birth and requiring CPR in the delivery room were not different from controls matched for gestational age, sex, and year of birth with respect to cognitive development at median 28 months.

In analysis of subgroup data from a randomized controlled trial, van Wassenaer found that infants <27 weeks gestation treated with thyroxine supplementation performed better than placebo-treated controls on Bayley MDI at 2 years of age. Larger birth weight subgroups did less well (van Wassenaer, Kok, Briet, et al., 1997; van Wassenaer, Kok, de Vijlder, et al., 1997). This warrants further study.

Evidence That VLBW Is Associated With Disabilities Of Speech/Language Delay, Hearing Loss, Behavioral Disorders, And Learning Disabilities (Evidence Tables 5-6)

VLBW infants are at high risk for developing cognitive, neuromotor, and neurosensory disabilities including blindness and hearing loss. These disabilities in turn may lead to other disabilities in speech and language, behavior problems and learning disabilities affecting school performance. This is illustrated in the following example. Speech is the motor act of communicating using verbal expression and language is any means or form of communication (signs, symbols, vocal). In order for one to successfully communicate between listener and speaker, there must be an intact system of 1) sensation by hearing or seeing gestures in speech, 2) perception or coding about the sound and gesture system, 3) comprehension or decoding of words and meanings in context, 4) formulation or organizing ideas into language structure with words and sentences, 5) motor planning of breathing, phonation, resonance, and articulation to output the message, and finally, 6) motor control or execution of motor plans (McMillan, DeAngelis, Feigin et al. 1999). Communication disorder results if there is impairment in any component of this input and output phases. Hearing loss leads to impaired sensation and

perception and therefore, impaired ability to produce spoken language. Mental retardation or cognitive deficit may impair comprehension and formulation of ideas. Impaired neuromotor control may hinder production of intelligible speech. Neurologic dysfunction frequently accompanies behavioral disturbances and attention problems. These impairments may ultimately have consequences in social development, school performance, learning and achievement.

All of the above problems have been identified in disproportionate numbers in the VLBW infants. In this section, the incidence and severity of important disabilities in VLBW infants namely hearing loss, speech/language delay, behavioral disorders, learning disabilities, and school performance will be reviewed. This narrative examines the evidence that VLBW and the medical conditions and clinical factors that VLBW infants experience are associated with these disabilities. One hundred articles were reviewed but only 41 were felt to contain sufficient information and methodological quality to present. They were divided into sections of speech/language/communication outcomes, hearing loss, behavioral/social outcomes, and school performance/learning disorder outcomes.

Speech, Language, And Communication Disorder Outcomes

Because language is a large component of cognitive assessment, its evaluation is included in many intelligence and psychological studies such as the Stanford-Binet Intelligence test and Wechsler Scales of Intelligence and Bayley Scales of Infant Development. Nine studies (Table 3.1) are included that focus on speech and language outcomes or specifically address the language subscale of cognitive studies with sufficient information and quality, rather than in aggregate with other subscales. The studies reviewed overwhelmingly corroborate strong association of VLBW with speech and language impairment.

Table 3.1. Association of LBW to Speech and Language Disorders

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with impairment	Applica -blity	Quality
Singer 2001 21163669	VLBW with BPD N=90 VLBW without BPD N=65 Term N=91	BW 956±248 (SD) GA 27 ± 2 BW 1252 ±178 GA 30 ± 2 BW 3451 ± 526 GA 40 ± 1	**Cardiovascular PDA or pulmonary predictors:** Bronchopul-monary dysplasia General : BW, Neurologic risk Other: Race, Socioeconomic status	Battelle Developmental Communication Subscale	Receptive DQ <85: 49% vs. 34% vs. 30% Expressive DQ <85: 44% vs. 25% vs. 25% Communication DQ < 85: 43% vs. 31%, vs. 28%		**A**
Wood 2000 20373840	283	GA: <25 weeks	**GA** Gender Perinatal Factors→ Multiple gestation	Bayley Scales of Infant Development	31 out of 283 infants at 30 months of age had various degrees of language delay		B
Lefebvre, 1998 98387703	121	BW: 961	Neurobiologic risk score (NBRS)	Griffiths Developmental Scales:	71%		A
Wolke 1999 10075095	Preterm N=264 Full-term N=264	GA 29.5wks (29.3-29.7), BW 1288g (1247-1330) GA 39.6 wks (39.5-39.7), BW 3407 (3351-3463)	GA, IQ, socioeconomics	Griffiths Scales of Babies Abilities, Kaufman Assessment Battery for Children, Heidelberger Sprachentwicklu ngstest language test	Preterm children tested significantly lower on all dimensions of cognition and language/speech		A
Smith 1996 97081985	High-risk preterm N=89, Low-risk preterm N= 123, Full-term N= 128	Preterm infants BW = 1600g and GA = 36 wks. Full-term infants GA 37-42 wks.	Illness acuity, maternal behaviors	The Sequenced Inventory of Communication Development by direct observation	High-risk infants scored significantly lower than full-term infants in language scores at 6 and 12 months corrected age		B

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with impairment	Applica -blity	Quality
Sajaniemi 2001 11227991	63	Mean BW 1246 437 g Excluded infants with major disabilities	Cognition, temperament, and behavior at 2 years of age	Bayley Scales of Infant development, Toddler Temperament Questionnaire, Infant Behavior Record, and Verbal scale of Wechsler Preschool-Primary Scale of Intelligence (WPPSI)	Cognition, temperament and behavioral characteristics at 2 years of age predict language impairment at 4 years of age.	! !	B
Briscoe 1998 98300800	Preterm N=26; Full-term N=26	GA: 26 (26-32) BW: 1209 (815-1985)	GA	The Bus Story Test, The BPVS-long form, The Oral Vocabulary component	31%	! !	B
Saigal 2001 11483807	ELBW N=154 NBW N=125	BW 835 BW 3401	Birthweight 500-1000g GA	Ontario Child Health Study Questionnaire National Health Interview Survey, Survey of Disabled Children	Hearing loss: 7% vs. 5% (NS) Emotional problems: 4%, Vs 1% (NS) Learning disability: 34%, vs10% (p<0.001) Limitations in school: 31% vs. 9% (p<0.002)	! !	**B**
Schendel 1997 98033417	VLBW N=367; MLBW N=553; NBW; N=555	GA: 28.4 BW: 1088; GA:35.6 BW:2184 GA:39.4 BW:3414	BW	Language component of Denver II	8.8% vs. 5.8% vs. 4%	! !	B

In a nonrandomized comparison trial by Singer, Siegel, Lewis, et al. (2001)**,** preschool language outcomes of infants < 1500 grams born between 1989-1991 with (n=98) and without BPD (n=70) were assessed and compared with that of healthy term infants at 3 years of age. BPD (Bronchopulmonary Dysplasia) was defined as oxygen requirement for >28 days with radiographic evidence of BPD. Using the Battelle Developmental Inventory Communication Subscale Domain, receptive language (discrimination, recognition, understanding of words, sounds and gestures), expressive language (production and use of speech) and total communication skills were measured. The scores of each domain were converted to developmental quotient (DQ) with a mean of 100 and standard deviation of 15. VLBW infants

with history of BPD not only scored significantly lower on all 3 language domains compared to the other 2 groups but the BPD group also had significantly higher incidence of DQ < 85 in the impaired range of functioning. The percentage of infants with receptive DQ < 85 were 49% in BPD group, 34% in VLBW without BPD group and 30 % in term group (BPD < VLBW and Term, p< 0.05 ANOVA). The percentage of infants with expressive DQ < 85 was 44% in BPD group, 25% in VLBW group and 25 % in term group (BPD vs. VLBW and Term, p< 0.05). The percentage of infants with communication DQ < 85 was 43% in BPD group, 31% in VLBW group, and 28% in Term group (p=NS). There were significant differences in receptive DQ: 84.7 ± 17 in BPD group, 91.5 ± 17 in VLBW group, and 97.3 ± 18 in Term group (BPD < VLBW < Term, p < 0.05). Expressive DQ between the three groups were also significant: 92.8 ± 22 in the BPD group, 99.7 ± 17 in VLBW group, and 101.3 ± 20 in term group (BPD < VLBW and Term, p< 0.05). In overall communication skills, BPD group again scored significantly lower than the other comparison groups: 89.4 ± 21 in BPD group, 96.4 ± 19 in VLBW group, and 99.8 ± 20 in Term group (BPD < VLBW and Term, p< 0.05). Even after controlling for lower IQ, VLBW infants with BPD have lower receptive language score while expressive and communication scores were no longer significant, indicating that BPD may specifically affect the receptive language domain above the effects of general IQ. Infants in the BPD group were significantly more immature and smaller, had higher neurologic risk score, intraventricular hemorrhage (IVH), seizures, retinopathy of prematurity, patent ductus arteriosus (PDA), and sepsis. Hearing loss was not more frequent in the BPD group. When controlled for these medical factors associated with BPD, BPD did not predict the 3-year Battelle scores. The medical factors that were predictive of language outcomes, however, were PDA and higher neurologic risk score (mainly due to IVH and seizures). In hierarchical stepwise multiple regression analysis, PDA lowered the DQ by 13 points, minority race by 6 points, lower socioeconomic status by 5 points and higher neurologic risk by 5 points. PDA (incidence 56% in BPD group and 18% in VLBW group; p=0.001) had a negative impact, not on cognitive and motor outcomes, but specifically on language development, even in the non-BPD group. BPD appeared to exacerbate the detrimental effect of PDA on language. This study does not report the number of infants in the BPD group having all of the above risk factors for developing language difficulties. It is not unusual in daily medical practice to care for an ELBW infant with BPD, PDA, IVH and born to a teenage single mother. The risk for these infants to develop significant speech/language delay is substantial.

Wood, Marlow, Costeloe, et al. (2000) studied outcomes of extremely premature infants born less than 25 weeks gestation (born in 1995). Twenty-three percent of the evaluated infants had speech delay: 5% had delay in speech and other systematized method of communicating, and 5% could not communicate by any method. Most of the infants did not have hearing loss.

In the study by Lefebvre, Gregoire, Dubois, et al. (1998), the predictability of the Neurobiologic Risk Score (NBRS) for neurodevelopmental outcome was determined in VLBW infants (born 1987-1992 at <28wks) at 18 months corrected age. Various items including duration of ventilation, pH, seizures, IVH, PVL, infection, and hypoglycemia were scored with absence being 0 and up to 4 points with increasing severity to obtain a total NBRS score ("low" = 4, "moderate" = 5-7 and "high" = 8) at discharge from the NICU. The NBRS scores significantly correlated (p = 0.0001) with severity of all subscales of the Griffiths' developmental scales including the hearing-speech and personal-social subscales (i.e. the higher the NBRS scores, worse the Griffiths' score for hearing, speech and personal-social dimensions). Infants with "low," "moderate" and "high" NBRS score had Griffiths' Hearing and Speech DQ of 96 ± 15, 89 ± 19, and 76 ± 22, respectively (p = 0.0001). Infants "low," "moderate" and "high"

NBRS score had Griffiths' Personal-Social DQ of 104 ± 11, 95 ± 19, and 79 ± 30, respectively (p= 0.0001).

Wolke and Meyer (1999) studied 264 preterm infants, born <32 weeks in 1985-1986 in Germany, at 6 years and 3 months of corrected age. There were 264 full-term control children matched for age, sex, socioeconomic status maternal education and marital status. Preterm birth was significantly associated with deficits in wide range of abilities including all measures of cognition, language comprehension and expression, articulation and prereading skills tested compared to that of full-term control children. Even when preterm children with severe mental retardation, and major neurosensory impairments were excluded from the analysis, scores of IQ, language and prereading tests were significantly lower. Problems in cognition and language occurred at multiple levels. Preterm children have specific deficit in simultaneous central information processing where their ability to perceive, process and logically reason/integrate stimuli at the same time is impaired. Specific deficits in language abilities included problems with grammatical rules, and detecting semantically incorrect sentences ($p< 0.001$), motor aspects of speech such as articulation and pronunciation ($p<0.001$), and prereading skills of rhyming tasks, sound-to-word matching and naming of number/letters ($p<0.001$). The incidence of serious language impairment in the preterm group was 13.7% vs. 0.8% in the control group ($p<0.001$). Deficits in speech <10th percentile were 3 to 5 times more frequent in the preterm group.

Smith, Landry, Swank et al. (1996) compared expressive and receptive language development in "high-risk") preterm, "low-risk" preterm and full-term infants at 6 and 12 month corrected ages for preterm infants recruited 1990-1992. "High risk" was defined as having one or more severe medical complications including BPD needing oxygen more than 28 days and/or severe IVH Grade III-IV/PVL. At 6 months of age, the "high-risk" group of preterm infants had significantly lower receptive and expressive language scores than the full-term control infants. At 12 months of age, the "high-risk" preterm infants showed slower rates of improvement in the language scores and scored significantly lower than full-term controls in expressive language scores.

Sajaniemi, Hakamies-Blomqvist, Makela, et al. (2001) studied language development in 4 year-old preterm infants born 1989-1991 in Helsinki. Children with major disabilities including cerebral palsy and mental retardation were excluded so that the final study group consisted of 63 preterm infants with no major neurological impairments and with MDI >70 (from Bayley Scales of Infant Development), mean BW 1246 ±472g, mean GA 29.4 ±3. The study showed that cognitive, behavioral and temperament assessments as early as 2 years of age predicted impaired language functioning at age 4 years in infants without major disabilities. Twenty-two percent of cognitively normal preterm children at 2 years had language impairment at 4 year of age. In a logistic regression model, Bayley scores of 72, 82, 92, 100 and 106 corresponded to the following percent risk of developing language impairment: 90, 75, 50, 25, and 10%, respectively. Temperament (assessed by the Toddler Temperament Questionnaire at 2 years of age) as a whole (but not individual dimension) was statistically associated with language impairment at 4 years of age ($p<0.05$). Temperamentally, they were less active, less persistent, and less goal-directed with passive attitude toward environmental stimulus. Low scores of the Infant Behavior Record of the Bayley Scales as a whole were also related to impaired language functioning ($p<0.01$). The preterm infants were less cooperative and less reactive to their environment with high distractibility. Behavioral factors were more closely associated with later language impairment than temperament. A tentative explanation that the authors offer for the relationship between

temperament and behavior at earlier age with later unfavorable language development is that these temperamental and behavioral tendency of premature infants inhibit early intentional communication leading to progressive language delay.

Briscoe, Gathercole, and Marlow (1998) demonstrated that across all measures of short-term memory and language outcomes, preterm infants (26-32 weeks and born 1991-1992) performed at a lower level, typically half standard deviation lower than full-term counterparts at 3-4 years of age. They scored lower on receptive and expressive vocabulary, expressive language, phonological short-term memory, and general nonverbal ability. These deficits were unrelated to the general IQ. By 24 months of age, at-risk preterm infants performed significantly worse on the Hearing and Speech subscale of the Griffiths' Mental Assessment Scales. The Bus Story test identified "at-risk" preterm infants who developed specific language impairment without being cognitively impaired. Authors suggest that up to 31% of "at-risk"infants having language impairment may be identified with the Bus Story Test at 5 years of age.

A Canadian study by Saigal, Stoskopf, Streiner, et al. (2001) polled parents of ELBW infants 501-1000 g born 1977-1982 at 12-16 years of age as well as term controls. Parents were polled using questionnaires (Ontario Child Health Study Questionnaire, National Health Interview Survey, and Survey of Disabled Children). The ELBW had significantly higher utilization rate of speech therapists ($p< 0.002$) but they had similar utilization rates as control group for social services or other counselors for emotional and/or behavioral problems. Parents of ELBW also reported more frequent disabilities: emotional problems (OR 2.5; 95% CI 1.07-6.32), learning disabilities (OR 4.8; 95% CI 2.35-10.4), special education (OR 8; 95% CI 4.1-15.4) and hyperactivity ($p= 0.04$). One child in each group required hearing aid. This study again emphasizes higher prevalence of functional limitations in most domains with ELBW who may require more educational and health care services.

The study by Schendel, Stockbauer, Hoffman, et al. (1997) compared neurodevelopment of VLBW (<1500g), MLBW (moderately low birth weight, 1500-2499g), and NBW (normal birth weight, =2500g) children who were born 1989-1991. Language delay was detected in 8.8%, 5.8%, and 4% of VLBW, MLBW, and NBW infants, respectively (VLBW vs. NBW $p = 0.01$). Incidence of those suspicious for delay was even higher at 17%, 12%, and 8.5%, respectively (VLBW vs. MLBW $p = 0.05$; VLBW vs. NBW $p = 0.001$).

Audiology Outcomes

Identification of hearing loss is critical since it may lead to lower cognition, speech and language delays as well as social, educational and behavioral problems. It is also frequently associated with other neurologic disabilities (Marlow, Hunt, and Marlow, 2000). The following 21 RCT and non-randomized comparison studies (Table 3.2) reported the incidence of hearing loss in LBW infants. Hearing impairment incidence ranged 0 to 14% among VLBW infants. In the outcome studies, the details of hearing loss (i.e. specific test used, definition for hearing loss, and statistical analyses of hearing loss with confounding factors) were not consistently reported. To exclude these studies in this report for these reasons would exclude virtually all studies. Therefore, these studies are reported. Inconsistent results may stem from methodological differences.

Table 3.2. Association of VLBW with Hearing Loss

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with hearing impairment	Applica-bility	Quality
Northern Neonatal Nursing Initiative Trial Group, 1996 96304894	Plasma N=257; Placebo N=261; Control N=258	GA: < 32 weeks	Use of fresh frozen plasma or plasma substitute	Hearing loss of >= 50 dB, Griffiths quotient	50-70 dB 2/203, >70 dB 2/203, Griffiths quotient for hearing and speech >3 SD below mean 19/203		A
Hack 1996 97066007	1982-1988 N=34; 1990-1992 N=49	BW :624 ± 24 GA 24.4 ± 2; BW 634 ± 75 GA 24.4 ±2	BW	Unilateral or bilateral Deafness	1982-1988 0% 1990-1992 6%		A
Hack 2000 20358826	221	BW: 813±125 GA: 26.4 ±1.8	BW, GA SGA/IUGR, Antenatal steroids Jaundice, IVH	Unilateral or bilateral deafness; Hearing aid	9% 7%		A
Wood 2000 20373840	424	GA: <25 weeks	GA Gender Perinatal Factors→ Multiple gestation	Impaired hearing (not needing hearing aid) Impaired hearing not corrected with aid)	12% 3%		B
Singer 1997 98049057	VLBW with BPD N=122 VLBW without BPD N= 84 NBW N=123	BW 956±248 (SD) GA 27 ± 2 BW 1252 ±178 GA 30 ± 2 BW 3451 ± 526 GA 40 ± 1	Bronchopulmonary dysplasia (BPD), GA	Use of hearing aid	VLBW without BPD: 1% VLBW with BPD: 3%. P=NS		A
Schmidt B 2001 21298249	1202	GA: 26 BW: Sample 1: 782 Sample 2: 783	Prophylactic indomethacin	Hearing loss Requiring amplification	2%		A
Battin 1998 99002694	44	GA: 23-25 BW: ND	Extremely lowGA, BPD	Sensori-neural hearing loss	9%		**B**
Vohr 2000 20295211	1151	GA: ND BW: 401-1000	BW	Hearing impairment Wearing hearing aid	11% 3%		**B**

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with hearing impairment	Applica-bility	Quality
Piecuch 1997 98012134	86	BW 500-999 GA: 24-25	GA IVH	Behavioral testing for hearing	2/86 (NS)	! !	**B**
Victorian Infant Collaborative Study Group, 1997 97466059	Born 1979-80 N=351 Born 1985-87 N=560 Born 1991-92 N=429	BW: 500-999 GA: ND	Time period of birth	Deafness requiring hearing aids	Incidence of deafness in each time period was 0.	! !	B
Victorian Infant Collaborative Study Group 1997 98026322	Born 1979-80 N=351 Born 1985-87 N=560 Born 1991-92 N=429 NBW 1991-92 N=242	ELBW 500-999g NBW >2499g	BW, Time period of birth	Deafness requiring hearing aids	1985-87 ELBW: 0.05% 1991-92 ELBW: 0.8%	! !	B
Ambalavanan 2000 21031370	218	GA: 26 BW: 829	BW, GA, IVH, AntenatalSteroids Apgar score	Hearing aid	1.4%	! !	**B**
Cheung 1999 99146391	500-749g N=26; 750-999g N=63; 1000-1249 N=75	BW 660±56 GA 25(22-29); BW 873±72 GA 26(24-30); BW 1127±71 GA 28 (23-32)	GA Apgar score IVH	Sensori-neural hearing loss	0.9% (3/164)	!	B
Doyle 2001 11433066	225	GA: 23-27 BW: ND	GA,SGA/IUGR IVH	Hearing aid	0.9% (2/22)	! !	B
Corbet 1995 95264244		BW GA BW GA 27	Exosurf synthetic surfactant	Any Sensori-neural hearing loss Deafness >90dB	0 1%	! !	B
Gerdes 1995 95264241	One dose N=314 Three dose N=283	BW 907±121 BW 911±125	Cardiovascular or Pulmonary: Surfactant use	Bilateral sensori-neural Deafness; Not requiring amplification	1 dose: 2% 3 dose: 0% 1 dose: 2% 3 dose: 1%	! !	B
Marlow 2000 20150342	SNHL N=15 Controls N=30	BW:960(600-2914) BW:1026 (410-2814)	BW Apgar Illness severity (CRIB)	SNHL (Sensori-neural Hearing Loss)	Strong associations to: bilirubin+acidosis, Bilirubin +netilmicin, Creatnine + furosemide, Netilmicin + furosemide	! !	B

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with hearing impairment	Applica-bility	Quality
Lee BE 1998 98442293	25	BW: <1250 g GA: ND	Candidemia and/or Candidal meningitis	Hearing loss (neuro-sensory hearing loss in the better ear > 30)	Case: 14% Control: 5%		B
DeReginer 1997 98041177	No CLD N=54; Mild CLD N=54; Severe CLD N=56	GA: 27-28 BW: 1007-1030	Chronic lung disease	Sensori-neural hearing loss of 30 dB in the better ear, Visual reinforced audiometry	No CLD 0% Mild CLD 0% Severe CLD5.3%; P< 0.05 in No CLD vs. Severe CLD group		B
Kurkinen-Raty 1998 98197235	PROM N=55; No PROM Control N=56	BW : 1138 GA: 28.2; BW: 1272 GA28.4	Preterm rupture of membranes	Hearing loss	Early PROM: 7% Control: 9%		B
Kurkinen-Raty, 2000 20284814	Indicated del N= 81; Spont del N= 94	BW:1240 GA 30.5; BW 1608 GA 30.4	Preterm delivery for maternal or fetal indications	Hearing loss	NS		B

[a] "DELAY" defined by 9 measures of performance on Denver Developmental Screening Test II at age 15 months corrected
NS: not significant; PROM premature rupture of membranes.

In a randomized controlled trial by the Northern Neonatal Nursing Initiative Trial Group (1996), infants <32 weeks born 1990-1992 were studied at 2 years of age for effect of prophylactic fresh frozen plasma infusion in reducing IVH. The incidence of hearing loss (in better ear) were as follows: 50-70 dB loss occurred in 2 out of 203 in FFP group, 4 out of 196 in gelatin group, 3 out of 205 in glucose group. Hearing loss > 70 dB occurred in 2 out of 203, 1 out of 196, 2 out of 205, respectively. The number of infants with Griffiths quotient for hearing and speech >3 SD below the mean were 19 out of 203, 13 out of 196 and 20 out of 205, respectively. There was no statistical difference among the groups.

At 20 month corrected age, evaluation of premature infants BW <750 g and born in periods I (1982 – 1988) and II (1990 – 1992) was undertaken by Hack, Friedman, and Fanaroff (1996). The incidence of deafness was 0 and 6% in the groups born in periods I and II, respectively.

In another excellent outcome study by Hack, Wilson-Costello, Friedman, et al. (2000), infants <1000g born between January 1992 and December 1995 were evaluated for major outcomes at 20 months corrected age. The incidence of deafness (unilateral or bilateral) was 9% (20/221) and 16 of 20 (7%) with hearing loss required hearing aid. The rate of deafness by birth weight group were as follows: 8% (n=12) in 500-599 g, 10% (n=31) in 600-699g, 8% (n=52) in 700-799g, 11% (n=57) in 800-899g, and 9% (n=68) in 900-999g group. The rate of deafness by gestational age were as follows: 25% (n=8) in 23 week, 5% (N=21) in 24 weeks, 12% (n=42) in 25 week, 9% (n=55) in 26 week, 12% (n=43) in 27 week, and 0% (n=24) in 28 week infants. The rate of deafness was similar in AGA vs. SGA infants 10% and 6%, respectively. Multiple

stepwise logistic regression analysis identified the following factors as predictors of deafness: male sex (OR 2.79; 95% CI 1.02-7.62), sepsis excluding meningitis (OR 3.15; 95% CI 1.05-9.48), and jaundice with maximum bilirubin level > 10 mg/dl (OR 4.8; 95%CI 1.46-15.73). Of note, in this study, formal hearing tests were not routinely performed so that the incidence of milder hearing loss may have been underestimated.

In a large prospective cohort study by Wood, Marlow, Costeloe, et al. (2000), overall outcome of premature infants 20 through 25 weeks gestational age was evaluated. Twelve percent had impaired hearing not requiring hearing aid, 1% had hearing impairment not corrected with hearing aid, and 2% had severe hearing impairment not corrected even with hearing aid.

In a study by Singer, Yamashita, Lilien, et al. (1997) comparing long-term outcome of VLBW infants <1500 g, with BPD (supplemental oxygen at 28 days with radiologic changes) and without BPD, the use of hearing aids was 3% and 1% (P=NS), respectively. The incidence of hearing loss in the full-term infant group was not reported. BPD, at least in this study, was not directly related to hearing loss.

In a randomized, placebo-controlled trial of prophylactic Indomethacin, Schmidt, Davis, Moddemann, et al. (2001) reported a similar incidence of "hearing loss requiring amplification" of 2% in both the treatment and control group of infants (BW 500-999g).

In the study by Battin, Ling, Whitfield, et al. (1998) in British Columbia, 23-28 week infants born January 1991 to December 1993 were evaluated at 18 months corrected chronological age. Formal hearing tests (not specified) were done and the incidence of sensorineural hearing loss requiring amplification in infants 23-25 weeks was 9%.

Vohr, Wright, Dusick et al. (2000) in the United States studied infants weighing 401-1000g and born January 1993 to December 1994. Infants were evaluated at 18-22 months-corrected age. Overall hearing impairment was 11% with highest incidence of 14% in the 601-700g BW group. Three percent of infants weighing 401-1000g required hearing aids with the highest rate in the 601-700 subgroup.

Piecuch, Leonard, Cooper, et al. (1997) evaluated neurodevelopmental outcomes in 24-26 week infants born 1990-1994 in the US. Eighty-six were evaluated at 32 months corrected age. Audiologic assessment occurred by behavioral testing and any questionable exam was evaluated further by brainstem-evoked responses or pure tone audiometry. Only 2 infants had conductive hearing loss attributed to recurrent otitis.

In the studies by the Victorian Infant Collaborative Study Group (1997 and 1997), the incidence of hearing loss requiring hearing aid was 3.4% in the 1979-80 cohort, 0.5% in the 1985-87 cohort and 0.8% in the 1991-92 cohort. There was no statistical difference in the incidence among the groups.

Ambalavanan, Nelson, Alexander, et al. (2000) reported the incidence of deafness to be 1.4% in infants < 1000 grams born January 1990 to December 1994. Cheung, Barrington, Finer, et al. (1999) reported the incidence of sensorineural hearing loss (measured by certified clinical audiologists) at 0.9% in infants <1250 grams (born 1990-1993) at 3 years of age. By birth weight stratification, incidence was 1/26 (3.8%), 1/63 (1.6%) and 1/75 (1.3%) in the 500-749g, 750-999 g and 1000-1249g group, respectively.

In the study by Doyle (2001), the incidence of sensorineural deafness requiring hearing aid in 23 - 27 weeks infants born in Australia between January 1991 and December 1992 was 0.9% (2/221) compared to 0% in full-term group at 5 years of age.

In a randomized controlled trial comparing outcomes of infants at 1year corrected age (born 1986-1989) receiving placebo vs. Exosurf surfactant with birth weights 500-1350g, Corbet, Long, Schumacher, et al. (1995) reported the incidence of bilateral sensorineural hearing deafness to be 0 and 1%, respectively, which were not different. Hearing loss not needing amplification was 0 and 1%, respectively; also not significant. Although hearing evaluations were performed during the first year, the testing method and timing of the evaluations were not uniform among institutions. Hearing loss was defined as any degree of loss and deafness was defined as hearing threshold >90 dB.

In a 1 year-outcome study by Gerdes, Gerdes, Beaumont, et al. (1995), premature infants (BW 700-1100 g, born 1989-1990) treated with 1 vs. 3 prophylactic doses of Exosurf synthetic surfactant were compared. There was no difference between the study groups in the incidence of bilateral sensorineural deafness or deafness not requiring amplification. The incidence of bilateral deafness was 2% and 0.4% in the 1 vs. 3 dose groups, respectively (RR 0.18; 95% CI 0.026, 1.287). The incidence of deafness not requiring amplification was 2% and 0.7% in 1 vs. 3 dose groups, respectively (RR 0.37; 95% CI 0.078, 1.709).

In a case-control retrospective study in United Kingdom, Marlow, Hunt, and Marlow (2000) studied clinical correlates of sensorineural hearing loss (SNHL) in 12 month-old infants <33 weeks and born January 1990 to December 1994. "SNHL" was defined as > 50 dBHL loss on auditory brainstem response testing. "Moderate SNHL" was 41-70 dBHL, "severe SNHL" was 71-95 dBHL and "profound SNHL" was >95 dBHL. The hearing loss was confirmed by later behavioral testing by distraction test, visual reinforcement, and pure tone audiometry appropriate to child's development. Fourteen out of the 15 children were fitted with hearing aids (parent of 1 child declined use). Of the 15 children with hearing loss, 2 had bilateral moderate loss at 4000 Hz frequency, 5 had bilateral moderate SNHL over 500-4000 Hz range, 3 had bilateral severe SNHL, and 5 had bilateral profound SNHL. The authors reported that 47% of children with sensorineural hearing loss have evidence of CP compared to 7% in the normal hearing control group. Infants with SNHL had longer duration of ventilation, oxygen therapy, acidosis and more frequent use of dopamine and furosemide, and blood culture-positive sepsis indicating greater severity of illness in these infants compared to their matched controls. Risk factors that further increased the likelihood of developing sensorineural hearing loss were as follows: 1) serum bilirubin level > 200 μmol/l with acidosis {31% vs. 4%, OR: 8, 95% CI 0.9-71.6}, 2) bilirubin level > 200 μmol/l with netilmicin use {87 % vs. 14%, OR: 14.2, 95% CI 1.8-113.6}, 3) creatinine > 60 mmol/l with furosemide use {64 %% vs. 27%, OR: 8.9, 95% CI 1.1-74.5}, and 4) netilmicin with furosemide use {67% vs. 37%, OR: 5, 95% CI 0.99-24.8). The main drawback of this study was its small size (n=15).

Lee, Cheung, Robinson, et al. (1998) reported that infants (BW <1250g) who suffered candida sepsis/meningitis were more likely to die (60% vs. 28% in controls, OR 3.9, 95% CI 1.2-12.6) but the survivors of candida infection did not have higher incidence of hearing loss or cerebral palsy.

In the study by deRegnier, Roberts, Ramsey, et al. (1997) of infants <1500 g (born 1987 to 1991), hearing loss was 0 in both the "No CLD" (room air at 28 days) and "Mild CLD" (oxygen at 28 days but not at 36 weeks PMA) groups. Hearing loss occurred in 3 out of 56 (5.3%) infants in the "Severe CLD" (oxygen at 28 days and at 36 weeks PMA) group ($p<0.05$, No CLD vs. Severe CLD group). Hearing at 1 year adjusted age was tested by visually reinforced audiometry.

In infants born with PROM (premature rupture of membranes) compared to no PROM, Kurkinen-Raty, Koivisto, and Jouppila (1998) reported no difference in hearing loss (7% vs. 9%, OR 0.8, 95% CI 0.2- 3.2) at 1 year corrected age. Preterm delivery due to maternal or fetal indications did not increase hearing loss when compared to infants born spontaneously premature (6% vs. 3%, RR 1.9, 95% CI 0.5-7.8) even though they had higher incidences of RDS and BPD, pulmonary air leaks, and longer hospitalization days. However, they also had higher mortality rate so that the healthiest of the PROM group survived.

Behavioral / Social Outcomes

Long-term behavioral outcome studies of premature infants born prior to 1980 showed that VLBW infants have higher incidence of behavior problems and attention-deficit/hyperactivity disorder (Botting, Powls, Cooke, et al., 1997; Hack, Breslau, Aram, et al., 1992; McCormick, Brooks-Gunn, Workman-Daniels, et al., 1992; McCormick, Gortmaker, and Sobol, 1990). The seven non-randomized comparison studies in this review (Table 3.3) explore whether there are persistent increased behavior problems in VLBW infants born since 1980 with utilization of significant technological and medical improvements in their neonatal care.

Table 3.3. Association of LBW to Behavior Outcomes

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with impairment	Applica-blity	Qualit y
Nadeau 2001 21163667	Extremely premature N=61 Full-term controls N=44	<1500g (1024± 204), <29 wks (27 ±1.1. GA 39. ± 1.6 BW 3453g ± 498 SD	GA, Neuromotor function, Intelligence, Family adversity	Peers (Interviews, Revised Class Play) report increased sensitivity/isolation behaviors in prematurely born children Teachers (Teacher Report Form) report significant inattention. Parents (Child Behavior checklist) report hyperactivity.		! !	A
Robson 1997 9055145	85	BW 1758± 522g, GA 32.6± 3.4	Home environment, medical risk, temperament, developmental status	McCarthy Scale of Children's abilities, Parents' Child Behavior Checklist, task performances. Attention problems are predicted by temperament, home environment and interaction between developmental status and quality of home environment.		! ! !	**A**
Breslau 1996 8836807	Urban: LBW N=238 NBW N=176 Suburban: LBW N=235 NBW 174	LBW = 2500g NBW = 2500g	Urban vs. suburban sites, Socioeconomics GA, BW	Parent interviews, Teacher Report Form. LBW is associate with ADHD more strongly in socially disadvantaged urban group than suburban group.		! ! !	**A**

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with impairment	Applica-blity	Quality
Breslau 2000 20298367	LBW: N=411 NBW N=306	Urban site: N=238 LBW <1500g Suburban site: N=235 LBW <1500g	Suburban vs. Urban, LBW vs. NBW	Parents (Child Behavior Checklist), Teachers (Teacher Report Form). LBW have attention problems only in the urban setting group. Urban LBW have more severe attention problems than urban NBW. Suburban LBW have similar attention problems as suburban NBW. Difference in externalizing behavior is accounted for by maternal smoking. No difference in internalizing behaviors.		! ! !	B
Hille 2001 21319264.	USA N=80; Canada N=150; Germany N=78; Netherlands N=100	BW853±114 GA 27 ± 2.3; BW834±126 GA 27 ± 2.3; BW888±101 GA 29 ± 2 BW882±105 GA29 ± 2.3	Countries, Gender, BW	Parents (Child Behavior checklist CBCL). Total problem score: Boys: 3.3-9.8 points higher in LBW vs. control. Girls: 3.7-5.9 points higher in LBW vs. control. Social and attention difficulty scales were 0.5-1.2 SD higher in LBW children vs. control. Internalizing and externalizing behavior scores: no difference for all 4 groups (except for one cohort for internalizing scores)		! ! !	**B**
Katz 1996 97145056	Premature infants N=64, Full-term infants N=40	GA: 29 wks, BW: 1227g (740-2240)	GA CNS lesions: IVH, PVL	Increasing severity of lesions associated with increased error of commission. Increased errors of both commission and omission in preterms compared to full term infants.		! ! !	**B**
Sajaniemi 1998 99041674	Preterm N=80 Full term N=80	BW: 1205 (560-2360) BW: 3461 (2510-5360)	Prematurity(BW >1000g vs. <1000g) Low Bayley scores, Days on ventilator, PVL, IVH, CP, Days in NICU	In temperament, preterms are less active, more adaptive, more positive in mood, less intense, lower in threshold to respond than controls. On behavior, preterms less goal directed, less attentive, and lower in endurance than controls.		! ! !	**B**

Nadeau, Boivin, Tessier, et al (2001) evaluated behavior of 61 extremely preterm infants (gestational age <29 weeks and VLBW < 1500g) and 44 NBW infants born 1987-1990. The behaviors were evaluated at 7 years of age by parents, peers, and teachers who corroborated a definite link between extreme prematurity and behavior problems in school, specifically sensitive/isolated behaviors, inattention and hyperactivity. Premature birth was clearly associated with cognitive and neuromotor delays at 5 years and 9 months and these deficits accounted for development of behavioral problems. The children born prematurely were more frequently viewed by their peers as shy and withdrawn. In the mediational model, delayed neuromotor development (and not cognition) directly contributed to isolated behaviors.

Intellectual functioning, namely deficits in sequential memory (concentrating and receiving auditory information in working memory and retrieving it in organized fashion) was uniquely related to inattention in a regression analysis. This suggested that prematurity acted through its association with intellectual delays in the specific dimension of sequential memory to result in inattention behaviors recognized by teachers. Hyperactivity frequently reported by parents was predicted by global IQ deficits. Family adversity examined at 5 years and 9 months was significantly associated with sequential memory problems and inattentive behaviors but not with sensitivity/isolation or hyperactive behaviors at 7 years.

Robson and Pederson (1997) took a multidimensional approach to measurement of attention problems in preterm infants and identifying predictors of attention problems in this prospective longitudinal study. The McCarthy Scales of Children's Abilities test of behavior assessed inattention, impulsivity and hyperactivity. Parental report from the Child Behavior Checklist as well as task performance tests based on the vigilance task and the Matching Familiar Figures Test were also administered to identify attention problems at 5.5 years of age. Developmental status and quality of home environment correlated with increased hyperactivity detected on the McCarthy behavior test. The quality of home environment correlated with the parental reports of hyperactivity. Medical risk, infant temperament, quality of home environment, and developmental status correlated with task measures of attention. All three forms of testing for attention problems supported the hypothesis that the care giving home environment played a significant role in the development of self-regulating behaviors in low birth weight children in which safe, responsive, nurturing social home environment facilitated development of self-regulating behavior. Multiple regression analyses indicated that temperament, environment and the interaction between development and quality of home environment predicted attention problems in childhood.

Breslau, Brown, and DelDotto et al (1996), examined the association between LBW and ADHD (Attention Deficit Hyperactivity Disorder) and other behavioral disturbances in the DSM-III (Diagnostic and Statistical Manual of Mental Disorders, Third Edition) book of psychiatric disorders in urban and suburban socioeconomic populations. The children were born 1983-1985 in Michigan with BW <2500 g and evaluated at 6 and 7 years of age. The study excluded children with severe mental retardation, severe CP and blindness and focused on the population of preterm infants in whom behavioral outcomes were less obvious than in severely impaired children. The National Institute of Mental Health Diagnostic Interview Schedule for Children-Parent version was used as well as Teacher's Report Form to evaluate behavior problems. LBW was significantly associated with ADHD but not with separation anxiety disorder, simple phobia, overanxious disorder, or oppositional defiant disorder. The data from the mothers' interviews, teachers' ratings and data based on combined algorithm all corroborated that LBW is significantly associated with ADHD and that this relationship is stronger in urban than in suburban community. When combining parents and teachers' data, the rate of ADHD was higher in LBW group compared to NBW (13.9% vs. 4.1%; RR=3.4, 95% CI 1.5 to 7.5) in the urban group but not as strongly in the suburban group (6.9% vs. 3%; RR2.3, 95% CI 0.9 to 6.8). This association correlated with level of IQ with the children of IQ < 80 having the highest rate of ADHD. The teachers' ratings also found a significant association between LBW and the Withdrawn Symptoms scale. There were significant differences in racial composition, maternal education, and single-parent status between the two socioeconomic groups. The urban group was primarily black, 25% of the mothers had not completed high school and greater than 30% were single. The suburban group was predominantly white, only 7% of the mothers failed to

complete high school and 10% were single. Perinatal risk factors including single –mother status, maternal history of substance abuse/dependence and smoking during pregnancy in a multivariate analysis did not have significant associations with ADHD.

The study by Breslau and Chilcoat (2000) reevaluated behavior of this same group of preterm children at age 11 years. Both the behavior ratings by the mothers and the teachers who were blinded to the birth weight status, indicated that LBW was associated with attention problems in socioeconomically disadvantaged urban setting but not in suburban middle class setting. The urban LBW children had significantly higher incidence of "severe" attention problems by 11 years of age compared to their urban normal birth weight counterparts whereas the suburban LBW had similar incidence compared to their suburban normal birth weight group. The effect of LBW on externalizing behaviors (delinquent and aggressive subscales of CBCL-Child Behavior Checklist) was eliminated when prenatal exposure to maternal smoking was considered. LBW did not contribute to internalizing problems (withdrawn, somatic complaints and anxious/depressed subscales of CBCL). However, the study does not report whether the behavior problems needed treatment or how they impacted their school performance.

Hille, den Ouden, Saigal, et al. (2001) evaluated the behavior of VLBW infants from 4 different countries (US, Netherlands, Canada, and Germany) at ages 8-10 years. Premature infants had similar behavior problems in attention, social and thought subscale scores of CBCL, which were 0.5 to 1.2 SD higher in LBW infants than in term controls across all countries. This suggests that these problems are not a function of cultural differences but are an indication of biological mechanisms specific to VLBW infants. There were no differences in internalizing or externalizing scales when LBW infants were compared to normative cohorts of their respective countries, except for internalizing score in one cohort. Problems with this study are that children in both the normative groups and the LBW groups were born in different years sometimes with wide gaps. For example, the LBW Canadian cohort was born 1977-1982 while the US LBW cohort was born 1984-1987. Also, each country assessed premature infants of different BW range. For example, US cohort included BW up to 2000g while the Canadian cohort included only infants <1000 gram. Because the CBCL were completed by the LBW parents, who were not blinded to their infant's birth weight, there was potential for significant bias in their assessment of their child's behavior.

Katz, Dubowitz, Henderson, et al. (1996), in a comparison trial, studied 26-34 week premature infants (born 1983-1985) with or without intracranial lesions and full term infants at 6-8 years of age. Attention was evaluated with 2 tests: Continuous Performance Test measuring errors of omission or commission, and the CBCL by parents. The authors observed increasing poor performance on attention skills with increasing severity of intracranial lesions. However, absence of intracranial lesions did not preclude development of attention problems (i.e. premature infants without identified lesions were also at risk for attention deficits compared to term controls).

Sajaniemi, Salokorpi, and von Wendt (1998) compared behavior and temperament of VLBW infants 23-34 weeks, born 1989-1991 with that of healthy full-term controls at 2 years of age. Temperament was assessed with the Toddler Temperament Questionnaire, neurodevelopment with Bayley Scales of Infant Development and behavior with the Infant Behavior Record (IBR, part of Bayley Scales). There was no difference in temperament types (easy, difficult, and slow to warm up) between the groups. Preterm infants scored significantly different than controls in 5 of the 9 dimensions of temperament: preterm infants were less active ($p < 0.008$), more adaptive ($p< 0.02$), more positive in mood ($p< 0.004$), less intense ($p< 0.01$), and lower in threshold to

respond ($p< 0.003$) than the controls. IBR showed that preterm infants were less goal directed ($p< 0.0001$), less attentive ($p< 0.002$), and lower in endurance ($p< 0.0002$) than the control infants. Preterm infants also performed less well on the Bayley test. Low Bayley scores were associated with temperament of high rhythmicity ($r= 0.24$, $p< 0.03$), positive mood ($r=0.21$, $p< 0.04$), lower persistence ($r= 0.33$, $p< 0.002$), and high threshold to response ($r= 0.29$, $p<0.008$). Low Bayley scores correlated with behavior scores of poor social orientation ($r= 0.42$, o<0.0001), negative emotional tone ($r=0.34$, $p< 0.001$), poor cooperation ($r= 0.48$, $p< 0.0001$), short attention span ($r=0.5$, $p< 0.0001$), poor goal directedness ($r= 0.47$, $p< 0.0001$) and poor endurance ($r= 0.49$, $p< 0.0001$). High rhythmicity on temperament correlated only with increase in number of days on the ventilator ($r=0.29$, $p< 0.009$) among the perinatal and neonatal factors evaluated. PVL and IVH significantly correlated with behavior of short attention span ($p< 0.006$). CP at 24 months is associated with IBR for object orientation ($p< 0.01$), shorter attention span ($p<0.01$), and lower endurance ($p<0.01$). Increased number of days in the NICU correlated with IBR scores for poor object orientation ($r= 0.21$, $p< 0.05$), and short attention span ($r= 0.32$, $p< 0.003$). Increased number of days on ventilator also correlated with IBR scores for poor object orientation ($r=0.26$, $p< 0.01$), negative emotional tone ($r= 0.21$, $p< 0.05$), short attention span ($r= 0.26$, $p< 0.01$), and poor endurance ($r= 0.22$, $p< 0.04$). Although some correlation was weak, this study indicates that preterm toddlers have different temperament than full term toddlers in that they are more passive, have low energy, and more easily adaptive. For example, they do not become upset about falling or having a toy taken away, accept playing alone, do not fight rules, and sit quietly. As these qualities may appear desirable, it also indicates that they do not run off to explore new areas, are unmoved when listening to stories or looking at pictures, lack initiative and curiosity, and allow environmental stimulation to pass over them. This can in turn is a risk factor for developmental delay. This study shows that temperament and behavior are influenced by factors related to gestational age and cognition, with weak correlation to PVL, IVH and CP.

Learning Disability/School Performance Outcomes

Four non-randomized comparison studies (Table 3.4) reported association of LBW and VLBW to learning disability and school performance in infants born since 1980. There was limited data identified based on the methodology of this review regarding learning disability and school performance outcomes of VLBW infants. This indicates important areas of research to identify problems, to institute assistance and maximize achievement.

Table 3.4. Association of LBW to Learning Disability and School Performance

Author, Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Predictor	Measure	Association / % of Subjects with impairment	Applica-blity	Qua-lity
Hille 1994 8071753	LBW N=813	<32 wks, <1500g	Perinatal factors:GA, BW, male gender. Socioeconomics Factors at 5 years: neuromotor and speech delay, inattention, hyperactivity, poor school performance	Questionnaire	VLBW infants more frequently experience school failure than the general population in The Netherlands.		A
Stathis 1999 99325758	ELBW N=87	BW 860 (837-833)	Head circumference, Head circumference growth velocity	ANSER Teacher questionnaire, Du Paul Rating Scale for ADHD	Learning difficulty 45%, Reading problem32% Math problems 33%, Spelling problem 28%, Writing problem 29%		**B**
Cherkes-Julkowski 1998 98262696	Preterm N=28 Full-term N=20	BW 1880 BW 3318	GA	Mothers' perception, Neurologic exam, IQ	ADHD: 17 vs. 7% Learning disabilities: 17 vs. 14% Language impairment: 3% vs. 0, Mild neurologic impairment: 7% vs. 0 School concerns: 28 vs. 21%		B
Marlow 1993 8466264	Preterm N= 51 Full-term N= 59	BW < 1250g	BW, IQ at 6 years, motor skills, socioeconomics	Test of motor impairment, Suffolk reading Test, The basic mathematics test, The Schonell S1 graded word spelling test and handwriting assessment.	48% of preterm children at 8 years of age have difficulty in one or more subjects compared to 19% in full-term.		B

Hille, den Ouden, Bauer, et al (1994) reported school performance of preterm infants (born 1983) at 9 years of age in The Netherlands. Data were collected via questionnaires. Of the 813 very premature infants (<32 wks or BW < 1500g) who participated in the study at 9 years of age, 19% were in special education, 81% in mainstream education. Of the 658 children in mainstream education, 32% were in a grade below the level appropriate for their age and 38% had special assistance. Only 44% of the nondisabled, prematurely born children were in mainstream education at an age-appropriate level without special assistance. Perinatal risk factors such as GA <28 wks, BW <1250g, male gender, and socioeconomic status were

significantly related to overall school outcome: 66% of infants GA <28 wks, and 55% of infants BW <1250g were either in a grade below their appropriate level or in special education. Twice as many boys than girls were in special education. Only 7% of the high socioeconomic children were in special education compared with 35% in low socioeconomic group. SGA, multiple pregnancy, congenital malformations, neonatal illness, serum bilirubin level, and thyroxine levels did not contribute to school outcome. Of the factors evaluated at 5 years of age, neuromotor delay, speech/language difficulties, behavioral problems including inattention, and hyperactivity were strongly associated with school performance at 9 years of age. Of the infants with severe developmental delay at 5 years, 98% were in a grade below their appropriate level or in special education compared with 20% without developmental delay. More than 50% of children with neuromotor or language delay required special education compared to only 10% of children with no delay. The majority of children needing special education at 5 years were still in special education at 9 years. Almost all children who performed poorly in school at 5 years performed poorly at 9 years. Of the children who were in mainstream education at 5 years of age, mild developmental delay, inattention, hyperactivity, speech delay, male gender, and low socioeconomic status but not neonatal illness predicted need for special education at 9 years of age.

Stathis, O'Callaghan, Harvey, et al. (1999) studied 87 infants weighing 500-999grams born 1977-1986. Learning difficulty was defined as delay by at least 1 year in 1 or more areas of writing, reading, mathematics or spelling as reported by teachers in the ANSER questionnaire. Forty-five percent had learning difficulty with 32% having reading problems, 33% having mathematics problems, 28 % having spelling problems, and 29% having writing problems. The authors found that head circumference (HC) <3% and 3-10% at 8 months corrected age was strongly associated with school age learning problems ($p = 0.004$). Low head circumference growth velocity from birth to 4 months was also associated with learning problems at school age ($p=0.01$). Low HC at 8 months and low head growth velocity correlated significantly with low General Cognitive Index (GCI) at 6 years of age. However, the relationship between low HC and learning difficulties was independent of GCI scores. When confounding variables of gestational age, birth weight, maternal age, number of days on ventilator, and history of IVH were considered, the strength of the relationship between HC and learning difficulties again did not change. ADHD was evaluated by using the Du Paul Rating Scale by both the parents and teachers. Eighteen of 83 children (22%) were identified to have attention-deficit-hyperactivity disorder (ADHD). No significant association was found between HC or head growth velocity and ADHD. There were no normal birth weight controls for the study. However, the study does identify low HC at 8 months of age as an important predictor of learning disability. Study of school learning problems at 6 years may be too early and may miss children with more subtle difficulties.

Cherkes-Julkowski (1998) studied 28 mildly preterm infants who were relatively well in their neonatal course and compared them with 20 full-term controls at 13, 15, 20, 30 months and 3 years of corrected age. The preterm group consisted of children born <38 weeks (mean 48.86 ± 21.56 days prior to term), birth weight less than 2250g, who had no congenital disorder, no ROP, and were discharged from the hospital prior to 42 weeks postconceptional age. Surprisingly, there was a significantly higher than expected incidence of minimal brain dysfunction including attention deficit disorder (17.8% vs. 7.1%), learning disabilities (17.8% vs. 14.2%), language impairment (3.5% vs. 0), mild neurologic impairment (7.1% vs. 0), and general school concerns (28.5% vs. 21.4%). In fact, only 25% had no concerns by Grade 5 compared to 57% in term

controls. The signs of these disabilities manifested as early as 13-15 months of age and early identification of problems opened the possibility of early treatment. The mother's perception of their infants' competence was a sensitive marker for disabilities. Definitions of the above outcomes used by the authors were reasonable to enhance objectivity: "mild neurologic impairment" as mild impairment needing occupational therapy and no grossly abnormal motor or cognitive function; "learning disability" as having at least a 1.5 standard deviation discrepancy from IQ in 1 or more achievement areas as well as deficiency in reading, writing, spelling and comprehension; "school concerns" as placement in transitional first grade, formally recorded teacher concerns, referral and review by a multidisciplinary team. This article reinforces the concept that even seemingly "healthy" premature infants may have later sequelae needing special assistance. Major limitations of this study included small sample population and lack of consideration of important confounding variables.

Marlow, Roberts and Cooke (1993) studied behavioral and school outcomes of premature children born (1980-1981) at 8 years of age. There were 51 preterm children and 59 full-term controls. This study found disturbing evidence that even in the presence of normal IQ, premature children were much more likely to underachieve in school. On subjective and objective measures of school performance, 43 and 55%, respectively, performed satisfactorily in school compared with 71 and 81% in control children. Forty-eight percent of preterm children had difficulty in one or more subjects compared with 19% in controls. The teachers' assessments correlated closely with testing results in reading, math and spelling. The IQ test at 6 years also correlated with the educational tests. Both teachers and parents consistently reported behavior disorder in premature children, in particular restlessness, inability to settle, and hyperactivity. Other behaviors preterm children scored higher in were "fearful /afraid of new situations" ($p= 0.01$), "unresponsive/apathetic" ($p=0.001$), "poor coordination" ($p= 0.001$), "inattention" ($p= 0.001$), and "lack leadership" ($p=0.003$). Perinatal factors including intraventricular hemorrhages and PVL were not associated with school difficulties. Motor difficulties (balancing skills, ball skills) and mathematics test were best indicators of later school performance problems.

Learning disabilities are difficult to identify at early school age and become more apparent with higher school levels. In fact, in the United States, only 28.7% of children with special needs are identified before the age of 5 years (Palfrey, Singer, Walker et al. 1987). Therefore, identification of early predictors of learning problems in VLBW infants may allow for early intervention.

Evidence That VLBW With Or Without Other Conditions Is Associated With Visual Disability (Evidence Tables 7-8)

This portion of the narrative provides evidence that VLBW infants with or without other conditions have increased visual disability. The narrative is organized as follows:

1. Evidence that VLBW infants have increased visual disability
2. Evidence that VLBW infants with ROP have visual disability
    - A. Visual disability related to increasing severity of ROP
    - B. Visual disability related to severe ROP: not treated vs. treated

C. Visual disability related to severe ROP: treated with cryotherapy vs. laser therapy

3. Evidence that VLBW infants with CNS abnormality have visual disability
4. Evidence that VLBW (i.e. prematurity) and/or ROP and/or CNS injury are positively associated with refractive error (myopia) and abnormal ocular motility (strabismus)
   A. Abnormal visual function due to myopia
   B. Abnormal visual function due to fixation instability (strabismus and nystagmus)
5. Evidence that VLBW infants with bronchopulmonary dysplasia and systemic glucocorticoid therapy have visual disability
6. Incidence of ophthalmic interventions in children with BW<1251 gm through 5 years age

Evidence That VLBW Infants Have Increased Visual Disability

Twenty-seven observational studies (Table 4.1) identified by this review clearly demonstrate that VLBW infants have increased visual disability compared to full term infants and that the risk of visual disability in VLBW infants varies inversely with gestational age (Cheung, Barrington, Finer, et al., 1999; Kurkinen-Raty, Koivisto, and Jouppila, 1998; O'Connor, Stephenson, Johnson, et al., 2002; Page, Schneeweiss, Whyte, et al., 1993; The Victorian Infant Collaborative Study Group, 1997; The Victorian Infant Collaborative Study Group, 1997; The Victorian Infant Collaborative Study Group, 1997; Vohr, Wright, Dusick, et al., 2000).

Table 4.1. Association of VLBW/Prematurity with Ophthalmology Outcomes

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
O'Connor 2002 21635822	505	BW : 1400 GA: 31	BW ROP	Visual impairment Blindness	↑	! ! !	A
Hack 1996 97066007	83	BW: Sample 1: 687 Sample 2: 671 GA: 26	BW	Blindness 1982-1988 1990-1992	↑ (10% vs 2%)	! !	A
Hack 2000 20358826	54	BW: 813 GA: 26.4	BW	Blindness	↑ (1%)	! ! !	A
Piecuch 1997 97456215	445	BW Sample 1: 668 Sample 2: 790 Sample 3: 842	GA BW IVH	Visual impairment	⇔	! ! !	A
The Northern Neonatal Nursing Initiative Trial Group 1996	876	ND	GA BW	Visual impairment Blindness	↑ (1%)	!	A

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Vohr 2000 20295211	1151	BW: 401-1000	Birth weight Maternal disease (HTN) Antenatal steroids	Blindness	↑	! !	A
Wood 2000 20373840	283	GA: 22-25 BW: ND	GA Gender Multiple gestation	Visual impairment Blindness	↑ 2%	! ! !	A
Saigal 2001 11483807	154	BW: 835 GA: 27	BW GA	visual impairment	↑ 57%	! !	B
Victorian Infant Collaborative study Group, 1997 97466059	35	BW: 500-999	Ttime period of birth	Blindness	↑ (5.6 % vs 6.2%)	! !	B
Victorian Infant Collaborative study Group, 1997 98026322	448	1985-1987 BW: 500-749 1991-1992 BW: 750-999	Prematurity/ LBW	Blindness	↑ (4.3% vs 2.1%)	! !	B
Kurfinen-Raty 1998 98387235	156	BW : Sample 1: 1138 Sample 2:1272	Preterm rupture of membranes	Visual blindness	↑	!	B
Kurfinen-Raty 2000 20284814	206	BW: Sample 1: 1284 Sample 2: 1605	BW GA Antenatal steroids Cord pH Bronchopul monary dysphasia	Visual impairment	↑	! !	B
O'Shea 1997 98049056	216	BW: Sample 1 673 Sample 2:670 Sample 3:688	BW GA IVH	Blindness:	↑ (4%)	! ! !	B
Gerdes 1995 95264241	Group 1= 410 Group 2= 416	BW : 700-1100g	Surfactant use	Visual impairment Blindness	↑	! !	B

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Doyle 2001 11433066	225	GA: 23-27 BW : ND	Prematurity/ LBW	Blindness	↑ (1.0%)	! ! !	B
Cheung 1999 99146391	164	BW <1250 GA < 32	BW GA Apgar score IVH Cardiovascular and pulmonary predictors	Blindness	↑ (4 %)	! !	B
Emsley 1998 98238139	192	Mean BW: Sample 1: 751.7 Sample 2: 697.1	Birth weight GA	Blindness Myopia Squint	↑	! !	C
Finnstrom 1998 99041345	370	BW: 798	Retinopathy of Prematurity (ROP)	Visual impairment	↑	!	C

O'Connor, Stephenson, Johnson, et al. (2002) recently published their assessment of long-term (10-12 year), prospective follow-up of ophthalmic outcome of low birth weight children (<1701 gm) with and without ROP who were born in the mid-1980s. The cohort of former premature infants was compared to 11-year old controls that were born at full term. The rate of ophthalmic morbidity was 50.8% in the study's premature cohort compared with 19.5% in the full-term control group. Ophthalmic morbidity was defined in terms of significant reduction in visual acuity tests (near and far acuity, contrast sensitivity) or presence of strabismus, myopia, color vision defect, or visual field defect. The rate of ophthalmic morbidity (i.e. greatest reduction in visual acuity or incidence of strabismus) was highest in eyes with severe (Stage 3 or 4) ROP. They found that children born prematurely who had no or regressed mild ROP had similar visual acuities, but that the visual acuities of these premature infants were slightly, though significantly ($p<0.001$) reduced compared with full-term controls. They concluded that no or regressed mild ROP, by itself, had no major important long-term effect at 10-12 years of age on visual acuity. The premature cohort differed significantly from the full-term cohort with reduced visual functions (distant and near visual acuities, stereoacuity, visual field) and increased incidence of strabismus (19.3% vs. 3%, $p<0.001$) and myopia (22.4% vs. 8.9%, $p<0.001$). The prevalence of strabismus and myopia increased with increasing severity of ROP. Compromised stereoacuity was associated with maximum stage of ROP. All ocular dimensions were significantly smaller than published norms. This study shows that premature infants with or without ROP, and especially those with severe ROP, are at increased risk of visual impairments and disability compared with children who were born at full term. Visual disabilities are associated with low birth weight and severe ROP. Although ~55% of the original cohort was successfully tracked at age 10-12 years, this study is important for several reasons: 1) It is a geographically-defined, well-documented, population-based cohort. 2) It provides a long-term,

natural history study of visual outcome in premature infants who did and did not have ROP in terms of acuity, myopia, strabismus, contrast sensitivity, and ocular growth. 3) It provides a long-term, natural history study of visual outcome in premature infants who did have severe ROP in an era prior to use of cryotherapy. 4) It compares ophthalmic outcome of children born prematurely with those born full-term. 5) It demonstrates the significant association between ROP, especially severe ROP, and ophthalmic morbidity and visual disability. It shows that more than 50% of infants born prematurely (<1701 grams) have an ophthalmic problem at 10-12 years of age. Some of these ophthalmic problems can be treated. This study emphasizes the fact that severe ROP is associated with the highest rates of visual impairments.

Hack, Friedman, and Fanaroff (1996) found that infants with 500-750 gram birth weights at 20 months of age, the incidence of blindness was 2% for those born in 1990-92, compared to 10% for those from 1982-88. A later study by Hack, Wilson-Costello, Friedman, et al. (2000), which examined the neurosensory status of ELBW infants (<1000 gm) born 1992-1995, found that the incidence of blindness was 1% for both birth weight strata of <750 gm and 750-999 gm. Piecuch, Leonard, Cooper, et al. (1997) found a similar incidence of blindness in the cohort of extremely premature infants (24-26 weeks gestation) followed from 1 to 4.5 years of age who were born during 1990-1994. One percent of these infants were blind (1/86) and 2% (2/86) had nystagmus related to severe ROP. Northern Neonatal Nursing Initiative Trial Group (1996) documented a 1% incidence of blindness in infants born less than 32 weeks gestational age in 1990-1991 during a 2-year regional follow-up in the United Kingdom. The blindness of these infants was due to ROP and cortical blindness.

Vohr, Wright, Dusick, et al. (2000) assessed multiple neurodevelopmental, neurosensory, and functional outcomes at 18-22 months age in 1151 extremely low birth weight survivors (ELBW=400-1000 gm) born between 1993-1994 in 12 USA neonatal intensive care units (NICUs) participating in the NICHD-sponsored Neonatal Research Network. This recent, large, prospective study reaffirmed the strong inverse association of neurodevelopmental, neurosensory, and functional impairments, including visual disabilities, with gestational age. Visual impairment was noted in 21% of infants with birth weights 401-500 gm, 10% to 13% in infants with birth weights 501-800 gm, 5% in infants with birth weight 801-1000 gm. Specifically blindness was noted in 14% of infants with birth weights 401-500 gm, and in 1-4% of infants throughout the '100 gm' birth weight strata from 501- 1000 gm. Overall, among infants between 401-1000 gm birth weight, 9% were visually impaired and 3% were legally blind in one or both eyes.

Saigal, Stoskopf, Streiner, et al. (2001) conducted a longitudinal cohort study of Extremely Low Birth Weight infants (ELBW= 5001-1000 gm) and compared neurosensory outcomes of ELBW infants with full term controls at 12-16 years of age. Neurosensory impairments were present in 28% of ELBW survivors compared to 2% of control subjects ($p<0.001$) Visual impairments were reported by participants' parents in 57% of ELBW survivors (n=154) compared to 21% of control subjects (n=125) ($p<0.0001$, OR 5.1, 95% CI 2.88,9.05). The proportion of premature infants reported to have an ophthalmic problem in Saigal's study is similar to that of O'Connor, although the patient population of Saigal's study is restricted to higher risk ELBW infants. This study again illustrates persisting morbidity among ELBW survivors during adolescence and teenage years.

The following studies report the incidence of the most extreme visual disability, blindness, which is a smaller subset of the larger category of 'visual impairment or disability'. The publications of the Victorian Infant Collaborative Study Group illustrate several important points

about risk of blindness in ELBW infants (500-999 gm). First, the risk of blindness decreased since 1979-1980, but leveled during the 1980s and early 1990s. Second, the risk of blindness is higher in ELBW infants compared to normal birth weight controls. And thirdly, the risk of blindness is inversely related to birth weight or gestational age (The Victorian Infant Collaborative Study Group, 1997; The Victorian Infant Collaborative Study Group, 1997; The Victorian Infant Collaborative Study Group, 1997). Specifically, investigators of the Victorian Infants Collaborative Study Group followed ELBW infants over 3 time periods (1979-80, 1985-87, 1991-92) and compared outcomes with normal birth weight controls. Survival and overall rate of disability, assessed at 2 years age, improved over the three time periods for both inborn and outborn ELBW infants, but the rates of disabilities were significantly greater in ELBW infants than in full-term controls at 2 years age. The proportion of inborn ELBW infants blind at 2 years age was 6.7% (6/89), 4.3% (9/211) and 2.1% (5/237) in 1979-80, 1985-87, and 1991-92 respectively. The proportion of outborn ELBW survivors assessed as blind was higher than inborn ELBW infants, and the incidence of blindness decreased in outborn ELBW infants from 27.8% (n=5 of 18) to 5-6% blindness in the later two eras (1985-87: 5.6%, 1/19; 1991-92: 6.2%, 1/16). None of the full-term controls was blind. When evaluated from the perspective of gestational age, the overall rates of blindness in infants born 23-27 weeks gestation was significantly lower in 1991-1992 (2.3%) compared with 1985-1987 (8.4%). The well-recognized inverse relationship of visual disability and birth weight was also demonstrated in further evaluation of children born in the era of 1991-1992 in which 9.3% of infants with birth weight between 500-749 gm had sensorineural disability (sight, hearing, cerebral palsy) in contrast to 6.0% of infants who weighed 750-999 gm at birth.

Two Finnish studies (Kurkinen-Raty, Koivisto, and Jouppila, 1998; Kurkinen-Raty, Koivisto, and Jouppila, 2000) and several American studies report incidences of blindness in premature infants similar to that reported in the Australian Victorian Studies. O'Shea, Klinepeter, Goldstein, et al. (1997) reported rates of blindness at 1-year follow-up in ELBW infants (501-800 gm) over three time periods spanning from 1979 through 1994. The proportion of children who sustained blindness were 2/24 (8%), 0/62 (0%), and 5/124 (4%) during 1979-1984, 1984-1989, 1989-1994 respectively. Gerdes, Gerdes, Beaumont, et al. (1995) documented 2-4% incidence of blindness at 1 year of age in a USA cohort of premature infants (birth weight 700-1100 grams) treated with two different dosing regimens of surfactant (1 vs. 3 surfactant doses) and born during an era (1989-1990). This incidence is similar to that reported during the latest era of the Victorian Study. Gerdes et al also noted that 8-10% of the infants in the two surfactant study groups had visual defects at 1 year of age.

Doyle, Casalaz, and The Victorian Infant Collaborative Study Group (2001) found that the prognosis of 5-year outcome of a geographically determined cohort of infants born between 23 and 27 weeks of gestation during 1991-1992 in Victoria, Australia varied with gestational age, postnatal age, and the number of adverse events (co-morbidities). These infants were compared to 'normal birth weight' controls (BW>2499 gm). They found that the rate of survival with major neurosensory disability increased with decreasing gestational age and with the number of adverse risk events in the NICU (intraventricular hemorrhage, cystic periventricular leukomalacia, surgery, postnatal glucocorticoid therapy). Similar to other studies of extremely low gestational age neonates, these authors found approximately 2% incidence of blindness.

Emsley, Wardle, Sims, et al. (1998) compared changes in survival and neurodevelopmental disability, including visual disability, between to two cohorts of extremely premature infants (23 to 25 weeks gestational age) over time (cohort 1: 1984 to 1989 v. cohort 2: 1990 to1994. In

addition to increasing survival and increasing neurodevelopmental disability over the two time eras, they found more survivors with blindness due to ROP (4% vs 18%), myopia (4% vs. 15%), and squints (8% vs. 13%) between cohort 1 (1984 to 1989) and cohort 2 (1990 to1994) respectively. The rise in neurodevelopmental disability was due to the rise in visual disability, which was related to ROP

Finnstrom, Otterblad, Sedin, et al. (1998) documented less favorable neurosensory outcome and growth at 3 years age in extremely premature infants (<1000 gm birth weight or ≥23 weeks gestation) born between 1990-1992 in Sweden. Four percent of the cohort had visual impairment at 3 years age. The visual impairment was primarily due to ROP (3% of all children), but also due to Candida infection and cortical blindness related to central nervous system injury. Kurkinen-Raty documented a 4-5% incidence of visual disability in infants born <37 weeks gestation (Kurkinen-Raty, Koivisto, and Jouppila, 1998) and 24-33 weeks (Kurkinen-Raty, Koivisto, and Jouppila, 2000) at 1 year corrected age during the period of 1990-1997. Wood, Marlow, Costeloe, et al. (2000) evaluated all children born ≤25 weeks gestational age in the United Kingdom and Ireland in 1995 at a median age of 30 months. They found that approximately 50% of the extremely, extreme premature infants had neurodevelopmental disability. Ten percent of the infants had visual disability that could not be fully corrected, and two percent of these infants were blind. Twenty-five percent had squint and 10 percent wore eyeglasses.

In a prospective study of the relationship between apnea during hospitalization and subsequent growth and neurodevelopment in preterm infants (birth weight <1250 gm, and gestational age ≤32 weeks), Cheung, Barrington, Finer, et al. (1999) documented that the incidence of blindness varied inversely by birth weight (birth weight 500-749 grams: n=26: 4%; birth weight 750-999 grams: n=63: 2%; birth weight 1000-1249 grams: n =75: 1%).

These articles provide evidence that VLBW infants have increased visual disability and that the risk of visual disability in VLBW infants varies inversely with gestational age.

Evidence That VLBW Infants With Retinopathy Of Prematurity (ROP) Have Visual Disability

Retinopathy of Prematurity (ROP) is a proliferative, fibrovascular disease of immature retinal vessels, and is a leading cause of visual disability and blindness in infants. ROP is associated with a disruption in the normal growth and development of retinal blood vessels. The incidence and severity of ROP are directly related to the degree of immaturity of an infant (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994; Dogru, Shirabe, Nakamura, et al., 1999; Palmer, Flynn, Hardy, et al., 1991; Schaffer, Palmer, Plotsky, et al., 1993). Thus, the more immature an infant, the greater the risk for any ROP and the greater the risk for severe ROP. Two thirds (66%) of infants with birth weight <1251 grams in the Multicenter Cryotherapy Trial for ROP had ROP, 17% developed moderately-severe ROP, and 6% developed severe (threshold) ROP (Palmer, Flynn, Hardy, et al., 1991).

Visual Disability Related To Increasing Severity Of ROP

Only 8 studies are noted in the following table (Table 4.2a). Ten studies clearly demonstrate that long-term visual function (visual acuity, myopia, strabismus, etc) in VLBW infants with ROP is related to the severity of ROP and its treatment. Visual disability and impairments increase with increasing severity of ROP, even in infants with no apparent retinal residual.

Table 4.2a. Visual disability related to increasing severity of ROP in VLBW infants

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
O'Connor 2002 21635822	505	Mean BW (range), g: 1400 (iqr 1150, 1562) Mean GA (range), wk: 31.06±3.09)	Birth weight ROP	Visual impairment Blindness	↑	! ! !	A
Cryo-ROP, 1990, 1996, and 2001 (x3) 91024693, 96180078, 21375786, 21375787, 21375788 Repka 1998 98426775	291	BW: 800 GA: 26.	Threshold retinopathy of prematurity At 1year& 5.5-year & 10-year follow-up: Cryotherapy vs. No Cryotherapy	Visual impairment Blindness	↑	! !	A
Dogru 1999 99168711	78	GA: 26-28 BW: 836-1016	Sever ROP	Low visual acuity scores	↑	!	B

As noted previously, O'Connor, Stephenson et al. (2002) studied visual function in children born prematurely with and without ROP along with children born at full term at 10 to 12 years of age. They found that premature infants with or without ROP, and especially those with severe ROP, are at increased risk of visual impairments and disability compared with children who were born at full term. The rate of ophthalmic morbidity (i.e. greatest reduction in visual acuity or incidence of strabismus) was highest in eyes with severe (Stage 3 or 4) ROP. O'Connor et al also found significant differences between the premature cohort and the full-term cohort in prevalence of myopia and strabismus, and that each of these were significantly related to the severity of ROP. Compromised stereoacuity was associated with maximum stage of ROP.

Similarly, Dogru et al found that infants with Stage 3 ROP had lower visual acuity compared to infants with Stage 1-2 ROP or no ROP at 18 to 24 months follow-up ($p<0.0001$). Infants who had regressed Stage 3 ROP are also at increased risk for myopia, astigmatism, anisometropia, amblyopia, and strabismus, and subnormal visual acuity. (Dogru, Shirabe, Nakamura, et al., 1999)

One of the best studies that provides evidence that severity of ROP is related to visual disability is the National Eye Institute's Multicenter Trial of Cryotherapy for ROP (CRYO ROP) (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1990; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1996; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001). CRYO ROP had both a natural history study of ROP and a randomized clinical trial for infants with severe (threshold) ROP. The following is a summary of the long-term outcomes of the natural history study of CRYO ROP. The 10-year visual outcomes of infants with severe (threshold) ROP who were randomized in the CRYO ROP trial for threshold ROP are noted later in this narrative.

The natural history study of the 2759 untreated eyes of the Multicenter Trial of Cryotherapy for ROP (CRYO ROP) clearly demonstrated that adverse anatomical and functional outcomes are associated with the severity of ROP as noted by the location of the ROP process, the stage of ROP, the extent of the stage (i.e. number of sectors of the retina involved with ROP), and the presence of plus disease. The more posterior the location of acute ROP, the more advanced the stage of ROP, the more extensive the number of sectors of ROP, and the presence of plus disease are individually and collectively high risk, poor prognostic factors. The eyes at highest risk of unfavorable 1-year outcome were eyes with posterior Zone 1 ROP, Stage 3 ROP, and eyes with 9 to 12 sectors in Zone II, Stage 3 ROP with plus disease. Eyes at lowest risk for unfavorable 1-year outcome were no ROP, Zone II ROP with no plus disease, and any ROP in Zone III (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994). The following table summarizes the proportion of eyes with unfavorable (i.e. disabling) visual function who had less than threshold ROP or threshold that was not treated with cryotherapy:

Table 4.2b. Proportion (%) of eyes with unfavorable visual function

ROP (<Th or Th no treatment)	Abnormal Fixation	Nystagmus	Strabismus	Myopia (>2D)
Zone 1	44	6	25	40
Zone 2, Stage 3+ (9-12 sectors)	57	39	33	63
Zone 2, Stage 3+ (5-8 sectors)	32	9	30	55
Zone 2, Stage 3+ (1-4 sectors)	19	11	35	46
Zone 2, no + dz	7	5	16	<25
Zone 3	3	2	12	3
No ROP	1	<1	6	3

Visual Disability Related To Severe (Threshold) ROP: (Treated and Not Treated)

Table 4.3 summarizes the functional outcomes throughout the 10-year follow-up of the eyes with severe ROP that did and did not have retinal ablation with cryotherapy.

Table 4.3. Unfavorable functional outcome (%) in eyes with threshold ROP by randomized treatment assignment (cryotherapy vs. no cryotherapy) during 1, 3.5, 5.5, and 10-year follow-up.

	1 YR	**3.5 YR**	**5.5 YR**	**10 YR**
N examined/ Original number	**246/291**	**236/291**	**234/291**	**255/291**
Threshold ROP with Cryotherapy	Grating Acuity 35% Blind 32%	Grating Acuity (TAC) 26.1% Recognition Acuity (HOTV) 46.6% Blind 37% (among eyes tested with HOTV)	Acuity 47.1% Blind 31.5%	Distance acuity 44.4% Near acuity 42.5% Contrast sensitivity 39.7%
Threshold ROP with No Cryotherapy	Grating Acuity 56% Blind 51%	Grating Acuity (TAC) 45.4% Recognition Acuity (HOTV) 57.5% Blind 53% (among eyes tested with HOTV)	Acuity 61.7% Blind 48%	Distance acuity 62.1% Near acuity 61.6% Contrast sensitivity 59.3%

The CRYO ROP Trial (table 4.2b) is the largest, prospective, longitudinal study of ophthalmic outcome of premature infants with severe (threshold) ROP in the USA (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1990; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1996; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001). This NEI-sponsored multicenter trial began in 1986 to provide critical information regarding the natural history of ROP, as noted above (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994), and to determine whether retinal ablation with cryotherapy for severe or 'threshold' ROP was beneficial in reducing retinal detachment and unfavorable retinal outcome. Threshold ROP was defined by the CRYO ROP trial as ≥5 contiguous or 8 cumulative clock hours of Stage 3 ROP with plus disease in Zone II. CRYO ROP confirmed the effectiveness and benefit of retinal ablation with cryotherapy for threshold ROP (versus no treatment) in terms of structural and functional outcomes at 1 yr, 3.5 yr, 5 yr, and 10 yr follow up (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1990; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1996; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001). 'Unfavorable' structural and functional outcomes included infants with poor visual function or blindness. Thus, unfavorable outcome represents extreme visual disability. Children with subnormal or normal vision were included in the 'favorable' outcome category. Functional outcomes at 10-years' follow-up of infants with threshold ROP (with and without cryotherapy) include visual acuity (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001), visual fields (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 2001), and contrast sensitivity (Cryotherapy for

Retinopathy of Prematurity Cooperative Group, 2001). This exceptional, successful effort of long-term tracking of high-risk infants vividly illustrates that ROP and its consequences are life-long and dynamic, not stagnant.

The important findings of the CRYO ROP natural history study and randomized cryotherapy trial can be summarized as follows:

- The more severe the acute ROP, the greater the risk for unfavorable ophthalmic outcome (i.e. visual function as well as late retinal and non-retinal complications). The increased risk for unfavorable outcome includes ROP that is moderately severe but less severe than threshold ROP, and thus never met study criteria for randomization for cryotherapy. The increased risk of unfavorable ophthalmic outcome was particularly true of ROP in Zone 1, Stage 3 ROP, and ROP with plus disease. The increased risk reflects the underlying severity of the retinal damage, and the consequences of disruption in normal growth and development of the retinal vessels. As a point of reference, Myers, Gidlewski, Quinn, et al. (1999) found that 99% of normal full-term children (n=106) had normal visual acuity (classified as 20/40 or better).

- Cryotherapy significantly reduced the incidence of blindness and unfavorable outcome, especially in Zone 2 threshold eyes. Despite this benefit, infants successfully treated with cryotherapy still had an unacceptably high risk of unfavorable functional outcome (44.4% of treated eyes). Again, unfavorable outcome was particularly true in eyes with Zone 1 threshold ROP regardless of whether or not the eye received cryotherapy (i.e. poor outcome in 75% of zone 1 treated eyes and 92% of not treated eyes). As noted above, the unfavorable outcome of successfully treated eyes is most likely a reflection of the severity of the underlying retinal injury and of the disruption in normal growth and development of the retina.

- The 10-year follow-up revealed that the rate of retinal detachment among control (no cryotherapy) threshold eyes increased at 5.5 years (38.6%) and again at 10 years age (41.4%), after having been 'stable' during the first 3 years of follow-up. The rate of retinal detachment remained stable in treated eyes (22.0%).

- Visual fields: Eyes with severe ROP and not treated, have smaller visual fields by 27% to 35% compared to eyes that never had ROP. Eyes treated with cryotherapy had a further reduction in the visual fields by 7%.

- Contrast sensitivity: Eyes treated with cryotherapy had a 33.1% reduction in unfavorable outcome in terms of contrast sensitivity compared to control "no cryotherapy' eyes (cryotherapy 39.7% vs control 59.3%). Unfavorable contrast sensitivity was defined as correct identification of <26 letters on the Pelli-Robson chart or blind. Favorable outcome included children who had normal or below normal contrast sensitivity (normal correct identification of 33 or more letters on the Pelli-Robson chart or roughly equivalent to a CS of 1.50 lu; below normal = detection of 27-32 letters (~1.2- to 1.5 lu)). Contrast sensitivity was outside the normal range in 3.1% of 'no ROP' eyes, 51.9% of cryotherapy eyes, and 65.4% of control 'no treatment' threshold eyes. Thus, with or without cryotherapy, eyes with threshold ROP had significantly worse color sensitivity than eyes

that never had ROP. Comparison of eyes in patients with bilateral threshold ROP showed that cryotherapy had no apparent adverse effect on contrast sensitivity at 10 years follow-up. As a point of reference, Myers, Gidlewski, Quinn, et al. (1999) found that 4% of normal full-term children (n=106) had visual acuity outside the normal range.

- At the 10-year outcome, treated and control threshold eyes are equally likely to have 20/40 visual acuity, but this is the minority of threshold eyes.

- Retinal ablative therapy (cryotherapy or laser therapy) for threshold ROP is cost effective therapy that can improve the quality of life.

Visual Disability Related To Severe (Threshold) ROP: (Treated With Cryotherapy Vs. Laser Therapy)

Table 4.4 summarizes the functional outcomes throughout the 10-year follow-up of the eyes with severe ROP that did and did not have retinal ablation with cryotherapy.

Table 4.4. Visual disability related to severe (threshold) ROP

Author, Year	Eyes Treated (N)	Mean BW, g; GA, week Baseline (Range)	Inter-vention	Outcomes	Efficacy	Applica-bility	Quality
Algawi 1994 95001766	53	BW: 620-1500 GA: 24-32	Diode Laser: 21 Eyes Cryotherapy: 32 Eyes	Myopia	Diode Laser Eyes: **40%** Cryotherapy Eyes: **92%**	!	B
				Hypermetropia <+3.0 Diopters	Diode Laser Eyes: **60%** Cryotherapy Eyes: **8%**		
				Clinical significant astigmatism	Diode Laser Eyes: 33**%** Cryotherapy Eyes: 20**%**		
Connolly 1998 98426776	46	BW: 731 (440-1318) GA: 25 (23-.32)	Laser: 23 Eyes - Argon (10) - Diode (13) Cryotherapy: 23 Eyes	Myopia (mean spherical equivalent)	Laser Eyes: **-3.05** Diopters Cryotherapy Eyes: **-5.08** Diopters	! !	B
				Visual Acuity 20/50 or better	Laser Eyes: **81%** Cryotherapy Eyes: **38%**		

Author, Year	Eyes Treated (N)	Mean BW, g; GA, week Baseline (Range)	Inter-vention	Outcomes	Efficacy	Applica-bility	Quality
Shalev 2001 21331013	19	BW: 631 (540-846) GA: 25 (23-27)	Diode Laser: 10 Eyes Cryotherap y: 9 Eyes	Unfavorable structural outcome	Diode Laser Eyes: **0%** Cryotherapy Eyes: **22%**	! ! !	B
				Geometric visual acuity	Diode Laser Eyes: **20/33** (20/20-20/70) Cryotherapy Eyes: **20/133** (20/25-phthisis)		
				Mean refractive error	Diode Laser Eyes: -6.50 Diopters Cryotherapy Eyes: -8.25 Diopters		

Retinal ablation for threshold ROP with laser photocoagulation has emerged as an effective alternative to cryotherapy in preventing retinal detachment. The following studies have evaluated long-term ophthalmic outcome of cryotherapy versus laser therapy for treatment of severe (threshold) ROP.

Algawi, Goggin, and O'Keefe (1994) evaluated ophthalmic outcome following diode laser versus cryotherapy for threshold ROP (CRYO ROP definition). The incidence of refractive error (myopia) is high in infants with threshold ROP regardless of whether they were treated with laser or cryotherapy. Algawi's study demonstrated that threshold ROP treated with laser (n=15 eyes) had less myopia (40%, range –1.5 to -3.5 D) than eyes treated with cryotherapy (n=25 eyes) (92%, range -0.5 to –8. D)($p<0.0006$). However, the cryotherapy group had less hypermetropia than the laser group (cryotherapy 8% vs laser: 60% at <+3.0 D, $p<0.006$). The authors concluded that myopia was a major complication of premature infants, especially in premature infants with severe ROP, and that laser therapy can reduce the risk and/ or severity of myopia. Any reduction in myopia is important in terms of long-term visual benefit. Connolly, McNamara, Sharma, et al. (1998) compared laser photocoagulation with trans-scleral cryotherapy in treatment of threshold ROP to determine if laser therapy resulted in better visual outcomes of eyes with threshold ROP. Twenty-five of 52 eyes randomized to cryotherapy vs. laser were assessed at 5.8 years (range 4.3 – 7.6 yrs). The odds that a threshold eye treated with laser had a good clinical outcome were 6.91 x greater than cryotherapy (95% CI 1.7-28.0,n=21), and laser treated eyes were less myopic (mean SE –3.05 D) than cryotherapy treated eyes (mean SE –5.08 D) ($p=0.0072$, n=23). The authors concluded that laser therapy was more likely to result in better visual acuity and less myopia compared to cyrotherapy. Shalev, Farr, and Repka (2001) randomized threshold ROP eyes to laser vs. cryotherapy and reassessed the visual outcome in 10 of 19 patients at 7 years. Laser therapy had more favorable outcome in terms of geometric mean visual acuity (laser 20/33, range 20/20-20/70 vs. cryotherapy 20/133, range 20/25 to phthsis) ($p=0.03$). The mean refractive error of laser-treated eyes was -6.5 D (+1.25-12.75D) compared to –8.25 D (-0.25 to –

16.00) for cryotherapy-treated eyes. The 7-year assessment showed little change from the 3-year outcome.

Evidence That VLBW Infants With CNS Abnormality Have Visual Disability (With No Or Mild ROP)

Six studies (Table 4.5) demonstrated that VLBW infants are also at increased risk for non-retinal ophthalmic diseases. Cortical visual impairment is visual impairment due to CNS damage to the optic radiation, striate cortex, and peristriate cortex (Hoyt and Good, 2001). Causes of cortical visual impairment in VLBW infants include hypoxic-ischemic-hemorrhagic and /or inflammatory injury (antenatal, perinatal, or postnatal) which may be manifested in the neonatal period as periventricular leukomalacia (echodense, echolucent, cystic), ventriculomegaly, intracranial hemorrhage, and posthemorrhagic hydrocephalus.

Table 4.5. Evidence that VLBW infants with CNS abnormality have visual disability (with no or mild ROP)

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applicability	Quality
Lefebvre 1998 98387703	121	Mean BW: 961±179g (585-1450	Neurobiologic risk score	Blindness	↑	! !	A
Cioni 2000 10685987	29	BW: ND GA: 31(24-36)	PVL	Multiple visual function Abnormalities.	↑ (50 %)	! !	B
Wilkinson 1996 97087405	10	Mean BW: 114 (range 700-1725) g	PVL	Visual impairment Blindness	↑	! ! !	B
Pennefather 1999 20002011	558	GA: < 32	ROP severity GA in Preterm infants	Visual impairment Cicatricial ROP Strabismus	↑	! ! !	B
Foreman 1997 97271716	16	BW: 1413 GA: 29	Prematurity/ LBW	Visual-motor Visual – perceptual skill	⇔	!	B

Lefebvre, Gregoire, Dubois, et al. (1998) studied all infants less than 28 weeks gestational age who were born between 1987 and 1992 at Hopital Sainte-Justine and had three timed-cranial

ultrasounds. They demonstrated that a Neurobiologic Risk Score, which was based on pulmonary, neurologic (seizures, IVH, PVL), infection, and hypoglycemia variables obtained during the NICU hospitalization, was significantly correlated with neurodevelopmental quotients, cerebral palsy, and other neurosensory disabilities, including visual-motor (eye-hand) coordination, i.e. the higher the score the worse the outcome

Neuroimaging of very low birth weight infants via cranial ultrasonography (US), cranial tomography (CT), and magnetic resonance imaging (MRI) techniques has provided strong evidence that central nervous system injury, especially periventricular leukomalacia, is associated with visual disability and other neurodevelopmental abnormalities, including motor and perceptual abnormalities. Visual disability is associated with abnormal MRI imaging in the postchiasmatic visual pathway, particularly the optic radiation and visual cortex. The concomitant occurrence of visual impairment with neurodevelopmental disability in premature infants is well documented and not surprising. Cioni, Bertuccelli, Boldrini, et al. (2000) showed that the degree of cerebral visual impairment (number of abnormal visual function tests) at 1 year of age was strongly associated with the degree of neurodevelopmental impairment at 1 year of age and with the extent of MRI evidence of cerebral white matter damage at full-term age. The degree of visual impairment was, in fact, the strongest independent determinant of neurodevelopmental scores in children born prematurely who had PVL and abnormal neurological examination at full-term equivalent. The degree of visual impairment at 1 year of age was also significantly associated with general developmental quotient at 3 years of age. Twenty-three of 29 (79%) children, who were born premature, developed PVL, and had abnormal neurological examination at full-term equivalent, had at least one abnormality of visual function at 1 year of age, and more than 50% had multiple abnormalities in visual function. Abnormal visual function was manifested in multiple ophthalmic outcomes, including abnormal visual acuity, ocular motility, and visual evoked potentials, as well as presence of strabismus and visual field deficits (Cioni, Bertuccelli, Boldrini, et al., 2000). This study illustrates the importance of assessing various aspects of visual function as well as the importance of a comprehensive neurodevelopmental assessment of children with a history of cerebral white matter damage.

Whitaker, Feldman, Van Rossem, et al. (1996) conducted a 6-year follow-up, population-based study in Central New Jersey of low birth weight infants (LBW = 501-2000 g, born 1984-1987) that examined the independent relationship of cranial ultrasound abnormalities to cognitive outcomes at school age. This study not only confirmed that cerebral white matter damage, defined as periventricular leukomalacia (PVL) and/or ventricular enlargement (VE), is strongly associated with mental retardation and cerebral palsy, but that PVL/VE had a significant, independent effect on three measures of visual perceptual organization (abstract visual reasoning, visual-motor integration, visual perceptual skills). In fact, among LBW infants with normal intelligence quotient (IQ), those with PVL/VE performed significantly worse specifically on visual perceptual organization compared to children who had had no evidence of PVL/VE.

Wilkinson, Bear, Smith, et al. (1996) evaluated the neurological outcome of a cohort of surviving premature infants (n=10) born weighing <1500 grams during 1989-1990 who subsequently developed severe cystic periventricular leukomalacia. The 10 infants were evaluated at a mean corrected age of 27.3 months (range 13-50 months). All 10 infants (100%) with severe PVL had global developmental delay, quadriparesis, and evidence of visual impairment.

Pennefather and Tin (2000) demonstrated that the ophthalmic outcome of VLBW infants may be affected by the presence of brain injury, such as white matter damage, in conjunction with or independent of ROP. Children with cerebral palsy (CP), who were <32 weeks gestation at birth and examined at 2 years of age, had a higher incidence of ocular abnormalities compared to preterm infants without cerebral palsy. Two-thirds (66.7%) of former premature infants with CP had significant ocular abnormality on examination at 2 years of age in contrast to only 20% of former preterm infants without CP. The following specific visual outcomes were documented in former preterm infants with CP vs. former preterm infants without CP (respectively): severe visual impairment (sufficient to cause nystagmus) was found in 16.7% of former preterm infants with CP vs. 0.6% in former preterm infants without CP: cicatricial ROP was present in 14.8% with CP vs. 1.6% without CP ($p<0.0001$): cortical visual impairment was found in 11.1% with CP vs. 0.2% without CP ($p<0.0001$): concomitant strabismus was present in 51.9% with CP vs. 8.4% without CP ($p<0.0001$).

Foreman, Fielder, Minshell, et al. (1997) evaluated visual-perceptual, attentional, and visual-motor skills in a highly-select group of school-age children, who were born at 27-32 weeks gestation and performed normally on all standard pediatric screening tests. This preterm cohort was compared to healthy children who were born at full term. The healthy, former preterm infants performed poorly on two measures of visual-motor skills at school age, but well on most tests of visual perception. This study is important because it illustrates that even in healthy preterm children with no detectable neurodevelopmental problems on screening examinations, may in fact have visual-motor disabilities when these functions are specifically tested.

Evidence That VLBW (i.e. Prematurity) and/or ROP and/or CNS Injury Are Positively Associated With Refractive Error (Myopia) And Ocular Motility (Strabismus)

Myopia in Premature Infants

There is long-standing evidence that the risk and degree of myopia increases with the degree of prematurity, degree of ROP severity, and with central nervous system injury (Algawi, Goggin, and O'Keefe, 1994; Connolly, McNamara, Sharma, et al., 1998; Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1994; Emsley, Wardle, Sims, et al., 1998; Ling, Fleck, Wright, et al., 1995; O'Connor, Stephenson, Johnson, et al., 2002; Page, Schneeweiss, Whyte, et al., 1993; Repka, Summers, Palmer, et al., 1998; Shalev, Farr, and Repka, 2001) (CRYO ROP 3.5 year outcome). Myopia is the most common ophthalmic sequelae of premature infants and requires optical correction. (Table 4.6)

Table 4.6. VLBW and/or ROP and/or CNS injury are positively associated with refractive error (myopia) and ocular motility (strabismus).

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	Outcome	Associ-ation	Applicability	Quality

Author, Year	N	Mean BW, g; GA, week Baseline	Predictors	Outcome	Associ-ation	Applicability	Quality
O'Connor, 2002 21635822	505	BW : 1400 GA: 31	BW ROP	Visual impairment Blindness	⬆	❗❗❗	A
Cryo-ROP 1990 91024693	291	BW: 800 GA: 26.	Threshold Retinopathy Of Prematurity At 5.5-year & 10-year follow-up: Cryotherapy vs. No Cryotherapy	Visual impairment Blindness	⬆	❗❗	A
Cryo-ROP 1993 93191597	291	BW: 800 GA: 26.	Threshold Retinopathy of Prematurity At 5.5-year & 10-year follow-up: Cryotherapy vs. No Cryotherapy	Visual impairment Blindness	⬆	❗❗	A
Page 1993 94051493	190	GA: 27 BW: 942	ROP severity	Myopia severity Odds of myopia	⬆	❗❗	B

Page, Schneeweiss, Whyte, et al. (1993) found that 16% incidence of myopia at 12 months (4.5% had severe myopia (>4.0 diopters) in a cohort of children born <1250 grams (18/110). The authors noted that the greater the degree of prematurity, the greater the incidence of myopia at 12 months corrected age. Children with birth weight <751 grams were 3.2 times more likely than 750-1000 grams to develop myopia in first year. Children with birth weight <751 grams were 10 times more likely than children with birth weight 1000-1250 gm to develop myopia in first year. Furthermore, the likelihood of myopia at 12 months age doubled with each increment of ROP stage. As a point of comparison, Page et al reported that approximately 10% of the general population develop myopia during childhood. Furthermore, the severity of myopia may progress over time. More than 80% of the 50 children evaluated at 24 months age, demonstrated deteriorating vision as demonstrated by the fact that myopia increased from 16% to 38% (4.5% to 24% with severe myopia) and strabismus increased. Other adverse ophthalmic outcomes, such as astigmatism and anisometropia, were highly correlated with severe myopia. All children who had had Grade III or IV intraventricular hemorrhage developed esotropia. Among premature infants with birth weight <1251 grams, 24% to 57% of infants with ROP may have myopia at 24 months age. There were higher rates of myopia with increasing severity of acute ROP (2.9% No

ROP; 40% for more severe ROP). This study illustrates the significant and independent contributions of prematurity, ROP, and central nervous system injury in the development of visual disability in terms of myopia and strabismus.

O'Connor, Stephenson, Johnson, et al. (2002) demonstrated that the smaller ocular dimensions, due to disrupted and reduced ocular growth in children born prematurely who had no or mild ROP, contributed to myopia in premature infants.

Among children with threshold ROP in the CRYO ROP randomized trial, myopia was high in both threshold ROP groups regardless of treatment. As reported in both the 1-year and 3.5-year follow-up studies, more treated eyes than control eyes could be refracted (due to media opacification and disruption in control eyes) (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1990; Cryotherapy for Retinopathy of Prematurity Cooperative Group 1993).

Abnormal Visual Function Due To Fixation Instability (Nystagmus And Strabismus)

There is a strong positive association between the occurrence of strabismus and the degree of prematurity, the severity of ROP, abnormal cranial ultrasounds and neurodevelopmental abnormality, especially CP (Page, Schneeweiss, Whyte, et al., 1993; Pennefather, Clarke, Strong, et al., 1999; Pennefather and Tin, 2000) (Table 4.7). The presence of strabismus and nystagmus implies a central nervous system component or insult, which may or may not be independent of ROP. The ocular misalignments may result from CNS injury and/or as a direct result of retinal disease (e.g. ROP) and its treatment. The reported incidence of strabismus ranges from 3% in premature infants with no ROP to 34% in patients with regressed ROP.

Table 4.7. Abnormal visual function due to fixation instability (nystagmus and strabismus) in VLBW infants

Author, Year	N	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Association	Applicability	Quality
Page 1993 94051493	190	GA: 27 (23-32) BW: 942 (400-1250)	ROP severity	Myopia severity Odds of Myopia	↑	❗❗	B
Pennefather 1999 20002011 Pennefather 2000 20217908	558	GA: < 32	ROP severity GA	Visual impairment Cicatricial ROP Strabismus CP	↑	❗❗❗	B

Page, Schneeweiss, Whyte, et al. (1993) reported that strabismus occurred in 6% of premature infants <1251 grams with no ROP, and in 38% of infants with Stage 3 ROP by 12

months age. Strabismus continued to increase in frequency through second year (62% of Stage 3 ROP had esotropia, which required surgical correction of esotropia). Among children with Grade III or IV IVH, 100% had strabismus (esotropia).

Pennefather, Clarke, Strong, et al. (1999) evaluated the risk factors for strabismus, diagnosed at 2 years of age, in children born <32 weeks gestation. Strabismus was present in 12.5% of this premature cohort. Strabismus increased with decreasing gestational age and with increasing severity of acute ROP. The increased risk of strabismus was independently associated with cicatricial ROP, refractive error, and poor neurodevelopment and cerebral palsy (particularly impaired motor skills and hand-eye coordination), and family history of strabismus. In Pennefather's cohort, gestational age and regressed acute ROP were not independent risk factors associated with strabismus once the other independent factors noted above were considered.

Evidence That VLBW Plus Bronchopulmonary Dysplasia (BPD) And Systemic Glucocorticosteroid Therapy For Bronchopulmonary Dysplasia Are Associated Visual Disability

Ophthalmic examinations revealed that premature infants with BPD (neonatal chronic lung disease) and no detectable severe neonatal neurological abnormalities and no ROP > Stage 2) (mean GA 27.1 ±1.9 wk; mean BW 984 ± 299 gm) had greater incidence of strabismus and high refractive error compared to premature infants with hyaline membrane disease but no BPD (mean GA 30.5±2.5 wk; mean BW 1492 ± 475 gm) and healthy preterm infants (mean GA 32.4 ±1.6; mean BW 1746±372). Also, recognition acuity (i.e. skills required to perform a recognition-acuity task) was worse in the BPD and HMD groups vs. the healthy preterm group at 36 and 48 corrected months age (significant at 36 months age). Grating acuity and visual field test did not differ among the 3 groups through 4 years age (Harvey, Dobson, and Luna, 1997).

The Victorian Infant Collaborative Study Group (2000) evaluated the association between postnatal corticosteroid therapy and sensorineural outcome in extremely premature infants (ELBW infants <1000 grams or <28 weeks gestation) born in Victoria, Australia 1991-1992. At 5 years of age, 98 survivors treated with postnatal systemic glucocorticosteroids had significantly higher rates of blindness (steroids 5.2% v. no steroids 0.5%) ($p<0.02$), in addition to significantly higher rates of cerebral palsy and lower intelligence quotients. In the Victorian study, extreme prematurity, brain injury, ROP, BPD, and glucocorticoid therapy individually and/or collectively have an impact on visual disability.

Table 4.8. Association between VLBW plus bronchopulmonary dysplasia (BPD) and systemic glucocorticosteroid therapy for bronchopulmonary dysplasia with visual disability

Author/ Year	Eyes Treated (N)	Mean BW, g; GA, week Baseline (Range)	Intervention	Outcomes	Efficacy	Applica-bility	Quality
Victorian Infant Collaborative study Group, 2000 20307288	346	GA : Sample 1: 26 Sample 2: 27 BW : Sample 1: 797 Sample 2: 932	Preterm infants(120): treated with corticosteroids infants not treated with corticosteroids (226)	Blindness	Cortocosteroids group **5.2%** No Cortocosteroids group **0.5%** P<0.02	! !	B

Evidence That VLBW Infants Have Increased Incidence Of Ophthalmic Interventions Due To Visual Disability

Repka, Summers, Palmer, et al. (1998) evaluated the number of ophthalmic interventions due to ophthalmic disability required by children in the CRYO ROP trial through 5.5 years of age. He compared children with threshold ROP randomized in the CRYO ROP trial to children with varying degrees of ROP, of which 69 of 1208 had untreated threshold ROP. The frequency of ophthalmic surgical and medical therapies was higher in infants with threshold ROP who had cryotherapy (0.9 interventions per child) compared to children with other ROP and no cryotherapy (0.4 interventions per child). They demonstrated that children who had ROP are at even greater risk for long-term ophthalmic sequelae in terms of anatomic and functional problems, and thus need close ophthalmic evaluation and interventions. The most common treatments conducted on the randomized threshold ROP children were vitrectomy (26%), lensectomy (18%), amblyopia therapy (20%), strabismus surgery (10%), and infrequent cataract surgery (2%). In contrast, for the “other ROP/ no cryotherapy” group, the most common treatments performed were strabismus surgery (6%), and amblyopia therapy (7%). Late retinal detachments and glaucoma are additional potential late sequelae in children who had ROP as premature infants. Amblyopia therapy increased with increasing severity of ROP (3% in children with no ROP; 26% % in children with severe ROP). This study illustrates that the frequency of procedures to correct visual disability increases with severity of ROP. Long-term costs of both extreme prematurity and ROP include not only the initial ablative therapy for ROP and individual/family/societal loss due to vision impairment and blindness, but ongoing costs of caring for eye problems in children who were VLBW. Expenses include doctor’s office visits, time lost from work, eyeglasses, surgery, and special education.

Evidence That VLBW With Or Without Other Conditions Is Associated With Pulmonary Disability (Evidence Table 9)

This portion of the narrative examines the evidence that VLBW infants with or without other conditions have increased long-term, pulmonary disability. This narrative is organized as follows:

1. Bronchopulmonary dysplasia: definition, background, and significance
2. Pulmonary outcome measures
3. Evidence that VLBW is associated with pulmonary disability by duration of pulmonary follow-up
4. Evidence that VLBW with BPD is associated with respiratory symptoms, use of respiratory medications, abnormal pulmonary function and exercise intolerance
5. Evidence that VLBW with BPD is associated with airway hyperreactivity, asthma
6. Evidence that VLBW with BPD is associated with rehospitalization
7. Evidence that VLBW infants with BPD is associated with long-term cognitive and /or motor disability

Bronchopulmonary Dysplasia (BPD): Definition, Background, And Significance

Bronchopulmonary dysplasia (BPD) is a chronic disease of the lung that effects almost exclusively premature infants. It is the most common chronic lung condition in childhood with the exception of asthma. The development of BPD occurs in infants who have immature lungs and/or require prolonged mechanical ventilation. BPD effects the entire tracheobronchial-pulmonary tree. BPD is thought to be the consequence of injury to an immature lung and subsequent aberrant healing and development that follow injury. Advances in the care of VLBW infants over the last ten years have included many measures that have reduced the lethality and severity of BPD. Such advances include: widespread acceptance of antenatal glucocorticoid therapy, surfactant replacement therapy, improved techniques for mechanical ventilation, improved understanding of the role of mechanical ventilation in injuring the lung, improved nutritional support, and reduction in infectious complications of NICU care. Together these measures have reduced lung injury and subsequent BPD in more mature premature infants, i.e., gestational age greater than 30 weeks and birth weight greater than 1200 grams. However, a new population of infants born at less than 28 weeks gestational age and birth weight less than 1,000 grams is at greatest risk for BPD due to improved survival of extremely premature infants over the last ten to fifteen years. The advances in care have not been sufficient to prevent the development of BPD in this new population. Thus there has been a shift in the population at risk for BPD.

The reported incidences of BPD also depend upon the definitions of BPD, neonatal care practices, and the characteristics of the study population. There is no consensus on a single definition of BPD. The most commonly used definitions of BPD are based on need for supplemental oxygen at 28 days age or at 36 weeks postmenstrual age (PMA), with or without radiologic changes consistent with chronic lung injury at each of these time points. The BPD

definitions by Shennan, Dunn, Ohlsson, et al. (1988) and by the recent NICHD/NHLBI BPD Workshop in June 2000 (Ehrenkranz and Walsh-Sukys, 2001) have diagnostic and prognostic importance. Shennan and associates' definition requires specific abnormal physical findings, a characteristic chest radiograph and the requirement for supplemental oxygen, all at 36 weeks PMA. Children who meet this definition of BPD have a high chance of respiratory symptoms throughout the first year of life, rehospitalization for respiratory- related illnesses during the first year of life and abnormal formal pulmonary function studies at two years of age. The BPD definition from the recent NICHD/ NHLBI workshop is a severity-based definition of BPD. It is likely that this severity based definition for infants with gestational age less than 32 weeks and birth weight below 1,000 grams will be predictive of both pulmonary and neurodevelopmental outcome.

The incidence and severity of BPD are inversely related to gestational age and birth weight. Data from the Vermont-Oxford Neonatal Network for 2000 (Vermont Oxford Neonatal Network Annual Report, 2000) are shown in Table 1 and provide a recent example of the clear relationship between birth weight and occurrence of BPD.

Table 5.1. Percent of infants with BPD* in Relation to Birth Weight in the Vermont Oxford Neonatal Network

Birth weight (g)	Percent with BPD
501-600	74%
601-700	62%
701-800	51%
801-900	44%
901-1000	32%
1001-1100	26%
1101-1200	18%
1201-1300	14%
1301-1400	11%
1401-1500	8%

*BPD was defined as a requirement for supplemental oxygen at 36 weeks PCA. Data are from 352 NICUs reporting on 29,177 live births with birth weights between 501 and 1500 grams.

Pulmonary Outcome Measures

Among the studies examined within this review, long-term pulmonary disability is assessed in numerous ways including formal measurement of pulmonary function and /or airway hyper-reactivity and clinical evidence of pulmonary impairment. Outcome measures for clinical evidence of pulmonary disability include presence of respiratory symptoms: recurrent wheezing, asthma, cough, recurrent bronchitis, pneumonia or other respiratory infections, exercise intolerance, chronic supplemental oxygen requirement, need for respiratory medications, and

recurrent hospitalization primarily for respiratory reasons. All of these signs, symptoms, and problems indicate an underlying chronic lung disease.

Evidence That VLBW With BPD Is Associated With Long-Term Pulmonary Morbidity And Disability By Duration Of Follow-Up

Due to the fact the many of the studies reviewed contain multiple pulmonary outcomes measures and the fact that the clinical relevance of the findings is influenced by the timing of the follow-up evaluation, the evidence is initially presented according to duration of follow-up.

1- 2 year follow-up

Nine randomized controlled trials and nonrandomized comparison studies provided evidence that VLBW with BPD is associated pulmonary morbidity and disability at 1-2 year follow-up: (Table 5.2a)

Table 5.2a. VLBW with BPD is associated with long-term pulmonary morbidity and disability by 1-2 year of follow-up.

Author, Year	N (with control)	Mean BW,g; GA,week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Kraybill 1995 95264242	118	Bw: Sample 1: 1022 Sample2: 1028	VLBW: 700-1350g	Need for O2 via nasal canula Need for O2 via CPAP CLD	↑	❗❗❗	A
Gerdes J 1995 95264241	508	BW 700-1100g	Surfactant use	Asthma CLD	↑	❗❗❗	A (RCT)
Chye 1995 95314864	158	BW:1000-1500g GA:26-33	Bronchopulmonary dysplasia	Growth Re-hospitalization	↑	❗❗	B
Kurkinen-Raty 1998 98387235	78	BW:1138 GA:28	Preterm rupture and no rupture	Chronic lung disease	↑	❗❗	B
Kurkinen-Raty 2000 20284814	103	BW: 1294 GA:30	Cesarean delivered singleton	Chronic lung disease	↑	❗❗	B

Author, Year	N (with control)	Mean BW,g; GA,week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Gregoire 1998 98232532	217	BW: 997 GA: 27	BPD CLD	Respiratory readmissions PICU admissions	⬆	❗❗	B
Cheung 1998 99059896	10	BW:860 GA: 25	BW<1500g	Chronic lung disease	⬆	❗	B
Als 1994 94358983	20	BW < 1250 g GA 24-30 wk	Participation In individualized developmental care	Pulmonary: BPD severity	⇔	❗❗	B
Iles 1997 97280982	33	BW:900g (589-1891g) GA:27 wk(24-31)	BPD	Pulmonary arterial pressure	⇔	❗❗	C

Kraybill, Bose, Corbet, et al. (1995) reported results of long-term outcome at 2 years adjusted age of 118 VLBW infants (birth weights 700-1350 grams) who were enrolled in a double-blind, randomized, placebo-controlled, single-dose surfactant trial. Respiratory outcomes assessed at 2 years adjusted age, which were not different between the two groups, revealed that 14% of the entire cohort were hospitalized during the second year, 14% still received regular bronchodilator therapy, 2 of 118 children had tracheostomies. These studies illustrate the increased long-term pulmonary morbidity in terms of need for regular respiratory medications and re-hospitalizations.

Gerdes, Gerdes, Beaumont, et al. (1995) reported the pulmonary outcome at 1-year adjusted age among other neonatal outcomes of premature infants (birth weight 700-1100 grams, born 1989-1990) who had been enrolled in a randomized, double-blind, parallel comparison of a single vs. triple-dose of surfactant therapy for respiratory distress syndrome. At 1-year follow-up evaluation, 16% had physical evidence of chronic lung disease, 3% were on respiratory support, 3% were on respiratory medications, 6% had diagnosis of asthma, and 43% had been re-hospitalized during the first year.

Chye and Gray (1995) compared the need for rehospitalization within 12 months of age between premature infants with BPD (GA 26-33 weeks) and BW-matched controls without BPD (GA 26-32 weeks). Re-hospitalization was high in both preterm groups (with and without BPD). However, there was a significant increase in any rehospitalization in first year of life in preterm infants with BPD (58%) vs. preterm infants with no BPD (35%) (RR 1.7; 95% CI 1.2,2.4). There was a significant 2-fold increase in rehospitalization for respiratory illness in the first year of life in preterm infants with BPD (39%) vs. preterm infants with no BPD (20%) (RR 1.9, 95% CI 1.1, 3.2). BPD infants with home oxygen therapy (N=20) had approximately three-fold increased re-hospitalization for failure to thrive (30%) compared to control preterm infants (9%) (RR=3.3, 95% CI 1.2,8.9). Growth failure was common in both preterm groups (i.e. in infants with no BPD (1%) and with BPD (14%).

Kurkinen-Raty, Koivisto, and Jouppila (1998) studied the long-term pulmonary outcome at 1-year of age in 2 groups of premature infants (1990-1996): One group experienced early premature rupture of membranes (PROM) between 17 and 30 weeks gestation; the second group's mothers delivered spontaneously without PROM. Later pulmonary complications included longer days of rehospitalization (PROM 5 vs. Spontaneous 1, P=0.01), and more symptomatic chronic lung disease at 1 year of age in PROM group than Spontaneous group (22% vs. 9%, OR 2.4, 95% CI 0.9, 6.5). This study illustrates that early PROM has long-term pulmonary consequences extending through 1-year of age.

Kurkinen-Raty, Koivisto, and Jouppila (2000) studied the incidence of chronic lung disease at 1 year of age in premature infants delivered between 24 and 33 weeks gestational age for either maternal or fetal indications and compared these to premature infants of similar gestational age born to mothers who had spontaneous preterm delivery. The diagnosis of chronic lung disease (CLD) at 1 year of age was made if infants required oxygen, continuous bronchodilator therapy or steroid therapy because of respiratory signs and symptoms. Among children born 'preterm delivered for maternal or fetal indications', 15% had CLD at 1 year compared to 3% of infants born 'preterm after spontaneous delivery' (RR 4.6, 95% CI 1.4, 1.6). This study demonstrated that premature infants who were born due to indicated maternal/fetal reasons vs. spontaneous preterm delivered infants had worse pulmonary outcome a 1 year age.

Iles and Edmunds (1997) studied 33 infants who were born between 24-31 weeks gestation (median BW, range: 900, 589-1891) and who had BPD as defined by age 28 days and receiving supplemental oxygen (all 33) or at 36 weeks gestational age (30/33). They tested the ability of measurements of mean arterial saturation ($MSaO_2$), arterial blood gases and pulmonary function to predict pulmonary outcome at 1 year of age when serial testing was performed every 3 months. A $MSaO_2$ of less than 90% in room air at 1 year of age was predicted between 35-40 weeks gestational age by an (A-a) D_{O2} greater than 29 kpa (sensitivity 0.85 and specificity 0.88) and a $PaCO_2$ greater than 7 kpa (sensitivity 0.88, specificity 0.78). The prediction was strengthened by combining the (A-a) D_{O2} > 29 kpa and PaCO2 > 7 kpa (sensitivity and specificity 1). This study demonstrates that an early laboratory abnormality is predictive of pulmonary dysfunction at one year of age.

More severe BPD (i.e., BPD at 36 wk equivalent gestational age) is associated with greater pulmonary impairment and increased re-hospitalization. Gregoire, Lefebvre, and Glorieux (1998) prospectively compared health, respiratory, and developmental outcomes at 18-months corrected age of three groups of premature infants (gestational age 24-28 weeks, born 1987-1992) according to duration of need for supplemental oxygen therapy. The reference group required oxygen for less than 28 days age; the BPD-1 group required O2 ≥28 days age but < 36 weeks corrected gestational age (CGA) and the BPD-2 group consisted of infants requiring oxygen ≥36 weeks CGA. The outcome measures of interest were persistent respiratory problems (asthma, tracheostomy, home oxygen therapy), hospitalizations, surgery, growth, and neurodevelopmental impairment. The BPD-2 group had more persistent respiratory problems (reference=4% vs. BPD-1= 4% vs. BPD-2=11%). Overall, 48% of the infants required re-hospitalization. The BPD-2 group required more days of hospitalization, more hospitalizations for respiratory problems (reference = 2 vs. BPD-1 = 2 vs. BPD-2 = 6.3), and more hernia repairs compared to the reference or BPD-1 groups. The results of this study are similar to that of Shennan, Dunn, Ohlsson, et al. (1988) which found that premature infants who are still oxygen-dependent at 36 weeks gestational age equivalent, have more abnormal pulmonary outcomes at 1 year. The BPD-

2 group had more neurodevelopmental disabilities at 18 months age. The differences remained even after adjusting for IVH or PVL (Gregoire, Lefebvre, and Glorieux, 1998).

Cheung, Peliowski, and Robertson (1998) reported on a highly-selected group of VLBW survivors (mean gestation = 25 weeks, range 24-30) born during 1993-1997. These infants experienced particularly severe respiratory disease with prolonged hypoxemia and required inhaled nitric oxide rescue therapy. These VLBW survivors (n=24) had an unusually high incidence of BPD (80%), of whom all had supplemental oxygen through 10 months corrected age. Follow-up at a mean age of 22 months revealed a 40% incidence of recurrent wheezing, 10% required bronchodilator therapy, and 70% poor neurodevelopmental outcome.

3 year follow-up

One cross-sectional study provided evidence that VLBW with BPD is associated pulmonary and disability at 3-year follow-up: (Table 5.2b)

Table 5.2b. VLBW with BPD is associated with long-term pulmonary disability by 3 years of follow-up.

Author, Year	Sample (with control)	Mean BW,g; GA,week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Brooks 2001 211531225	8071*	ND	BW<1500g BW 1500-2499g	Asthma	↑ ↑	! ! !	B

Brooks, Byrd, Weitzman, et al. (2001) studied over 8,000 infants at 3 years of age to estimate the independent contribution of birth weight to asthma prevalence among children <4 years age. They conducted a cross-sectional analysis using the 1988 National Maternal-Infant Health Survey and 1991 Longitudinal Follow-up Survey. They compared the diagnosis of asthma (based on parental report of physician-diagnosis of asthma) among three different birth weight (BW) groups: The reference group with birth weight (BW) ≥ 2500 gm; LBW group, BW≥1500-2499gm; and VLBW group, BW < 1500 grams. Asthma was diagnosed in 6.7% of children < 4 years age in the reference group; in 10.9% of the LBW group (OR=1.4, 95% CI 1.1-1.8); and in 21.9% of the VLBW group (OR=2.9, 95% CI 2.3-3.6). More than half of the increased risk for asthma in VLBW children was explained by birth weight alone (attributable risk, 68%). This study found a strong, independent association between low birth weight and asthma, and that the effect of birth weight was most pronounced in the lowest birth weight category. The authors estimated that 4000 excess asthma cases were attributable to birth weight < 2500 grams in this 1988 national birth cohort. The incidence of asthma in children with history of BPD was 20.4% (OR 3.4, 95% CI 2.4,4.8). The odds ratio of a physician diagnosis of asthma in VLBW/African-American children was 2.5 (95% CI 2.0, 3.3). The odds ratio of a physician diagnosis of asthma in VLBW/white children was 3.1 (95% CI 2.2,4.3). These data support findings in other studies not included in this review that link an independent association between low birth weight and

asthma. The authors emphasize the importance of identifying specific risk factors that contribute to the burden of asthma in young children since children <4 years of age account for 50% of total direct asthma costs (Pelkonen, Hakulinen, and Turpeinen, 1997).

6-12 years

Two nonrandomized comparison studies provided evidence that VLBW with BPD is associated pulmonary disability at 6-12 year follow-up: (Table 5.2c)

Table 5.2c. VLBW with BPD is associated with long-term pulmonary disability by 6-12 year of follow-up.

Author, Year	Sample (with control)	Mean BW,g; GA,week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Gross 1998 98375435	96	BW:1173g GA:28 wk	Preterm	Pulmonary function Respiratory symptoms Asthma Respiratory Meds Rehospitalization	Worse ⇧ ⇧ ⇧ ⇧	❗❗	B
Santuz 1995 96023205	12	BW: 1400 ± 335 (890-1900) GA:30 wk: (27-32)	BPD	Pulmonary function	⇧	❗❗❗	B

Gross, Iannuzzi, Kveselis, et al. (1998) compared long-term pulmonary outcomes at 7 years of age of a regional cohort of children born <32 weeks' gestation (1985-1986) to a matched term group. The preterm cohort was divided in to those who in the neonatal period had no BPD (n=53) and those who had BPD (n=43). The two premature groups were compared to each other and to the children born full-term (38-42 weeks) (controls) (n=108). Pulmonary function studies revealed that the BPD group had significantly greater airway obstruction with reduced forced expiratory flow indices compared to either the preterm no BPD group or the control term group (all P<0.0001). Lung function in preterm group with no BPD was similar to control term group. Pulmonary function tests revealed significantly worse pulmonary function in preterm infants with BPD at rest and after exercise compared to either preterm infants without BPD or control term group. With respect to the exercise results, there was no statistically significant difference in baseline heart rate, oxygen consumption, respiratory quotient, or endurance among groups. Asthma was observed twice as often in the BPD group compared to the no BPD group or control term infants (BPD, 47% vs. No BPD 25% vs. Control 21%, P<0.001). With respect to use of

respiratory medications, bronchodilator therapy was used more commonly for asthma in the BPD group (16%) compared to No BPD (6%) or term control group (3%) (P<0.01). Both preterm groups had more respiratory symptoms than the term group (wheezing in BPD, 30% vs. No BPD, 24% vs. Term, 7%, P<0.005; chronic cough: BPD, 12% vs. No BPD, 13% vs. Term, 0%, P< 0.01). Importantly, respiratory symptoms were significantly more common in both of the premature groups in comparison to term controls at 7 years of age. The former BPD group were twice as likely to be rehospitalized during the first 2 years of life compared to former preterm children with no BPD or term control group (BPD 53% vs. No BPD 26%, P<0.005). Both preterm groups were hospitalized more than the term group (3%, P<0.001). Collectively, these data demonstrate that former preterm children with no BPD had similar pulmonary function to term controls and that chronic respiratory disability related to BPD and VLBW status may continue to cause disability into school age.

Santuz, Baraldi, Zaramella, et al. (1995) assessed long-term pulmonary function at rest and during exercise in 12 children who had BPD during the neonatal period (gestational age 30 ± 2 wk) at 6-12 years of age. They compared the former BPD patients to 16-year-old healthy children born at term. The authors demonstrated that asymptomatic school-age survivors of BPD showed clinically significant evidence of disturbances in ventilatory response to exercise and reduced aerobic capacity compared with healthy children, even if pulmonary function at rest was only slightly impaired.

12-16 years follow-up

Two nonrandomized comparison studies provided evidence that VLBW with BPD is associated pulmonary disability at 12-16 year follow-up: (Table 5.2d)

Table 5.2d. VLBW with BPD is associated with long-term pulmonary disability by 12-16 year of follow-up.

Author, Year	N (with control)	Mean BW,g; GA,week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Saigal 2001 21376729	154	BW: 501-1000	ELBW Infants	Pulmonary Problem (asthma or recurrent bronchitis/ pneumonia)	⬆	❗❗	B
Doyle 2001 21064379	180	BW:1079g GA: 27 wk	BW<1501 g	Respiratory health and lung function at 14 years age	⇔	❗❗	B

Saigal, Stoskopf, Streiner, et al. (2001) followed a regional cohort of ELBW survivors (birth weight 501-1000 grams, born in 1977-1982 in Canada) well into adolescence (12-16 years). With respect to pulmonary problems at the time of assessment, the proportion of adolescents who had asthma or recurrent bronchitis/pneumonia was 22% in former ELBW infants compared to 12% of full-term controls. With respect to past health problems and asthma, the proportion of

children who had had a history of asthma or recurrent bronchitis/ pneumonia was 39% of the ELBW group compared to 17% of the controls. Although this excellent long-term study into adolescent years describes the outcomes of ELBW born during an earlier era of neonatal care (1977-1982), these data are still important in that they demonstrate that clinically relevant respiratory illnesses of ELBW infants may persist even through adolescence, and that they occur more frequently in ELBW infants compared to full-term controls.

Doyle, Cheung, Ford, et al. (2001) conducted a prospective cohort study in Australia to compare respiratory health and lung function in adolescent children who were born weighing <1501 grams (1/ 77 to 3/ 82) with those of adolescents of normal birth weight. The preterm babies were divided into two groups: ELBW infants with BW 500-999 grams (n=78); VLBW infants with BW 1000-1500 grams (n=102). The controls were term infants with BW greater than 2499g (n=42). BPD was diagnosed in 23% of the preterm group in the neonatal period. Readmission to the hospital due to respiratory illness was similar and high for both preterm groups. The incidence of asthma was similar in all three groups (ELBW, 15%; VLBW, 21%; and NBW, 21%). The respiratory health at 14 years of age was comparable between former preterm infants compared to full term controls in terms of asthma and most of the lung function tests. Preterm children who had BPD had significantly lower flow values. This study provides optimistic information about the long-term pulmonary outcome in former preterm children who had no BPD.

Pulmonary Function Testing and Exercise Tolerance

With respect to monitoring long-term pulmonary outcomes in premature infants with BPD, several publications indicate that formal pulmonary function testing is abnormal in VLBW infants who develop BPD: (Baraldi, Filippone, Trevisanuto, et al., 1997; Gerhardt, Hehre, Feller, et al., 1987; Gross, Iannuzzi, Kveselis, et al., 1998) . Specific abnormalities reflect restrictive lung disease: reduction in forced expiratory flow volumes, reduction in forced expiratory flow rates, elevation in residual volumes and reduced compliance (Baraldi, Filippone, Trevisanuto, et al., 1997; Gerhardt, Hehre, Feller, et al., 1987; Gross, Iannuzzi, Kveselis, et al., 1998) . Other studies, not included in this review, have shown that these abnormalities improve gradually over the first two years of life with the greatest improvement seen in the first year (Baraldi, Filippone, Trevisanuto, et al., 1997; Gerhardt, Hehre, Feller, et al., 1987). Compliance and flow measurements are usually in the normal range by the age of two years (Baraldi, Filippone, Trevisanuto, et al., 1997; Gerhardt, Hehre, Feller, et al., 1987). However, evidence of residual lung dysfunction has been consistently found, especially in VLBW infants with severe BPD. Such dysfunction has included increased airway responsiveness to methacholine challenge, residual mild obstruction of flow and elevated residual volumes (Bader, Ramos, Lew, et al., 1987; Blayney, Kerem, Whyte, et al., 1991).

Other reported measures used to assess the association(s) between VLBW, BPD, and subsequent pulmonary disability include the following: 1) exercise testing in children who have reached an age that allows cooperation; 2) presence of childhood wheezing, asthma; 3) parental questionnaire for respiratory symptoms; 4) rehospitalization (either all readmissions or those related specifically to respiratory illness); 5) echocardiographic determination of right ventricular dysfunction and/ or pulmonary vascular disease. (Bader, Ramos, Lew, et al., 1987; Blayney, Kerem, Whyte, et al., 1991; Brooks, Byrd, Weitzman, et al., 2001; Chye and Gray, 1995; Gross,

Iannuzzi, Kveselis, et al., 1998; Jacob, Lands, Coates, et al., 1997; Mitchell and Teague, 1998; Santuz, Baraldi, Zaramella, et al., 1995; Subhedar and Shaw, 2000).

There is evidence that measures of lung dysfunction in older children who have had BPD are associated with some degree of impairment in the area of aerobic exercise (Bader, Ramos, Lew, et al., 1987; Jacob, Lands, Coates, et al., 1997; Mitchell and Teague, 1998; Santuz, Baraldi, Zaramella, et al., 1995). At ages of six years and greater, arterial desaturation during exercise (Jacob, Lands, Coates, et al., 1997; Santuz, Baraldi, Zaramella, et al., 1995), carbon dioxide retention during exercise (Bader, Ramos, Lew, et al., 1987), and an increased occurrence of post exercise restriction of airflow which is reversible by bronchodilators has been found (Bader, Ramos, Lew, et al., 1987). However, as judged by the literature within this review, the deficits in exercise are subtle and do not interfere with daily activities.

The most frequently described consequences of pulmonary disability in the first two years of life are the need for respiratory medications and re-admission to the hospital. The evidence for this is noted below.

Evidence That VLBW Is Associated With Asthma Or Hyper-reactive Airway Disease

Three studies support associations between both VLBW and asthma and between VLBW with BPD and asthma. (Table 5.3).

Table 5.3. Association of VLBW/Prematurity with asthma or hyper-reactive airway disease

Author, Year	Sample (with control)	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applicability	Quality
Brooks 2001 21153125	8071*	ND	BW<1500g	Asthma	⬆	❗❗❗	B
			BW 1500-2499g				
Cheung 1998 99059896	10	BW: 860 GA: 25	BW < 1500 g,	Mosaic trisomy 18 Potter's syndrome	⬆	❗	B
Gross 1998 98375435	96	BW: 1173 g GA: 28 wk	Preterm	Respiratory symptoms	⇧	❗❗	B
				Asthma	⇔		

More than one definition of asthma was used in the literature reviewed. A more restrictive definition was physician-diagnosed asthma (Brooks, Byrd, Weitzman, et al., 2001); an alternate definition was responsiveness to inhaled bronchodilator therapy (Gross, Iannuzzi, Kveselis, et al., 1998). Cheung et al defined asthma as recurrent wheezing in infancy (Cheung, Peliowski, and Robertson, 1998). The principle strength of the studies that address 'VLBW and asthma' as well as 'VLBW with BPD and asthma' is that the follow-up period is generally long, on the order of several years. The following studies support associations between both 'VLBW and

asthma' and 'VLBW with BPD and asthma' (Brooks, Byrd, Weitzman, et al., 2001; Cheung, Peliowski, and Robertson, 1998; Corbet, Long, Schumacher, et al., 1995; Gross, Iannuzzi, Kveselis, et al., 1998).

As noted previously, Brooks, Byrd, Weitzman, et al. (2001) studied over 8,000 infants (VLBW, LBW, and normal BW) at 3 years of age to estimate the independent contribution of birth weight to asthma prevalence among children <4 years age. This study found a strong, independent association between low birth weight and asthma, and that the effect of birth weight was most pronounced in the lowest birth weight category.

Gross, Iannuzzi, Kveselis, et al. (1998) used the definition of asthma as 'responsiveness to inhaled bronchodilators', assessed with pulmonary function tests, as indicating the presence of asthma at the age of 7 years. Infants with a gestational age of 24 to 31weeks (n = 204) had a 47% incidence of asthma if they developed BPD in contrast to a 25% incidence of asthma if BPD did not develop. These figures compare with a 21% incidence of asthma in well, full term infants. Although bronchodilator responsiveness as studied by Gross and associates may not be equivalent to asthma these data at the least demonstrate persistent airway hyper-responsiveness associated with VLBW and with BPD.

Cheung, Peliowski, and Robertson (1998) reported recurrent wheezing, which may represent asthma and at the least represents hyper-reactive airways, in 40% of VLBW survivors. Saigal, Stoskopf, Streiner, et al. (2001) followed a regional cohort with BW less than 1,000 g in Canada through age 12 to 16 years. They found 25% of surviving ELBW infants had asthma in comparison to 14% of controls born at full term.

Several authors (Bader, Ramos, Lew, et al., 1987; Gross, Iannuzzi, Kveselis, et al., 1998; Mitchell and Teague, 1998; Santuz, Baraldi, Zaramella, et al., 1995) have addressed the issue of exercise-induced airflow limitation. Alternative terminology for this phenomenon is exercise-induced asthma or excerise-induced bronchospasm. Although these studies have generally involved relatively small numbers of patients they have the strength of being performed in childhood to early adolescence. These such studies have consistently reported increased exercise-induced airflow limitation in infants with BPD (Bader, Ramos, Lew, et al., 1987; Santuz, Baraldi, Zaramella, et al., 1995).

Evidence That VLBW Infants Have Increased Rehospitalization For Respiratory Illness

Rehospitalization of former VLBW infants is a common event, especially among VLBW infants with BPD. Most hospitalizations are for respiratory conditions or growth failure, sometimes referred to as failure to thrive (Corbet, 1995).

Eight studies provided the evidence that VLBW infants have increased rehospitalization for respiratory illness (Table 5.4).

Table 5.4. Association of VLBW/Prematurity with rehospitalization for respiratory illness: pulmonary outcomes

Author, Year	Sample (with control)	Mean BW, g; GA, week Baseline (Range)	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Corbet A 1995 95264244	1046	BW: 934 GA: 27	Single dose synthetic surfactant at birth (vs air placebo)	Growth Re-hospitalization	⬆	👤👤👤	A
Cheung 1998 99059896	10	BW: 860 GA: 25	BW < 1500 g,	Mosaic trisomy 18 Potter's syndrome	⬆	👤	B
Doyle 2001 21064379	180	BW: 1079 g GA: 27 wk	BW<1501g	Respiratory health and lung function	⇔	👤👤	B
Chye 1995 95314864	158	BW: 1000-1500 g GA: 26-33	Bronchopulmonary dysplasia	Growth Re-hospitalization	⬆	👤👤	B
Gross 1998 98375435	96	BW: 1173 g GA: 28 wk	Preterm	Respiratory symptoms	⇧	👤👤	B
				Asthma	⇔		
Santuz 1995 96023205	12	BW : 1400±335 g (890-1900) GA: 30 wk (27-32)	BPD	Pulmonary hypertension	⇧	👤👤👤	B
Gregoire 1998 98232532	217	BW: 997 GA: 27	BPD CLD	Respiratory readmissions PICU admissions	⇧	👤👤	B

Up = More severe pulmonary conditions associated with Lower birth weight
Applicability: 3 people = well applicability; 1 people = narrow applicability
NHIHS = National Maternal-Infant Health Survey
BPD = Bronchopulmonary dysplasia
CLD = chronic lung disease
* = with control

Re-admission to the hospital for respiratory illness becomes less frequent after two years of age. Thereafter, rehospitalization begins to approximate the rates seen in full term infants. This is approximately the same time that formal pulmonary function measures begin to enter the normal range as judged by the studies that have followed children long enough to be able to provide such data (Cheung, Peliowski, and Robertson, 1998; Chye and Gray, 1995; Corbet, Long,

Schumacher, et al., 1995; Doyle, Cheung, Ford, et al., 2001; Gross, Iannuzzi, Kveselis, et al., 1998).

Chye and Gray (1995) demonstrated that 58% of VLBW infants with BPD required rehospitalization within the first year of life in contrast to 35% of VLBW infants without BPD. In this same report 39% of children with BPD were rehospitalized for respiratory problems as compared with 20% of controls. These differences are significant with RR for overall hospitalization of 1.7 (1.2, 2.4) and RR for hospitalization due to respiratory illness of 1.9 (1.1, 3.2). There was no full term control group, but hospitalization rates for full term infants within the first year of life are generally 3% or less (Gross, Iannuzzi, Kveselis, et al., 1998). Fourteen percent of patients with BPD were hospitalized for reasons related to poor growth, as compared with 1% of VLBW infants without BPD, RR 1.4 (1.7, 82).

Gross, Iannuzzi, Kveselis, et al. (1998) also reported that 53% of patients with VLBW and BPD, as compared with 26% of their VLBW patients without BPD, required rehospitalization ($P < 0.005$). This study did report a control group born at term to have a 3% incidence of hospitalization in the first year of life ($P < 0.001$ versus both groups of VLBW infants). These data demonstrate that rehospitalization in the first two years of life is associated with both BPD with VLBW and VLBW. Although the former association is stronger the latter is significant.

Evidence That VLBW With Or Without Other Conditions Is Associated With Growth Impairment (Evidence Tables 10-12)

VLBW infants are at high risk for poor growth during the first years of life due to acute neonatal illnesses, developmental delays, chronic illnesses (e.g. bronchopulmonary dysplasia, gastroesophageal reflux, short-gut syndrome). Attaining appropriate growth and nutrition in VLBW infants continues to be a challenge during the initial hospitalization and after discharge from the neonatal unit. Long-term studies demonstrated definitive problems with postnatal growth. Understandably, the degree of prematurity and severity of the illness/hospital course have great impact and influence on growth. This narrative examines the evidence identified by the methods of this review that VLBW infants, with or without other conditions, are at increased risk for growth impairment. The narrative regarding VLBW and growth outcome is organized as follows:

- Evidence that VLBW is associated with growth impairment
- Evidence that VLBW plus bronchopulmonary dysplasia is associated with growth impairment
- Evidence that VLBW plus antenatal glucocorticoid exposure is associated with growth impairment
- Evidence that VLBW plus necrotizing enterocolitis is associated with growth impairment
- Evidence linking VLBW plus postnatal nutrition with growth impairment

Evidence That VLBW Is Associated With Growth Impairment

Twelve observational studies provide evidence that VLBW is associated with growth impairment

Table 6.1. Association of VLBW/Prematurity with Growth Impairment

Author, Year	N	Mean BW,g;GA. week Baseline Range	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Ford 2000 20380862	206	GA: 29 BW:1075	BW< 1500 g	Growth in Wt/Ht/HC	⬇	❗❗❗	A
Wang, 1998 98244087	514	GA: 28 BW: 955	BW < 1250 g	Growth in Wt/Ht	⬇	❗❗	A
Connors 1999 11483801	198	BW:823 GA:27	BW Weight Growth <3%tile High perinatal risk	Growth quotient	⬇	❗❗	A
				Motor ability	⬇		
Avila-Diaz, 2001 21334039	34	BW: 1294 GA: 30	Prematurity Birth weight	Bone mineral content and bone area	⬇	❗❗	A
Kurkinen-Raty 2000 20284814	175	GA: 30 BW: 1450	"Indicated" preterm / SGA	Wt/Ht/HC	⬇	❗❗	B
Saigal 2001 11483807	154	GA: 27 BW: 835	BW 500-1000 g	Weight z score	⬇	❗❗	B
Scherjon 1998 98429216	96	GA: 30 (26-32) BW: 1295 (605-2295)	Raised U/C ratio	Wt/Ht HC	⇔ ⬇	❗❗	B
Lee 1998 98442293	35	GA: ND BW: 789	Candidemia and/or Candidal meningitis	Growth retardation (Wt, Ht, HC > 2 SD below the mean)	⇔	❗	B
Finnström 1998 99041345	362	GA: = 23 BW: 798	BW = 1000 g	Wt/Ht/HC	⬇	❗❗❗	C

Author, Year	N	Mean BW,g;GA. week Baseline Range	Predictors	Outcome	Associ-ation	Applica-bility	Quality
Forslund 1992 93044002	41	BW: ND GA: 27-34	Prematurity	Growth in wt/ht/HC	⇔	!	C
Duvanel 1999 99207097	85	GA: 32 BW: 1154	Recurrent episodes of Hypoglycemia	Growth rates for Wt, Ht, HC	⇔	!	C
				HC at 12, 18 mo, 5 yrs	↓		
Gosch 1997 97379896	5	GA:28(26-29) BW: 880	ELDW	Growth in Wt/Ht/HC/BMI	↓	!	C

Ford, Doyle, Davis, et al. (2000) compared growth and pubertal development in VLBW children (birthweight <1500 grams) and normal birth weight children (birth weight >2499 grams) through 14 years of age. Children with CP were excluded. At ages 2,5, 8, and 14 years, the VLBW children were significantly shorter, lighter, and had smaller head circumference compared to normal birth weight group. The differences between the two groups were less apparent over time. At age 14, pubertal development was similar between the groups.

Wang and Sauve, (1998) compared growth outcomes of VLBW infants (≤1250 grams birth weight) according to different growth references for normal term infants (NHCS/WHO reference, Canadian reference, and WHO reference) and validated the adjustments made for growth by corrected age. Children were followed through 3 years of age. More infants were identified as underweight at 12 and 18 months with the NCHS/WHO reference compared to the other two references. Postnatal growth was recorded according to chronologic age and adjusted age and expressed as standard deviation scores or Z-scores. The age adjusted Z-scores were always closer to zero compared to chronological age. The differences in Z-scores diminished over time, they still remained statistically significantly different, thus validating use of the corrected age through 3 years age. Regardless of the growth reference and whether the growth was plotted by adjusted age or chronologic age, the mean weight and height were still significantly lower in VLBW than term infants at 4-36 months of age.

Connors, O'Callaghan, Burns, et al., (1999) determined that weight <3rd and <10th percentile at 2 years of age in ELBW infants (born 1987-1992) at high perinatal risk or neurological impairment is strongly associated with neurosensory developmental abnormalities and motor skills.

Gosch, Brambring, Gennat, et al. (1997) reported that ELBW blind children also had significantly lower head circumference, length, and body mass indices than term blind children. Avila-Diaz, Flores-Huerta, Martinez-Muniz, et al. (2001) studied the bone density of 26 infants with mean GA 30 weeks and mean birthweight of 1294 grams for 6 months postnatally. Full term infants (n=16) had significantly higher ($P<0.05$) bone mineral content and bone area compared to preterm infants (n=26) even after correction for age. Preterm infants had a

significantly higher rate of increase in bone mineral content /weight ratio in months 2 to 6 suggesting "catch up" mineralization ($P<0.001$).

Evidence That VLBW Plus BPD Is Associated With Growth Impairment

It is well documented (Table 6.2) that VLBW infants with BPD are smaller and have difficulty gaining weight while in the neonatal intensive care unit (NICU). Recurrent illness and pulmonary exacerbations of BPD, increased metabolic needs and inadequate nutrient intakes all contribute to compromise growth in VLBW infants with BPD.

Table 6.2. Association of VLBW plus BPD with Growth impairment

Author, Year	N	Mean BW,g;GA.week Baseline	Predictors	Outcome	Association	Applica-bility	Quality
DeReignier 1997 98041177	174	BW:1015 GA:28	GA Apgar score Severity of CLD Necrotizing "enterocolitis"	Wt. Ht/HC	↓ ⇔		B
Chye 1995 95314864	78	BW: 1055 GA: 28	BPD BPD on home O2 (20)	Growth in Wt/Ht/HC	⇔		B
				Re-hospitalization for poor growth	↑		
				Re-hospitalization for poor FTT	↑		

Two studies reported these associations. deRegnier, Roberts, Ramsey, et al. (1997) retrospectively studied 174 VLBW infants; 58 of each with no BPD, mild BPD, and severe BPD (mean gestation age 27.5 weeks, mean birth weight 1015 grams, born 1987-1991). Infants were matched for birth weight, sex, and race. Infants with severe chronic lung disease were found to be significantly lighter ($P<0.01$) and shorter ($P<0.001$) than infants with no or mild BPD at one year of life.

Chye and Gray (1995) studied rehospitalization and growth of 78 VLBW infants with BPD (mean birth weight of 1055 grams, mean gestational age of 28 weeks) matched with infants without BPD. As noted previously in the pulmonary discussion, rehospitalization was significant in both groups in the first year of life. Growth failure (plotted on sex specific National Center for Health Statistics growth charts) was common in both preterm groups as demonstrated by the proportion of infants below the 10 percentile for corrected age at 4 months (BPD 30% vs. Controls 15%, $P<0.05$). In the BPD group, weight, length, and head circumference were always below that of the control group, but the differences were not significant at 8 and 12 months. Additionally, BPD infants with home O2 had a 3-fold increase in rehospitalization for failure to thrive. This finding is linked to the fact that more children in the BPD group required re-hospitalization for poor growth in the first year of age compared to controls (BPD 14% vs.

Control 1%, RR 14.0, 95% CI, 1.7,82). The primary reasons were related to poor feeding and gastroesophageal reflux.

Evidence That VLBW Plus Antenatal Glucocorticoid Exposure Is Associated With Growth Impairment

Table 6.3. Association of VLBW plus antenatal glucocorticoid exposure growth impairment

Author, Year	N	Mean BW,g;GA. week Baseline Range	Predictors	Outcome	Assoc-iation	Applicability	Quality
French 1999 99115141	477	BW1416 (905-1810) GA:30(26-32)	Antenatal corticosteroids	Growth in Wt/ Ht/HC	⇔	! ! !	B

French, Hagan, Evans, et al. (1999) evaluated the effects of multiple courses of antenatal glucocorticoid therapies on birth size, growth, and neurodeveloment at 3 years age in preterm infants (born <33 weeks, born 1990-1992). Increasing number of repeated courses of antenatal steroids was associated with decreased birth weight ratio, and a reduction in birth weight of as much as 9% (P=0.014) and reduction in head circumference as much as 4% (P=0.0024). Growth at age 3 years was not related to increasing number of corticosteroid courses.

Evidence That VLBW Plus Necrotizing Enterocolitis Is Associated with Growth Impairment

There is limited data (Table 6.4), based on the methods of this review, regarding the association between VLBW plus necrotizing enterocolitis and growth impairment. Thus the lack of evidence should not be interpreted as no association. It is biologically plausible, and highly possible as suggested by the study of Ladd et al, that there is an association between VLBW plus NEC and growth impairment depending upon the severity of NEC and its long-term complications.

Table 6.4. Association of VLBW plus necrotizing enterocolitis exposure growth impairment

Author, Year	N	Mean BW,g; GA,week Baseline Range	Predictors	Outcome	Association	Applicability	Quality
Ladd 1998 9835745	148	BW:1661 GA:31	Length of bowel resected or status of ICV	Severe growth retardation(<1 0 % tile	⇔	! ! !	C

Ladd, Rescorla, West, et al. (1998) retrospectively reviewed the long-term factors affecting outcome, including growth, of 249 premature infants (mean gestational age of 30 weeks; average birth weight 1500 grams; born between 1989 and 1994) who required surgical intervention for NEC. Postoperatively, the presence of an ileocecal valve (ICV) had no relation to survival unless there was less than 20 cm of small bowel remaining. When followed, there was no difference in weight percentiles with or without the presence of the ICV. At each visit, weight percentiles were below the 25 percentile and 60 % of patients reached below the 10th percentile at 1 year of life. However, by two years of life, less than 35% of subjects had weights less than the 10th percentile. When 125 of the infants were stratified based on the amount of bowel resected, there was a trend towards reduced growth as bowel length resected increased.

Evidence Linking VLBW Plus Postnatal Nutrition With Growth Impairment

This review identified two studies (Table 6.5) which addressed the relationship between VLBW and postnatal nutrition with growth impairment. This is an important topic, given the improved long-term survival of VLBW infants, in which there is limited, current, good information in the literature.

Table 6.5. Association of VLBW plus postnatal nutrition with growth impairment

Author/ Year	N	Mean BW, g; GA, week Baseline (Range)	Intervention	Outcomes	Efficacy	Applica-bility	Qua-lity
O'Connor 2001 11483801	415	GA: 29 (27-31) BW: 1253 (965-4543)	Group 1: EHM-T fed (43) Group 2: AA+OHA (finsh/fungal) (120) Group 3: AA+DHA (egg-TG/fish) (126) Group 4: Formula-fed (126)	Growth in Wt/Ht/HC	Growth (Wt, Ht, HC) no difference among the 4 preterm groups in terms of gm/kg/day for weight; mm/wk for Ht and HC.		A
Wauben 1998 98387708	37	GA: 30 BW: 1300	Group 1: Milk + Fortifier (12) Group 2: Milk + Calcium phosphorus (13) Group 3: Preterm formula-fed (12)	Growth in Wt/Ht/HC	No association was found between neonatal diet (Milk+Fortifier, Milk+Calsium phosphorus, or Preterm formula) and the Weight, Height, or HC		B
				Body composition Growth assessment at 9 and 18 months posterm	No association was found between neonatal diet (Milk+Fortifier, Milk+Calsium phosphorus, or Preterm formula) and whole body mass composition (Lean mass, Fat mass)		

Author/ Year	N	Mean BW, g; GA, week Baseline (Range)	Intervention	Outcomes	Efficacy	Applica-bility	Qua-lity
Morley 2000 20167446	420	Trial 1 GA: 31 BW: 1397	Group A: Banked donor Breast milk fed until weight 2000 g or discharge (207) Group B: Preterm formula-fed (213)		No association was found between the neonatal diet (banked donor milk vs preterm formula) and the 6 anthropometrics at any follow up point (9 mo, 18 mo and 7.5-8 yrs)	!	C
	394	Trial 2 GA: 31 BW: 1387	Group A: Standard term formula-fed until weight 2000 g or discharge (181) Group B: Premature formula-fed (213)	Growth Assessment at 9 and 18 months post term	No association was found between neonatal diet (term vs preterm formula) and the Weight, Height, HC and skinfold thickness at any follow up point (18 mo and 7.5 yrs), except for a significantly lower waist to hip ratio at 7.5 yrs in infants fed preterm vs term formula solely (without supplementation with mother's milk) (0.86 vs 0.89, p<0.001)		

Wauben, Atkinson, Shah, et al. (1998) studied the impact of multi-nutrient fortification of breast milk compared to supplementation of breast milk with calcium and phosphorous in the hospital, and of feeding breast milk only after discharge compared to formula feeding after discharge. They found no differences between groups with the multi-nutrient vs. calcium/phosphorous formulas in the hospital, but they did find a difference between groups fed only breast milk vs. premature formula after discharge in terms of less bone mineralization and greater percent body fat to 12 months age. They conclude that post-discharge dietary practices do have an impact on body composition.

Morley and Lucas (2000) randomized 926 infants into two parallel neonatal diet trails for a total of approximately 4 weeks. Trial I included banked donor breast milk vs preterm formula (with or without mother's milk supplementation). Trial 2 preterm formula vs. term formula (with or without mother's milk supplementation. They found better neonatal growth in infants fed the preterm formula in contrast to those fed either banked donor breast milk or standard formula. The early, 4-week diet had no measurable influence on weight, length, head circumference at 9 or 18 months post term or at 7-8 years of age.

Table 6. 6. Association of LBW/Prematurity to Growth Delay

Author Year	N (Controls)	Mean BW, g; GA, week Baseline (Range)	Measure	% of Subjects	Applica-bility	Quality
Cheung 1998 99059896	10	GA: 25 (24-30) BW: 860 (340-1460)	Wt < 3rd %tile	20%	!	B
			Ht < 3rd %tile	40%		
			HC < 3rd %tile	30%		

[a] All AGA
Abbreviation:
HC = head circumference
FTT = failure to thrive
NEC = necrotizing enterocolitis
ICV = ileocecal valve
EHM-T = exclusively human milk-fed until term CA